Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion
Office on Smoking and Health

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Message from Tommy G. Thompson
Secretary of Health and Human Services

Forty years have passed since the first landmark Surgeon General's report on smoking and health. Yet, smoking remains the leading preventable cause of death in this country. It continues to cost our society too many lives, too many dollars, and too many tears.

This new Surgeon General's report illustrates the harmful impact of smoking on nearly every organ in the body. Its statistics and conclusions underscore the necessity of remaining vigilant in our smoking prevention efforts. We've made significant progress in our fight against smoking, but we still have much more work to do. Some of the important findings in this report include:

- Smoking causes cancers in parts of the body (including the kidney, cervix, and bone marrow) that have not been previously linked to smoking in this series of reports.

- Smoking diminishes health generally. Adverse health effects begin before birth and continue across the life span. Smoking also causes cataracts and contributes to the development of osteoporosis, thus increasing the risk for fracture in the elderly.

- During 1995-1999, smoking caused approximately 440,000 premature deaths in the United States annually, leading to 13.2 years of potential life lost for male smokers, and 14.5 years lost for female smokers.

- Changes in cigarettes that reduce machine yields of tar and nicotine have not had any clear benefits for public health.

The scientific evidence contained in this new report provides an even stronger reason for action at all levels of society. Measures to prevent smoking initiation need to be strong and enforced, especially among adolescents and young adults. We need to deny our youth access to cigarette purchases and prevent advertising from being directed at them. We need to motivate the millions of addicted smokers to quit and facilitate access to cessation programs and therapies that have evidence of effectiveness.

In recent years, the Department of Health and Human Services (HHS) has committed itself to developing creative and innovative preventative approaches. This year, the Department will establish a new toll-free telephone number that will serve as a single access point to the national network of quitlines. This number will give all smokers in this country access to support and to the latest information to help them quit. We're also developing strategies to help pregnant smokers quit through a coalition with more than 50 national, state, and local organizations. The Centers for Medicare & Medicaid Services has funded a demonstration project to examine the best ways to help Medicare beneficiaries quit smoking. A media campaign resource center, sponsored by the Centers for Disease Control and Prevention (CDC), shares high-quality advertising materials on smoking cessation and prevention with states and other partners. In addition, CDC is moving to become a smoke-free campus by the end of the year, and I am exploring making HHS the first smoke-free department in the federal government. These are a few examples of the work this Department does every day to discourage youth from smoking and to support smokers who want to quit.

This report is the 28th Surgeon General's report to outline the negative health effects of smoking. Each report since 1964 has added proof that smoking causes disease. I trust this report will be another effective tool in educating Americans about this lethal addiction. I appreciate the efforts of Surgeon General Richard Carmona and the CDC in preparing this timely report, and I am particularly grateful to the many scientists and researchers from around the world who contributed to its development.

The Health Consequences of Smoking

Foreword

This new report of the Surgeon General on the health effects of smoking provides a startling picture of the damage to health caused by tobacco use. Smoking injures almost all bodily organs, and tragically this injury often leads to incurable disease and death. The comprehensive review process that is the foundation of this series of reports has found new causal associations of smoking with disease, reemphasizing the need for continued monitoring of scientific evidence on the health effects of smoking. This report also addresses changes in the cigarette and whether these changes present increased risks to smokers.

With this latest report, the format has been updated. The core of previous reports has always been the evaluation of the evidence, with general summaries of the evidence relevant to a particular disease or an adverse effect presented in various tables. These tables have been the basis for assessing the scope and consistency of the evidence and for assessing the presence of critical indicators of causality, including the findings of a dose-response relationship and a decline in risk following cessation. The printed format of these tables is supplemented with a new and dynamic database that includes the results of key studies in a format accessible through the World Wide Web, enabling readers to access additional tables and figures. The Office on Smoking and Health at the Centers for Disease Control and Prevention will maintain the database, selectively adding new critical studies as they are published. The scope of the literature is so broad that not all studies can be entered, but this new format offers a useful complement to the Smoking and Health Database that is already maintained by the Office on Smoking and Health and is readily available at http://www.cdc.gov/tobacco.

I am grateful to the leadership from the Office on Smoking and Health in preparing this report and to the Surgeon General for his guidance. These reports would not be possible without the contributions of many scientists from throughout the world who wrote and reviewed this volume. These reports remain a cornerstone of our nation's strategy to combat the ongoing epidemic of tobacco-related disease and death.

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and
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Preface

from the Surgeon General,
U.S. Department of Health and Human Services

Forty years have passed since Surgeon General Luther Terry released the landmark 1964 report of the Surgeon General's Advisory Committee on Smoking and Health. Dr. Terry had asked the committee to evaluate all available scientific evidence to determine whether smoking caused lung cancer and other diseases. The approach adopted by this committee has become a model for the many Surgeon General's reports that have followed: identify all relevant scientific data, evaluate and summarize the evidence, and apply the criteria for causal inferences to determine whether the weight of the evidence supports a definitive conclusion.

In 1964, the Surgeon General's committee concluded that cigarette smoking causes chronic bronchitis and cancers of the lung and larynx. Using these established, now standard, causal criteria, other reports of the Surgeon General have linked active smoking to many other diseases and conditions. Secondhand smoke has also been found to adversely impact health, a conclusion first reached in the 1986 Surgeon General's report.

This report returns to the topic of that first Surgeon General's report, the health consequences of active smoking. It has been many years since active smoking and health has been the sole topic of a Surgeon General's report, and this report provides a comprehensive overview only touched on in recent reports. During the last four decades, the scientific evidence on smoking and disease has expanded substantially, linking active smoking with an ever-growing list of diseases. In fact, some long-term studies of smokers are now providing a picture of how the risks of smoking play out across a lifetime. Even for diseases that we have long known were caused by smoking, such as lung cancer, there are new questions related to unexplained changes in the characteristics of the diseases. There are also questions about how changes in the cigarettes smoked in the United States and other countries have affected risks to smokers.

This report looks not only at active smoking but also examines the issue of causal criteria, laying out in terms agreed upon by national and international scientific bodies what evidence is required in order to declare that a disease or condition is causally related to smoking. Conclusions from previous reports have been updated using new uniform standards of both causality and language, and, in addition, there are a number of new causal conclusions for cancer, cataract, and general health status. Cataract, a common problem in older Americans, is now known to be causally related to active smoking. This report also concludes that at all ages, smokers are generally less healthy than nonsmokers.

This report provides a tragic picture of the consequential effects of active smoking across a lifetime. Active smoking affects reproduction and the hearts and lungs of adolescents and young adults. Even by early middle age, it causes death from cancer and cardiovascular diseases, shortening the life expectancy of smokers. With increasing age, the frequency of smoking-caused diseases rises.

I am encouraged by the declining smoking rates in the United States in recent decades. However, every day nearly 5,000 people under 18 years of age try their first cigarette, and in 2001, an estimated 46.2 million American adults smoked. These numbers represent an enormous emotional and financial burden for their families and for our health care system. This report documents the path leading to disease and death that these smokers inevitably face if they continue to smoke.

Over the years the harmful effects of smoking have been well documented. Although great progress has been made, a challenging struggle remains. This report will hasten the day when many of the findings herein are no longer true and we will be able to view smoking as a scourge of the past. We all need to strengthen our efforts to prevent young people from ever starting to smoke, and to encourage smokers of all ages to quit.

Richard Carmona, M.D., M.P.H., F.A.C.S.
Surgeon General

Chapter 1
Introduction and Approach to Causal Inference

Introduction

This report of the Surgeon General on the health effects of smoking returns to the topic of active smoking and disease, the focus of the first Surgeon General's report published in 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). The first report established a model of comprehensive evidence evaluation for the 27 reports that have followed: for those on the adverse health effects of smoking, the evidence has been evaluated using guidelines for assessing causality of smoking with disease. Using this model, every report on health has found that smoking causes many diseases and other adverse effects. Repeatedly, the reports have concluded that smoking is the single greatest cause of avoidable morbidity and mortality in the United States.

Of the Surgeon General's reports published since 1964, only a few have comprehensively documented and updated the evidence on active smoking and disease. The 1979 report (USDHEW 1979) provided a broad array of information, and the 1990 report on smoking cessation (U.S. Department of Health and Human Services [USDHHS] 1990) also investigated major diseases caused by smoking. Other volumes published during the 1980s focused on specific groups of diseases caused by smoking (USDHHS 1982, 1983, 1984), and the 2001 report was devoted to women and smoking (USDHHS 2001). Because there has not been a recent systematic review of the full sweep of the evidence, the topic of active smoking and health was considered an appropriate focus for this latest report. Researchers have continued to identify new adverse effects of active smoking in their ongoing efforts to investigate the health effects of smoking. Lengthy follow-ups are now available for thousands of participants in long-term cohort (follow-up) studies (National Cancer Institute [NCI] 1997).

This report also updates the methodology for evaluating evidence that the 1964 report initiated. Although that model has proved to be effective, this report establishes a uniformity of language concerning causality of associations so as to bring greater specificity to the findings of the report. The following section of this chapter describes the approach and its rationale. Beginning with this report, conclusions concerning causality of association will be placed into one of four categories with regard to strength of the evidence: (1) sufficient to infer a causal relationship, (2) suggestive but not sufficient to infer a causal relationship, (3) inadequate to infer the presence or absence of a causal relationship, or (4) suggestive of no causal relationship.

This approach separates the classification of the evidence concerning causality from the implications of that determination. In particular, the magnitude of the effect in the population, the attributable risk, is considered under "implications" of the causal determination. For example, there might be sufficient evidence to classify smoking as a cause of two diseases but the number of attributable cases would depend on the frequency of the disease in the population and the effects of other causal factors.

This report covers active smoking only. Passive smoking was the focus of the 1986 Surgeon General's report and subsequent reports by other entities (USDHHS 1986; U.S. Environmental Protection Agency [EPA] 1992; California EPA 1997; International Agency for Research on Cancer [IARC] 2002). The health effects of pipes and cigars, also not within the scope of this report, are covered in another report (NCI 1998).

In preparing this report, the literature review approach was necessarily selective. For conditions for which a causal conclusion had been previously reached, there was no attempt to cover all relevant literature, but rather to review the conclusions from previous Surgeon General's reports and focus on important new studies for that topic. The enormous scope of the evidence precludes such detailed reviews. For conditions for which a causal conclusion had not been previously reached, a comprehensive search strategy was developed. Search strategies included reviewing previous Surgeon General's reports on smoking, publications originating from the largest observational studies, and reference lists from important publications; consulting with content experts; and conducting focused literature searches on specific topics. For this report, studies through 2000 were reviewed.

In addition, conclusions from prior reports concerning smoking as a cause of a particular disease have been updated and are presented in this new format based on the evidence evaluated in this report (Table 1.1). Remarkably, this report identifies a substantial number of diseases found to be caused by smoking that were not previously causally associated with smoking: cancers of the stomach, uterine cervix, pancreas, and kidney; acute myeloid leukemia; pneumonia; abdominal aortic aneurysm; cataract; and periodontitis. The report also concludes that smoking generally diminishes the health of smokers.

Table 1.1   Diseases and other adverse health effects for which smoking is identified as a cause in the current Surgeon General's report

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
Cancer		
Bladder cancer	"Smoking is a cause of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking." (1990, p. 10)	"The evidence is sufficient to infer a causal relationship between smoking and. . .bladder cancer."
Cervical cancer	"Smoking has been consistently associated with an increased risk for cervical cancer." (2001, p. 224)	"The evidence is sufficient to infer a causal relationship between smoking and cervical cancer."
Esophageal cancer	"Cigarette smoking is a major cause of esophageal cancer in the United States." (1982, p. 7)	"The evidence is sufficient to infer a causal relationship between smoking and cancers of the esophagus."
Kidney cancer	"Cigarette smoking is a contributory factor in the development of kidney cancer in the United States. The term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site." (1982, p. 7)	"The evidence is sufficient to infer a causal relationship between smoking and renal cell, [and] renal pelvis. . . cancers."
Laryngeal cancer	"Cigarette smoking is causally associated with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . ." (1980, p. 126)	"The evidence is sufficient to infer a causal relationship between smoking and cancer of the larynx."
Leukemia	"Leukemia has recently been implicated as a smoking-related disease. . .but this observation has not been consistent." (1990, p. 176)	"The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia."
Lung cancer	"Additional epidemiological, pathological, and experimental data not only confirm the conclusion of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the causal relationship of smoking to lung cancer in women." (1967, p. 36)	"The evidence is sufficient to infer a causal relationship between smoking and lung cancer."
Oral cancer	"Cigarette smoking is a major cause of cancers of the oral cavity in the United States." (1982, p. 6)	"The evidence is sufficient to infer a causal relationship between smoking and cancers of the oral cavity and pharynx."

Table 1.1   Continued

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
Pancreatic cancer	"Smoking cessation reduces the risk of pancreatic cancer, compared with continued smoking, although this reduction in risk may only be measurable after 10 years of abstinence." (1990, p. 10)	"The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer."
Stomach cancer	"Data on smoking and cancer of the stomach. . .are unclear." (2001, p. 231)	"The evidence is sufficient to infer a causal relationship between smoking and gastric cancers."
Cardiovascular diseases		
Abdominal aortic aneurysm	"Death from rupture of an atherosclerotic abdominal aneurysm is more common in cigarette smokers than in nonsmokers." (1983, p. 195)	"The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm."
Atherosclerosis	"Cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral vascular disease." (1983, p. 8)	"The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis."
Cerebrovascular disease	"Cigarette smoking is a major cause of cerebrovascular disease (stroke), the third leading cause of death in the United States." (1989, p. 12)	"The evidence is sufficient to infer a causal relationship between smoking and stroke."
Coronary heart disease	"In summary, for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States." (1979, p. 1-15)	"The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease."
Respiratory diseases		
Chronic obstructive pulmonary disease	"Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis." (1964, p. 302)	"The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality."
Pneumonia	"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (1990, p. 11)	"The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease."

Table 1.1   Continued

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
Respiratory effects in utero	"In utero exposure to maternal smoking is associated with reduced lung function among infants. . . ." (2001, p. 14)	"The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants."
Respiratory effects in childhood and adolescence	"Cigarette smoking during childhood and adolescence produces significant health problems among young people, including cough and phlegm production, an increased number and severity of respiratory illnesses, decreased physical fitness, an unfavorable lipid profile, and potential retardation in the rate of lung growth and the level of maximum lung function." (1994, p. 41)	"The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence." "The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood. " "The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea." "The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence."
Respiratory effects in adulthood	"Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers." (1990, p. 11)	"The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function." "The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked."

Table 1.1   Continued

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
Other respiratory effects	"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (1990, p. 11)	"The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea." "The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control."
Reproductive effects		
Fetal death and stillbirths	"The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy."
Fertility	"Women who smoke have increased risks for conception delay and for both primary and secondary infertility." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women."
Low birth weight	"Infants born to women who smoke during pregnancy have a lower average birth weight. . .than. . .infants born to women who do not smoke." (2001, p. 307)	"The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight."
Pregnancy complications	"Smoking during pregnancy is associated with increased risks for preterm premature rupture of membranes, abruptio placentae, and placenta previa, and with a modest increase in risk for preterm delivery." (2001, p. 307)	"The evidence is sufficient to infer a casual relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption." "The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation."

Table 1.1   Continued

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
Other effects		
Cataract	"Women who smoke have an increased risk for cataract." (2001, p. 331)	"The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract."
Diminished health status/morbidity	"Relationships between smoking and cough or phlegm are strong and consistent; they have been amply documented and are judged to be causal. . . ." (1984, p. 47) "Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is the overwhelmingly most important cause of cough, sputum, chronic bronchitis, and mucus hypersecretion." (1984, p. 48)	"The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may be manifest as increased absenteeism from work and increased use of medical care services." "The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications."
Hip fractures	"Women who currently smoke have an increased risk for hip fracture compared with women who do not smoke." (2001, p. 321)	"The evidence is sufficient to infer a causal relationship between smoking and hip fractures."
Low bone density	"Postmenopausal women who currently smoke have lower bone density than do women who do not smoke." (2001, p. 321)	"In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density."
Peptic ulcer disease	"The relationship between cigarette smoking and death rates from peptic ulcer, especially gastric ulcer, is confirmed. In addition, morbidity data suggest a similar relationship exists with the prevalence of reported disease from this cause." (1967, p. 40)	"The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive."

Sources: U.S. Department of Health, Education, and Welfare 1964, 1967, 1979; U.S. Department of Health and Human Services 1980, 1982, 1983, 1984, 1989, 1990, 1994, 2001.

Despite the many prior reports on the topic and the high level of public knowledge in the United States of the adverse effects of smoking in general, tobacco use remains the leading preventable cause of disease and death in the United States, causing approximately 440,000 deaths each year and costing approximately $157 billion in annual health-related economic losses (see Chapter 7, "The Disease Impact of Cigarette Smoking and Benefits of Reducing Smoking"). Nationally, smoking results in more than 5.6 million years of potential life lost each year. Although the rates of smoking continue to decline, an estimated 46.2 million adults in the United States still smoked cigarettes in 2001 (Centers for Disease Control and Prevention [CDC] 2003). In 2000, 70 percent of those who smoked wanted to quit (CDC 2002a). An increasingly disturbing picture of widespread organ damage in active smokers is emerging, likely reflecting the systemic distribution of tobacco smoke components and their high level of toxicity. Thus, active smokers are at higher risk for cataract, cancer of the cervix, pneumonia, and reduced health status generally.

This new information should be an impetus for even more vigorous programs to reduce and prevent smoking. Smokers need to be aware that smoking carries far greater risks than the most widely known hazards. Health care providers should also use the new evidence to counsel their patients. For example, ophthalmologists may want to warn patients about the increased risk of cataract in smokers, and geriatricians should counsel their patients who smoke, even the oldest, to quit. This report shows that smokers who quit can lower their risk for smoking-caused diseases and improve their health status generally. Those who never start can avoid the predictable burden of disease and lost life expectancy that results from a lifetime of smoking.

Preparation of the Report

This report of the Surgeon General was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, USDHHS. Initial chapters were written by 19 experts who were selected because of their expertise and familiarity with the topics covered in this report. Their various contributions were summarized into six major chapters that were then reviewed by more than 60 peer reviewers. The entire manuscript was then sent to more than 20 scientists and experts, who reviewed it for its scientific integrity. After each review cycle was completed, the drafts were revised by the editors on the basis of the experts' comments.

Subsequently, the report was reviewed by various institutes and agencies within USDHHS.

Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, there may be additional published studies or data. To provide published information as current as possible, this report includes an appendix of more recent studies that represent major additions to the literature.

This report is also accompanied by a companion database of key evidence that is accessible through the Internet (see http://www.cdc.gov/tobacco). The database includes a uniform description of the studies and results on the risks of smoking that were presented in a format compatible with abstraction into standardized tables. Readers of the report may access these data for additional analyses, tables, or figures. The Office on Smoking and Health at CDC intends to maintain this database and will periodically update its contents as new reports are published.

Organization of the Report

This report covers major groups of the many diseases associated with smoking: cancers, cardiovascular diseases, respiratory diseases, reproductive effects, and other adverse health consequences. This chapter (Chapter 1) includes a discussion of the concept of causation and introduces new concepts of causality that are used throughout this report. Chapter 2 discusses each of the main sites of cancer and their relationship to smoking. Cardiovascular diseases, including atherosclerosis, coronary heart disease, stroke, and abdominal aortic aneurysm are the focus of Chapter 3, which begins with an extensive review of newer findings on the mechanisms by which smoking causes this group of very common diseases. Chapter 4 includes both acute respiratory diseases associated with smoking and the chronic respiratory diseases long known to be caused by smoking, including accelerated loss of lung function with aging. The full scope of adverse reproductive effects caused by smoking in both men and women is covered in Chapter 5. Chapter 6 discusses other specific effects of smoking on the eyes, the bones, and oral health, along with evidence on more general adverse effects related to health status overall. Chapter 7 updates prior estimates of the burden of diseases caused by smoking. Finally, Chapter 8 discusses "A Vision for the Future" outlining broad strategies and courses of action for tobacco control in the future.

Smoking: Issues in Statistical and Causal Inference

The U.S. Surgeon General's reports on the health effects of smoking have long had a central role in the translation of scientific evidence into policies for tobacco control. A critical and essential aspect of this role has been the judgment that smoking is a cause of specific diseases or health conditions. The statement that an exposure "causes" a disease in humans represents a serious claim, but one that carries with it the possibility of prevention. Causal determinations may also carry substantial economic implications for society and for those who might be held responsible for the exposure or for achieving its prevention. The qualitative judgment that an exposure causes a particular disease signifies that in the absence of exposure some fraction of cases or deaths would not occur or would occur at a later age (USDHEW 1964; Rothman and Greenland 1998). Given these implications, the grounds for making the causal designation must be well founded and clear.

The need for guidelines for causal determination was recognized by the committee that authored the first Surgeon General's report, and by the scientists whose work served as the foundation for that report (Cornfield et al. 1959). The difficulty of attempting to both adjudicate causal relationships and choose the language to describe them was apparent then (USDHEW 1964). In a section titled "Criteria for Judgment" in the 1964 report, the committee wrote that after "vigorous discussions," they could neither precisely define nor replace the word "cause," a reflection of the same problem that philosophers have confronted over the centuries. The main approach is summarized below:

> When a relationship or an association between smoking. . .and some condition in the host was noted, the significance of the association was assessed.
>
> The characterization of the assessment called for a specific term. . . .The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host.

No member was so naive as to insist upon mono-etiology in pathological processes or in vital phenomena. All were thoroughly aware. . . that the end results are the net effect of many actions and counteractions.

> Granted that these complexities were recognized, it is to be noted clearly that the Committee's considered decision to use the words "a cause," or "a major cause," or "a significant cause," or "a causal association" in certain conclusions about smoking and health affirms their conviction (USDHEW 1964, p. 21).

The key descriptors in the above passage include "effectual," "significant," and "major." Reading these phrases now, it is unclear whether the committee intended to describe the underlying causal relationship itself, the size of an estimated effect, the degree of statistical evidence for that estimated effect, the strength of the causal claim, or some combination of these elements of the evidence. The report further described the criteria for determining a causal relationship. These criteria, which were just emerging into public health, have since become widely accepted and used in epidemiology and public health: that any alleged association should demonstrate consistency, strength, specificity, temporality, and coherence. This report has served as a lasting model for the comprehensive evaluation of scientific evidence.

However, at that time strict terminology was not in place for describing the status of the evidence. Thus, in the 1964 and subsequent Surgeon General's reports, as well as in other reports, the language used to characterize conclusions about relationships between smoking and disease varied. Table 1.2 contains examples of these variations used in every Surgeon General's report published between 1964 and 1990. For example, for atherosclerosis outcomes there is the following sequence of terms: "likely risk factor" (USDHEW 1971, p. 9), "major risk factor" (USDHEW 1973, p. 23), "strong associations" (USDHEW 1974, p. 19), "major risk factor" (USDHEW 1979, p. 1-14), "major, independent risk factor" (USDHHS 1980, p. 7), "the most powerful risk factor" (USDHHS 1983, p. 8), and finally, "a cause of and the most powerful risk factor" (USDHHS 1989, p. 63). For pancreatic

Table 1.2   Variations in terminology from previous Surgeon General's reports concerning smoking as a cause of the listed diseases*

Disease and statement	Surgeon General's report
Atherosclerosis/peripheral vascular disease	
"Autopsy studies suggest that cigarette smoking is **associated with a significant increase** in atherosclerosis of the aorta and coronary arteries." (p. 4)	1969
"Data from a number of retrospective studies have indicated that cigarette smoking is **a likely risk factor** in the development of peripheral vascular disease. Cigarette smoking also appears to be a **factor** in the aggravation of peripheral vascular disease." (p. 9)	1971
"Data from several epidemiological and experimental studies suggest that cigarette smoking is a **major risk factor** in the development of peripheral vascular disease." (p. 23)	1973
"Epidemiologic data reveal **strong associations** between cigarette smoking and development of peripheral vascular disease." (p. 19)	1974
"Smoking cigarettes is a **major risk factor** for arteriosclerotic peripheral vascular disease and is **strongly associated** with increased morbidity from arteriosclerotic peripheral vascular disease and with death from arteriosclerotic aneurysm of the aorta." (p. 1-14)	1979
"Cigarette smoking is a **major, independent risk factor** for the development of arteriosclerotic peripheral vascular disease in women." (p. 7)	1980
"Cigarette smoking is **the most powerful risk factor** predisposing to atherosclerotic peripheral vascular disease." (p. 8)	1983
". . . cigarette smoking is a **cause of and the most powerful risk factor** for atherosclerotic peripheral vascular disease." (p. 63)	1989
Bladder cancer	
"Epidemiological studies have demonstrated a **significant association** between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the **risk** of developing bladder cancer **increases** with inhalation and the number of cigarettes smoked." (p. 75)	1972
"Epidemiological studies have demonstrated a **significant association** between cigarette smoking and bladder cancer in both men and women." (p. 1-17)	1979
"Cigarette smoking acts independently and synergistically with other factors, such as occupational exposures, to **increase the risk** of developing cancer of the urinary bladder." (p. 1-17)	1979

*Words in boldface are for emphasis only here and do not indicate emphasis in the original reports.

Table 1.2   Continued

Disease and statement	Surgeon General's report
"A **dose-response relationship** has been demonstrated between cigarette smoking and cancer of the lung, larynx, oral cavity, and urinary bladder in women." (p. 127)	1980
"Smoking is a **cause** of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking." (p. 178)	1990
Cerebrovascular disease	
"Additional evidence strengthens the **association** between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic [*sic*] considerations pertinent to coronary heart disease may also apply to cerebrovascular disease." (p. 28)	1967
"Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease, it is concluded that cigarette smoking can **contribute** to the development of cardiovascular disease and particularly to death from coronary heart disease." (p. 3)	1968
"Women cigarette smokers experience an **increased risk** for subarachnoid hemorrhage. . . ." (p. 7)	1980
"Cigarette smoking is a **major cause** of cerebrovascular disease (stroke), the third leading cause of death in the United States." (p. 12)	1989
Chronic obstructive pulmonary disease[†] **(COPD)**	
"Cigarette smoking is **the most important of the causes** of chronic bronchitis in the United States, and **increases the risk of dying** from chronic bronchitis." (p. 302)	1964
"Cigarette smoking is **the most important of the causes** of chronic non-neoplastic bronchopulmonary diseases in the United States. It **greatly increases the risk of dying** not only from both chronic bronchitis but also from pulmonary emphysema." (p. 31)	1967
"Epidemiological and laboratory evidence supports [*sic*] the view that cigarette smoking can **contribute** to the development of pulmonary emphysema in man." (p. 5)	1969
"Cigarette smoking is **the most important cause** of chronic obstructive bronchopulmonary disease in the United States. Cigarette **smoking increases the risk of dying** from pulmonary emphysema and chronic bronchitis." (p. 9)	1971
"Recent autopsy studies confirm that pulmonary emphysema is **much more frequent and severe** in **cigarette smokers** than nonsmokers." (p. 55)	1973

[†]Chronic obstructive pulmonary disease has been known by several terms over the years, including chronic bronchitis, emphysema, chronic obstructive lung disease, and chronic obstructive bronchopulmonary disease.

Table 1.2   Continued

Disease and statement	Surgeon General's report
Coronary heart disease	
"It is also more prudent to assume that the **established association** between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains." (p. 327)	1964
"Additional evidence not only confirms the fact that cigarette smokers have increased death rates from coronary heart disease, but also suggests how these deaths may be **caused by** cigarette smoking. There is an increasing convergence of many types of evidence concerning cigarette smoking and coronary heart disease which strongly suggests that cigarette smoking **can cause death** from coronary heart disease." (p. 27)	1967
"Because of the increasing convergence of epidemiological and physiological findings relating cigarette smoking to coronary heart disease it is concluded that cigarette smoking can **contribute** to the development of cardiovascular disease and particularly to death from coronary heart disease." (p. 3)	1968
"In summary, for the purposes of preventive medicine, it can be concluded that smoking is **causally related** to coronary heart disease for both men and women in the United States." (p. 1-15)	1979
Esophageal cancer	
"Epidemiological studies have demonstrated that cigarette smoking is **associated** with the development of cancer of the esophagus." (p. 12)	1971
"Cigarette smoking is a causal factor in the development of cancer of the esophagus, and the **risk increases** with the amount smoked." (p. 1-17)	1979
"Cigarette smoking is **causally associated** with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . ." (p. 126)	1980
"Cigarette smoking is a **major cause** of esophageal cancer in the United States." (p. 7)	1982
Kidney cancer	
"Cigarette smoking is a **contributory factor** in the development of kidney cancer in the United States. The term 'contributory factor' **by no means excludes** the possibility **of a causal role** for smoking in cancers of this site." (p. 7)	1982
Laryngeal cancer	
"Evaluation of the evidence leads to the judgment that cigarette smoking is a **significant factor** in the causation of laryngeal cancer in the male." (p. 37)	1964
"Cigarette smoking is **causally associated** with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . ." (p. 126)	1980

Table 1.2   Continued

Disease and statement	Surgeon General's report
Lung cancer	
"Cigarette smoking is **causally related to** lung cancer in men; the magnitude of the effect of cigarette smoking **far outweighs all other factors**. The data for women, though less extensive, point in the same direction." (p. 196)	1964
"Additional epidemiological, pathological, and experimental data not only confirm the conclusion of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the **causal relationship** of smoking to lung cancer in women." (p. 36)	1967
"Cigarette smoking is **causally related** to lung cancer in women. . . ." (p. 4)	1968
"Cigarette smoking is **causally associated** with cancer of the lung. . .in women as well as in men. . . ." (p. 126)	1980
Oral cancer	
"Smoking is a **significant factor**. . .in the development of cancer of the oral cavity." (p. 4)	1968
"Recent epidemiologic data strongly indicate that cigarette smoking plays **an independent role in** the development of oral cancer." (p. 59)	1974
"Epidemiological studies indicate that smoking is **a significant causal factor** in the development of oral cancer." (p. 1-17)	1979
"Cigarette smoking is **causally associated** with cancer of the. . .oral cavity. . .in women as well as in men. . . ." (p. 126)	1980
"Cigarette smoking is a **major cause** of cancers of the oral cavity in the United States." (p. 6)	1982
Pancreatic cancer	
"Epidemiological evidence demonstrates a **significant association** between cigarette smoking and cancer of the pancreas." (p. 75)	1972
"Recent epidemiologic data **confirm the association** between smoking and pancreatic cancer." (p. 59)	1974
"Cigarette smoking is **related** to cancer of the pancreas, and several epidemiological studies have demonstrated a **dose-response relationship**." (p. 1-17)	1979
"Cigarette smoking is a **contributory factor** in the development of pancreatic cancer in the United States. The term 'contributory factor' **by no means excludes** the possibility of a **causal role** for smoking in cancers of this site." (p. 7)	1982

Table 1.2   Continued

Disease and statement	Surgeon General's report
Peptic ulcer disease	
"Epidemiological studies indicate an **association** between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer." (p. 340)	1964
"The **relationship** between cigarette smoking and death rates from peptic ulcer, especially gastric ulcer, **is confirmed**. In addition, morbidity data suggest a similar relationship exists with the prevalence of reported disease from this cause." (p. 40)	1967
"The finding of a **significant dose-related excess mortality** from gastric ulcers among both male and female Japanese cigarette smokers, in a large prospective study, and in the context of the genetic and cultural differences between the Japanese and previously investigated Western populations, **confirms and extends the association** between cigarette smoking and gastric ulcer mortality." (p. 162)	1973
"Epidemiological studies have found that cigarette smoking is **significantly associated** with the incidence of peptic ulcer disease and **increases the risk** of dying from peptic ulcer disease." (p. 1-23)	1979
"Female smokers show a **prevalence** of peptic ulcer **higher** than that of nonsmokers by approximately two-fold." (p. 12)	1980
"The 1979 Report stated that the relationship between cigarette smoking and peptic ulcer is **significant** enough to suggest a **causal relationship**." (p. 76)	1989
"The 1979 Report stated that the evidence of an association between cigarette smoking and peptic ulcer was **strong** enough to suggest a **causal relationship**." (p. 429)	1990
Diminished health status/respiratory morbidity	
"Cough, sputum production, or the two combined are **consistently more frequent** among cigarette smokers than among non-smokers." (p. 302)	1964
"Even relatively young cigarette smokers frequently have **demonstrable respiratory symptoms** and reduction [*sic*] in ventilatory function." (p. 31)	1967
"Cigarette smokers have **higher rates of disability** than nonsmokers, whether measured by days lost from work among the employed population, by days spent ill in bed, or by the most general measure–days of 'restricted activity' due to illness or injury." (p. 24)	1967
"Cigarette smokers show **an increased prevalence** of respiratory symptoms, including cough, sputum production, and breathlessness, when compared with nonsmokers." (pp. 9–10)	1971

Table 1.2   Continued

Disease and statement	Surgeon General's report
"Respiratory infections are **more prevalent and severe** among cigarette smokers, particularly heavy smokers, than among nonsmokers." (p. 10)	1971
"Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are **more common** in smokers than nonsmokers." (p. 48)	1972
"Cigarette smokers have also been shown to have a **significantly longer duration** of respiratory symptoms following mild viral illness than nonsmokers." (p. 78)	1975
"In addition to an increased risk of COPD, cigarette smokers are more **frequently subject to and require longer convalescence from** other respiratory infections than nonsmokers. Also, if they require surgery, they are **more likely to develop** postoperative respiratory complications." (p. 61)	1975
"The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes." (p. 1-12)	1979
"A **wide variety of alterations** in the immune system have been observed due to cigarette smoking." (p. 1-18)	1979
"**Cessation** of smoking **definitely improves** pulmonary function and **decreases the prevalence of** respiratory symptoms." (p. 1-18)	1979
"Cigarette smokers have an **increased frequency** of respiratory symptoms, and at least two of them, cough and sputum production, are **dose-related**." (p. 1-18)	1979
"The relationship between smoking and an **increased prevalence** of respiratory symptoms in the adult has been **well established** in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community." (p. 6-20)	1979
"In summary, many recent studies demonstrate a **higher frequency** of respiratory symptoms in women who smoke as compared to women who do not smoke. This is true in surveys including children, adolescents, young adults, working age, and elderly women. The effect of cigarette smoking is related in terms of both the number of cigarettes and years smoked." (p. 156)	1980
"Relationships between smoking and cough or phlegm are **strong and consistent**; they have been amply documented and are judged to be **causal**." (p. 47)	1984
"Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is **the overwhelmingly most important cause** of cough, sputum, chronic bronchitis, and mucus hypersecretion." (p. 48)	1984

Table 1.2   Continued

Disease and statement	Surgeon General's report
"Smoking **cessation reduces rates** of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (p. 349)	1990
"**Former smokers have better health status** than current smokers as measured in a variety of ways, including days of illness, number of health complaints, and self-reported health status." (p. 92)	1990

Sources: U.S. Department of Health, Education, and Welfare 1964, 1967, 1968, 1969, 1971, 1972, 1973, 1974, 1975, 1979; U.S. Department of Health and Human Services 1980, 1982, 1983, 1984, 1989, 1990.

cancer the sequence proceeds in a similar manner: "significant association" (USDHEW 1972, p. 75), "data confirm the association" (USDHEW 1974, p. 59), "a dose-response relationship" (USDHEW 1979, p. 1-17), and in 1982 "a contributory factor" that "by no means excludes the possibility of a causal role. . ." (USDHHS 1982, p. 7). For some other outcomes, statements on causality were more qualified, such as "for the purposes of preventive medicine, it can be concluded that smoking is causally related to coronary heart disease. . . " (USDHEW 1979, p. 1-15).

One would not expect that conclusive language in these earlier reports would be identical, as each committee analyzed successively larger bodies of evidence, often with different cumulative support for causal claims. But without standardized terminology, authors contributing to the reports sometimes introduced their own phrasing to convey the extent of the evidence and attendant uncertainty. The intent of this chapter is to establish a more structured framework for reporting conclusions for this report and for those that follow.

Twenty-seven Surgeon General's reports on the health effects of smoking and related issues have been published since 1964. They contain the full range of information available on smoking and health for the purpose of evaluating the evidence. This evidence has come from studies of the composition of tobacco smoke, toxicologic investigation of smoke and of particular smoke components in experimental systems, and observational or epidemiologic studies of associations of smoking with diseases or other adverse health consequences. The observational evidence has also extended to mortality statistics, cancer incidence data, and disease prevalence figures, all of which capture the occurrence of diseases possibly caused by smoking. Changes in disease patterns across the twentieth century were a substantial impetus for hypotheses proposing that smoking causes disease. The epidemiologic evidence, now abundant for many diseases caused by smoking, has been given substantial weight in identifying smoking as a cause of disease. The observational data have been complemented by experimental data from the laboratory, which support the plausibility of causation and give an ever-deepening understanding of the mechanisms by which tobacco smoking causes disease.

Since the earliest reports of the Surgeon General, evidence has become available on the benefits of smoking cessation, primarily from observations of smokers who have stopped and from observations of patterns of disease occurrence over time.

Across these 27 reports the strength of evidence has mounted, new conclusions have been added, and older conclusions have been strengthened and expanded. Since the 1964 report, there has never been any reason to reverse earlier conclusions of causality.

This chapter returns to the topic of causality, including causal inference and terminology for characterizing the strength of evidence for causality. This topic has not been addressed comprehensively since the 1964 report. In view of the continued importance and public health relevance of causal conclusions, updating the 1964 report was considered necessary.

Terminology of Conclusions and Causal Claims

The first step in introducing this revised approach is to outline the language that will be used for summary conclusions regarding causality, which follows hierarchical language used by Institute of Medicine

committees (Institute of Medicine 1999) to couch causal conclusions, and by IARC to classify carcinogenic substances (IARC 1986). These entities use a four-level hierarchy for classifying the strength of causal inferences based on available evidence as follows:

A. Evidence is **sufficient** to infer a causal relationship.

B. Evidence is **suggestive but not sufficient** to infer a causal relationship.

C. Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).

D. Evidence is **suggestive of no causal relationship**.

For this report, the summary conclusions regarding causality are expressed in this four-level classification. Use of these classifications should not constrain the process of causal inference, but rather bring consistency across chapters and reports, and greater clarity as to what the final conclusions are actually saying. As shown in Table 1.1, without a uniform classification the precise nature of the final judgment may not always be obvious, particularly when the judgment is that the evidence falls below the "sufficient" category. Experience has shown that the "suggestive" category is often an uncomfortable one for scientists, since scientific culture is such that any evidence that falls short of causal proof is typically deemed inadequate to make a causal determination. However, it is very useful to distinguish between evidence that is truly inadequate versus that which just falls short of sufficiency.

There is no category beyond "suggestive of no causal relationship" as it is extraordinarily difficult to prove the complete absence of a causal association. At best, "negative" evidence is suggestive, either strongly or weakly. In instances where this category is used, the strength of evidence for no relationship will be indicated in the body of the text.

In this new framework, conclusions regarding causality will be followed by a section on implications. This section will separate the issue of causal inference from recommendations for research, policies, or other actions that might arise from the causal conclusions. This section will assume a public health perspective, focusing on the population consequences of using or not using tobacco and also a scientific perspective,

proposing further research directions. The proportion of cases in the population as a result of exposure (the population attributable risk), along with the total prevalence and seriousness of a disease, are more relevant for deciding on actions than the relative risk estimates typically used for etiologic determinations. In past reports, the failure to sharply separate issues of inference from policy issues resulted in inferential statements that were sometimes qualified with terms for action. For example, based on the evidence available in 1964, the first Surgeon General's report on smoking and health contained the following statement about the relationship between cardiovascular diseases and smoking:

> It is established that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning, than to suspend judgment until no uncertainty remains (USDHEW 1964, p. 32).

Using this framework, this conclusion would now be expressed differently, probably placing it in the "suggestive" category and making it clear that although it falls short of proving causation, this evidence still makes causation more likely than not. The original statement makes it clear that the 1964 committee judged that the evidence fell short of proving causality but was sufficient to justify public health action. In this report, the rationale and recommendations for action will be placed in the implications section, separate from the causal conclusions. This separation of inferential from action-related statements clarifies the degree to which policy recommendations are driven by the strength of the evidence and by the public health consequences acting to reduce exposure. In addition, this separation appropriately reflects the differences between the processes and goals of causal inference and decision making.

Implications of a Causal Conclusion

The judgment that smoking causes a particular disease has immediate implications for prevention of the disease. Having reached a causal conclusion, one of the immediate and appropriate next steps is to

estimate the burden of disease that might be avoided through prevention and cessation of smoking. This estimation is made with the population attributable risk, a measure first proposed by Levin (1953) to calculate the proportion of lung cancer caused by smoking. Levin's attributable risk is central to the estimates made by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) application developed by CDC (2002b).

The burden of avoidable disease in a population depends on the strength of smoking as a factor causing the disease and the prevalence of smoking in the population of interest. The attributable risk could vary across populations that have different patterns of smoking or in the same population over time as smoking changes. The attributable risk may also be influenced by the population's exposures to other causes of this disease of interest and by whether those other causes modify the effect of smoking.

Because the attributable risk is population dependent, the report separates the causal conclusion from this quantitative assessment of its implications. This assessment is placed in the separate section, "Implications," immediately following the statement of conclusions.

There are also implications of not reaching a causal conclusion. The attributable risk can still be calculated to estimate how much disease is potentially avoidable, given a causal determination. Additionally, the evidence review may indicate needed areas of research to address remaining gaps and uncertainties that have precluded a causal designation.

Judgment in Causal Inference

A causal conclusion conveys the inference that changing a given factor will actually reduce a population's burden of disease, either by reducing the overall number of cases or by making disease occur later than it would have (Robins and Greenland 1989). Without the mantle of "causal," the identification of a "risk factor" does not necessarily carry with it the certainty of disease prevention or delayed onset following exposure reduction or removal. As noted in the 1964 Surgeon General's report, the characteristics of evidence that merit calling an association causal involve extra-statistical judgments. Because the claim is so central to disease prevention, it is important to review some of the complexities inherent in this concept and the epidemiologic criteria that have been proposed to decide whether the causal designation should be made.

In this report, the definition of cause is based on the notions of a "counterfactual" state, a concept with origins at least as far back as the English philosopher David Hume (1711–1776) (Steinberg 1993). In the twentieth century, this concept was further developed and applied by statisticians, philosophers, and epidemiologists (Bunge 1959; Lewis 1973; Rubin 1974; Robins 1986, 1987; Greenland 1990; Splawa-Neyman 1990; Greenland et al. 1999; Pearl 2000; Parascandola and Weed 2001). A counterfactual definition holds that something is a cause of a given outcome if, when the same person is observed with and without a purported cause and without changing any other characteristic, a different outcome would be observed. For example, the counterfactual state for a smoker is the same individual never having smoked. The word "counterfactual" comes from the fact that no person can actually be observed under exactly the same conditions twice. For example, it is not possible to actually observe the same human being under identical conditions (including being the same age) except for smoking status. The situation that cannot be observed is called the counterfactual state; literally, counter to the observed facts. The unobservability of the counterfactual state is what makes causal relationships based on observational data subject to uncertainty and questioning.

Properly designed studies provide a scientific basis for inferring what the outcome of the counterfactual state would be, and permit related uncertainty to be properly quantified. In a laboratory, scientists are able to predict, fairly confidently, the outcome in this counterfactual state by repeating an experimental procedure with every important factor tightly controlled, varying only the factor of interest. But in observational studies of humans, scientists must try to infer what the outcome would be in a counterfactual state by studying another group of persons who, at least on average, are substantively different in only one relevant variable, the exposure under study. The outcome of this second group is used to represent what would have occurred in the original group if it had been observed with a different exposure, as in its counterfactual state (Greenland 1990). In the case of smoking and disease, this comparison is between disease risk in smokers and nonsmokers. Because experiments cannot be ethically done that randomize people to smoke or not to smoke, most evidence on smoking and disease is observational.

In the absence of a randomized assignment of exposure, two groups may differ on average in more factors than just the variable of interest. If these other factors affect outcome, then their effects can combine

with the causal effect of the factor of interest, biasing the measured effect of that factor. These ancillary causes are called confounders. An example of a confounding factor might be a characteristic associated both with taking a medication and cardiovascular risk, which appears to be the current situation with hormone replacement therapy (HRT) in women. The observational studies showed a clearer cardiovascular benefit from HRT than did a large randomized trial, suggesting that there may be some cardioprotective characteristics or behaviors of women who voluntarily take HRT that are at least partly responsible for the apparent benefit of HRT in the observational studies (Hulley et al. 1998; Blumenthal et al. 2000). In fact, the results of the Women's Health Initiative Trial of HRT showed increased risk for cardiovascular disease incidence in women randomized to HRT (Pradhan et al. 2002). Confounding by cardioprotective characteristics associated with taking HRT may have obscured this unanticipated consequence of HRT in the observational studies.

If confounders are recognized and their effects measured, these effects can often be statistically minimized or removed by the analysis of a study. However, if a confounder is poorly measured, or its effects poorly characterized, then its effects cannot be controlled for in the analysis phase of a study, resulting in a causal effect that is distorted or confounded by the unwanted factor. The most extreme version of this phenomenon occurs with unmeasured confounding, causal factors that are not measured at all and whose effects are therefore not controllable, which can result in biased estimates and underestimates of uncertainty, because standard analyses implicitly assume an absence of confounding from all unmeasured factors.

One solution to this problem of unmeasured or poorly controlled confounding is to randomize the factor of interest between different groups of people. This solution is obviously not applicable to harmful agents or behaviors such as smoking cigarettes (although randomization to cessation is possible because a benefit is anticipated), but understanding the role of randomization can deepen insights into the interpretation of nonrandomized designs used to study smoking effects. Randomization makes a proposed causal factor independent of potentially confounding factors, and provides a known probability distribution for the potential outcomes in each group under a given mathematic hypothesis (i.e., null) (Greenland 1990). It does not mean that inference from an individual randomized study is free of unmeasured confounding (it is free of unmeasured confounding only on average), but it does mean that measures of uncertainty about

causal estimates from randomized studies have an experimental foundation. In the absence of randomization, uncertainty about causal effects depends in part on the confidence that all substantive confounding has been eliminated or controlled either by the study design or by the analysis. Such confidence is ultimately based on scientific judgment.

One way to reduce the uncertainty that occurs with both randomized and observational designs is to repeat the studies. Similar results in a series of randomized studies make it increasingly unlikely that unmeasured confounding is accounting for the findings, since the process of randomization makes the mathematic probability of such confounding progressively smaller as the total sample size or number of studies increases. In observational studies, however, increasing the number of studies may reduce the random component of uncertainty, but not necessarily the systematic component attributable to confounding. Without randomization, there is no mathematic basis to assume that imbalance in unknown confounders will decrease with an increase in the number of studies. For example, many observational studies of HRT use in women have shown a strong cardioprotective effect. If unmeasured cardioprotective characteristics are consistently more common among women who use HRT, then having multiple studies will not necessarily reduce the effect of unmeasured confounding. However, if observational studies are repeated in different settings, with different subjects, different eligibility criteria, and/or different exposure opportunities (e.g., therapeutic HRT use after hysterectomy), each of which might eliminate another source of confounding from consideration, then confidence that unmeasured confounders are not producing the findings is increased. How many studies need to be done, how diverse they need to be, and how relevant they are to the question at hand are matters of scientific judgment.

Confidence that unmeasured confounding is not producing the observed results is further increased by understanding the biologic process by which the exposure might affect the outcome. This understanding allows better identification and measurement of relevant confounders, making it more unlikely that what is unmeasured is of concern. It can also serve as the basis for a judgment that the observed difference could be produced only by an implausible degree of confounder imbalance between exposed and unexposed groups. Thus, causal conclusions from observational studies typically require more and stronger biologic evidence to support plausibility and the absence of confounding than is required for causal inferences based on randomized studies.

Making causal inferences from observational data can be a challenging task, requiring expert judgment as to the likely sources and magnitude of confounding, together with judgments about how well the existing constellation of study designs, results, and analyses addresses this potential threat to inferential validity. To aid this judgment, criteria for the determination of a cause have been proposed by many philosophers and scientists over the centuries. The most widely cited criteria in epidemiology and public health more generally were set forth by Sir Austin Bradford Hill in 1965 (Weed 2000). Five of the nine criteria he listed were also put forward in the 1964 Surgeon General's report as the criteria for causal judgment: consistency, strength, specificity, temporality, and coherence of an observed association. Hill also listed biologic gradient (dose-response), plausibility, experiment (or natural experiment), and analogy. Many of these criteria have been cited in earlier epidemiologic writings (Lilienfeld 1959; Yerushalmy and Palmer 1959; Sartwell 1960), and Susser has extensively refined them by exploring their justification, merits, and interpretations (Susser 1973, 1977; Kaufman and Poole 2000).

Hill (1965) clearly stated that these criteria were not intended to serve as a checklist:

> Here are then nine different viewpoints from all of which we should study association before we cry causation. What I do not believe. . . is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the facts before us, is there any other answer equally, or more, likely than cause and effect? (Hill 1965, p. 299)

All of these criteria were meant to be applied to an already established statistical association; if no association has been observed, then these criteria are not relevant. Hill explained how, *if* a given criterion were satisfied, it strengthened a causal claim. Each of these nine criteria served one of two purposes: either as evidence against competing noncausal explanations or as evidence supporting causal ones. Noncausal explanations for associations include chance; residual or unmeasured confounding; model misspecification;

selection bias; errors in measurement of exposure, confounders, or outcome; and issues regarding missing data (which can also include missing studies, e.g., publication bias). The criteria are briefly discussed below.

Consistency

This criterion refers to the persistent finding of an association between exposure and outcome in multiple studies of adequate power, and in different persons, places, circumstances, and times. Consistency can serve two purposes. The first purpose, which was discussed previously, is to make unmeasured confounding an unlikely alternative explanation for an observed association. Such confounding would have to persist across diverse populations, exposure opportunities, and measurement methods. The confounding is still possible if the exposure (in this case smoking) were very strongly tied to an alternative cause, as was claimed in the form of the "constitutional hypothesis" put forward in the early days of the smoking-disease debate (USDHEW 1964). This hypothesis held that there was a constitutional (i.e., genetic) factor that made people more likely to both smoke and develop cancer. So consistency serves mainly to rule out the hypothesis that the association is produced by an ancillary factor that *differs* across studies, but not one factor that is common to all or most of them (Rothman and Greenland 1998).

The second purpose of the consistency criterion is to make the hypothesis of a chance effect unlikely by increasing the statistical strength of a finding through the accumulation of a larger body of data. It does not include the qualitative strength of such studies, which Susser subsumes under his subsidiary concept of "survivability," relating to the rigor and severity of tests of association (Susser 1991).

Strength of Association

This criterion includes two dimensions of strength: the magnitude of the association and its statistical strength. An association strong in both aspects makes the alternative explanations of chance and confounding unlikely. The larger the measured effect, the less likely that an unmeasured or poorly controlled confounder could account for it completely. Associations that have a small magnitude or a weak statistical strength are more likely to reflect chance, modest bias, or unmeasured weak confounding. However, the magnitude of association is reflective of underlying biologic processes and should be consistent with understanding the role of smoking in these processes.

Specificity

Specificity has been interpreted to mean both a single (or few) effect(s) of one cause, or no more than one possible cause for one effect. In addition to specific infectious diseases that are caused by specific infectious agents, some other examples include asbestos exposure and mesothelioma and thalidomide exposure during gestation and the resulting unusual constellation of birth defects. This criterion is rarely used as it was originally proposed, having been derived primarily from the Koch Postulates for infectious causes of disease (Evans 1993). When specificity exists, it can strengthen a causal claim, but its absence does not weaken it (Sartwell 1960). For example, most cancers are known to have multifactorial etiologies, many cancer-causing agents can cause several types of cancer, and these agents can also have noncancerous effects. Similarly, there are multiple causes of cardiovascular disease.

In considering specificity in relation to the smoking-lung cancer association, the 1964 Surgeon General's report (USDHEW 1964) provides a rich discussion of this criterion. The committee recognized the linkage between this criterion and strength of association and offered a symmetric formulation of specificity in the relationship between exposure and disease; that is, a particular exposure always results in a particular disease and the disease always results from the exposure. The committee acknowledged that smoking does not always result in lung cancer and that lung cancer has other causes. The report notes the extremely high relative risk for lung cancer in smokers and the high attributable risk, and concludes that the association between smoking and lung cancer has "a high degree of specificity."

Temporality

Temporality refers to the occurrence of a cause before its purported effect. Temporality is the *sine qua non* of causality, as a cause clearly cannot occur after its purported effect. Failure to establish temporal sequence seriously weakens a causal claim, but establishing temporal precedence is by itself not very strong evidence in favor of causality.

Coherence, Plausibility, and Analogy

Although the original definitions of these criteria were subtly different, in practice they have been treated essentially as one idea: that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data, such as ecologic patterns of disease (Rothman and Greenland 1998). In addition, if biologic understanding can be used to set aside explanations other than a causal association, it offers further support for causality. Together, these criteria can serve both to support a causal claim (by supporting the proposed mechanism) or refute it (by showing that the proposed mechanism is unlikely).

Biologic understanding, of course, is always evolving as scientific advances make possible an ever deeper exploration of disease pathogenesis. For example, in 1964 the Surgeon General's committee found a causal association of smoking with lung cancer to be biologically plausible. Nearly 40 years later, this association remains biologically plausible, but that determination rests not only on the earlier evidence but on more recent findings that address the genetic and molecular basis of carcinogenesis.

Biologic Gradient (Dose-Response)

The finding of an increment in effect with an increase in the strength of the possible cause provides strong support in favor of a causal hypothesis. This is not just because such an observation is predicted by many cause-effect models and biologic processes, but more importantly, because it makes most noncausal explanations very unlikely. One would have to posit that some unmeasured factor was changing in the same manner as the exposure of interest if that factor, rather than the factor of interest, is to explain the gradient. Except for confounders that are very closely related to a causal factor, it is very difficult for such a pattern to be created by virtually any of the noncausal explanations for an association listed earlier. The finding of a dose-response relationship has long been a mainstay of causal arguments in smoking investigations; virtually all health outcomes causally linked to smoking have shown an increase in risk and/or severity with an increase in the lifetime smoking history, generally number of cigarettes smoked per day, duration of smoking, or a cumulative measure of consumption. This criterion is not based on any specific shape of the dose-response relationship.

Experiment

This criterion refers to situations where natural conditions might plausibly be thought to imitate conditions of a randomized experiment, producing a "natural experiment" whose results might have the force of a true experiment. An experiment is typically

a situation in which a scientist controls who is exposed in a way that does not depend on any of the subject's characteristics. Sometimes nature produces similar exposure patterns. The reduction in risk after smoking cessation serves as one such situation that approximates an experiment; an alternative noncausal explanation would have to posit that an unmeasured causal factor of that health outcome was more frequent among those who did not stop smoking than among those who did. The causal interpretation is further strengthened if risk continues to decline in former smokers with increasing length of time since quitting. Similar to the dose-response criteria, observations of risk reduction after quitting smoking have the dual effects of making most noncausal explanations unlikely, and supporting the biologic model that underlies the causal claim.

Applying the Causal Criteria

The more that an association fulfills the previous criteria, the more difficult it is to offer a more compelling alternative explanation. Which of these criteria may be more important, and whether some can be unfulfilled and still justify the causal claim, is a judgmental issue. Temporality, however, cannot be violated. When there is a still incompletely understood pathogenic mechanism, the causal claim might still be justified by very strong, direct empirical evidence of higher rates in smokers (i.e., strong, consistent associations). Less strong associations (e.g., relative risks between 1 and 2) in only a few studies, without adequate understanding of potential confounders or with weak designs, might result in a suspicion of causal linkage.

The process of applying the criteria extends beyond simply lining the evidence up against each criterion. Rather, the criteria are used to integrate multiple lines of evidence, coming from chemical and toxicologic characterizations of tobacco smoke and its components, epidemiologic approaches, and clinical investigations. Those applying the criteria weigh the totality of the evidence in a decision-making process that synthesizes and, of necessity, involves a multidisciplinary judgment.

The 1964 Surgeon General's report still stands as one of the finest examples of the power of applying these criteria systematically and comprehensively. Starting with the criterion for consistency, the committee noted that all 29 retrospective (i.e., case-control) and 7 prospective (i.e., cohort) studies at the time reported strong smoking-lung cancer relationships. They further noted that all of the studies comparing smokers with nonsmokers showed very high relative risks for lung cancer (ranging from approximately 5 to 20). Dose-response effects were also observed in almost every study that provided the necessary data. The temporal sequence was reported to be not absolutely certain, but seemed to be very unlikely in the lung cancer-smoking direction, as cancer typically appears many years or decades after the onset of smoking. With regard to coherence of the association with known facts, the studies noted the ecologic increase in lung cancer rates with increased smoking in the population; the gender differential in lung cancer, which at the time was consistent with more smoking by men; an urban-rural difference, which air pollution could not completely explain; socioeconomic differentials in lung cancer for which smoking seemed to be the strongest explanation; and the localization of cancer within the respiratory tract in relation to the type of smoking. The studies also cited the known reduction in risk among former smokers, with greater risk reductions correlated with more time spent not smoking. These observations, in combination with histopathologic evidence, basic biologic observations, and an in-depth discussion of each competing nonsmoking-related explanation (e.g., occupation, constitutional hypothesis, infections, and environmental factors such as pollution), produced a case for causation that was essentially irrefutable.

Statistical Testing and Causal Inference

Hill made a point of commenting on the value, or lack thereof, of statistical testing in the determination of cause: "No formal tests of significance can answer those [causal] questions. Such tests can, and should, remind us of the effects the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that, they contribute nothing to the 'proof' of our hypothesis" (Hill 1965, p. 299).

Hill's warning was in some ways prescient, as the reliance on statistically significant testing as a substitute for judgment in causal inference remains today (Savitz et al. 1994; Holman et al. 2001; Poole 2001). To understand the basis for this warning, it is critical to recognize the difference between inductive inferences about the truth of underlying hypotheses, and deductive statistical calculations that are relevant to those inferences but that are not inductive statements themselves. The latter include p values, confidence intervals, and hypothesis tests (Greenland 1998; Goodman 1999). The dominant approach to statistical inference today, which employs those statistical measures,

obscures this important distinction between deductive and inductive inferences (Royall 1997), and has produced the mistaken view that inferences flow directly and inevitably from data. There is no mathematic formula that can transform data into a probabilistic statement about the truth of an association without introducing some formal quantification of external knowledge, such as in Bayesian approaches to inference (Goodman 1993; Howson and Urbach 1993). Significance testing and the complementary estimation of confidence intervals remain useful for characterizing the role of chance in producing the association in hand.

There are many kinds of statements that appear to be, but are not, formal inferences about a hypothesis. For example, consider the statement "the frequency of cirrhosis in smokers is statistically significantly greater than the frequency in nonsmokers." This statement is based on a deductive mathematic calculation that assumes the truth of the null hypothesis of no association. It is not a knowledge claim of an inductive statement about the likely truth of the cirrhosis-smoking relationship, although it may serve as a foundation for that claim. An inductive inference would be a statement based on this and other evidence, that smokers are likely to have a higher risk of cirrhosis than nonsmokers. Determining whether or not this elevated risk was causally related to smoking would represent a causal judgment.

In this report, language is used to make as clear as possible what kind of statement is being made, and to avoid certain kinds of ambiguities that are widespread in the scientific literature. Certain words imply causal conclusions by suggesting an active effect of smoking on disease (Petitti 1991). For example, the statement that smoking "is associated" with disease could mean that disease frequency is higher in smokers, that it is statistically significantly higher, or that an inferential conclusion about the association has been reached. Depending on the context, words like "effect" or "contributor" can fall into that category, as do statements like smoking "increases risk." Such language often appears to be a causal conclusion, albeit without consideration of all of the causally relevant evidence.

Another type of claim is that smoking is a "risk factor" for disease, or that the observed association is "real" or "true." This claim represents an inference, a conclusion that the risk of disease differs in at least an actuarial sense, at different levels; that is, more events overall and at younger ages can be expected in smokers. Such a statistical finding does not yet have the status of a causal claim. In addition, this phrasing does not make it clear whether the factor has predictive value over and above all other known risk and causal factors, which would be indicated by the words "independent risk factor" or "independent contributor."

Statements like these will be avoided, or at least qualified, to make clear whether they are statements about the data, about statistical significance, or are actual statistical or causal inferences. All causal claims in this report will be clearly identified using the word "cause," and classified according to the previously outlined criteria.

Conclusions

Inferences, whether about causality or statistical associations, are always uncertain to a degree. The goal of this report, as in all previous ones, is to explain and communicate scientific judgments as to whether observed associations between smoking and disease are likely to be causal, based on the totality of scientific evidence. This report will employ an ordinal scale and standardized language to express the strength of the evidence bearing on causality. This approach will help not only to clarify what the assessment is, but will make it possible for subsequent groups to measure progress or calibrate standards by comparing their summary judgments with those expressed here. This structure also encourages the articulation of the sources of uncertainty in the evidence, which hopefully will stimulate necessary research.

In addition, causal conclusions are separated from public health recommendations. This decoupling is necessary, as decision making in the face of uncertainty involves different issues than those that pertain to the uncertainty itself, and past reports have sometimes combined the two perspectives.

Just as this series of reports has documented progress in understanding the connections between smoking and disease, this report represents progress in how that understanding is assessed and communicated. A debt is owed to the many scientists who have both performed and synthesized smoking-related research in the past. The framework used in this report should assist researchers, the readers, and those who must perform this task in the future to accurately represent what is and what is not known about the impact of smoking on human health.

Major Conclusions

Forty years after the first Surgeon General's report in 1964, the list of diseases and other adverse effects caused by smoking continues to expand. Epidemiologic studies are providing a comprehensive assessment of the risks faced by smokers who continue to smoke across their life spans. Laboratory research now reveals how smoking causes disease at the molecular and cellular levels. Fortunately for former smokers, studies show that the substantial risks of smoking can be reduced by successfully quitting at any age. The evidence reviewed in this and prior reports of the Surgeon General leads to the following major conclusions:

1. Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general.

2. Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general.

3. Smoking cigarettes with lower machine-measured yields of tar and nicotine provides no clear benefit to health.

4. The list of diseases caused by smoking has been expanded to include abdominal aortic aneurysm, acute myeloid leukemia, cataract, cervical cancer, kidney cancer, pancreatic cancer, pneumonia, periodontitis, and stomach cancer.

Chapter Conclusions

Chapter 2. Cancer

Lung Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and lung cancer.

2. Smoking causes genetic changes in cells of the lung that ultimately lead to the development of lung cancer.

3. Although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined.

4. Adenocarcinoma has now become the most common type of lung cancer in smokers. The basis for this shift is unclear but may reflect changes in the carcinogens in cigarette smoke.

5. Even after many years of not smoking, the risk of lung cancer in former smokers remains higher than in persons who have never smoked.

6. Lung cancer incidence and mortality rates in men are now declining, reflecting past patterns of cigarette use, while rates in women are still rising.

Laryngeal Cancer

7. The evidence is sufficient to infer a causal relationship between smoking and cancer of the larynx.

8. Together, smoking and alcohol cause most cases of laryngeal cancer in the United States.

Oral Cavity and Pharyngeal Cancers

9. The evidence is sufficient to infer a causal relationship between smoking and cancers of the oral cavity and pharynx.

Esophageal Cancer

10. **The evidence is sufficient to infer a causal relationship between smoking and cancers of the esophagus.**

11. **The evidence is sufficient to infer a causal relationship between smoking and both squamous cell carcinoma and adenocarcinoma of the esophagus.**

Pancreatic Cancer

12. **The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer.**

Bladder and Kidney Cancers

13. **The evidence is sufficient to infer a causal relationship between smoking and renal cell, renal pelvis, and bladder cancers.**

Cervical Cancer

14. **The evidence is sufficient to infer a causal relationship between smoking and cervical cancer.**

Ovarian Cancer

15. **The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and ovarian cancer.**

Endometrial Cancer

16. **The evidence is sufficient to infer that current smoking reduces the risk of endometrial cancer in postmenopausal women.**

Stomach Cancer

17. **The evidence is sufficient to infer a causal relationship between smoking and gastric cancers.**

18. **The evidence is suggestive but not sufficient to infer a causal relationship between smoking and noncardia gastric cancers, in particular by modifying the persistence and/or the pathogenicity of *Helicobacter pylori* infections.**

Colorectal Cancer

19. **The evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.**

Prostate Cancer

20. **The evidence is suggestive of no causal relationship between smoking and risk for prostate cancer.**

21. **The evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in non-smokers.**

Acute Leukemia

22. **The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia.**

23. **The risk for acute myeloid leukemia increases with the number of cigarettes smoked and with duration of smoking.**

Liver Cancer

24. **The evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer.**

Adult Brain Cancer

25. **The evidence is suggestive of no causal relationship between smoking cigarettes and brain cancer in men and women.**

Breast Cancer

26. **The evidence is suggestive of no causal relationship between active smoking and breast cancer.**

27. **Subgroups of women cannot yet be reliably identified who are at an increased risk of breast cancer because of smoking, compared with the general population of women.**

28. **Whether women who are at a very high risk of breast cancer because of mutations in *BRCA1* or *BRCA2* genes can lower their risks by smoking has not been established.**

Chapter 3. Cardiovascular Diseases

Smoking and Subclinical Atherosclerosis

1. **The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis.**

Smoking and Coronary Heart Disease

2. The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease.

3. The evidence suggests only a weak relationship between the type of cigarette smoked and coronary heart disease risk.

Smoking and Cerebrovascular Disease

4. The evidence is sufficient to infer a causal relationship between smoking and stroke.

Smoking and Abdominal Aortic Aneurysm

5. The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm.

Chapter 4. Respiratory Diseases

Acute Respiratory Illnesses

1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.

3. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.

Chronic Respiratory Diseases

4. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants.

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy.

6. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood.

7. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.

8. The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence.

9. The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood.

10. The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function.

11. The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked.

12. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.

13. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.

14. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.

15. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.

16. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.

18. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyper-responsiveness.

19. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control.

20. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.

21. The evidence is suggestive but not sufficient to infer a causal relationship between lower machine-measured cigarette tar and a lower risk for cough and mucus hypersecretion.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in forced expiratory volume in one second decline rates.

23. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.

24. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and idiopathic pulmonary fibrosis.

Chapter 5. Reproductive Effects

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality.

2. The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women.

Pregnancy and Pregnancy Outcomes

3. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

4. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

5. The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption.

6. The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia.

7. The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation.

8. The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight.

Congenital Malformations, Infant Mortality, and Child Physical and Cognitive Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general.

10. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts.

11. The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neuro-cognitive development of children.

Chapter 6. Other Effects

Diminished Health Status

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Loss of Bone Mass and the Risk of Fractures

3. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

4. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

5. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

6. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.

7. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Dental Diseases

8. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

9. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

10. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Erectile Dysfunction

11. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Eye Diseases

12. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.

13. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

14. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

15. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

16. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

18. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Peptic Ulcer Disease

19. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.

20. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

21. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of nonsteroidal anti-inflammatory drugs.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

Chapter 7. The Impact of Smoking on Disease and the Benefits of Smoking Reduction

1. There have been more than 12 million premature deaths attributable to smoking since the first published Surgeon General's report on smoking and health in 1964. Smoking remains the leading preventable cause of premature death in the United States.

2. The burden of smoking attributable mortality will remain at current levels for several decades. Comprehensive programs that reflect the best available science on tobacco use prevention and smoking cessation have the potential to reduce the adverse impact of smoking on population health.

3. Meeting the *Healthy People 2010* goals for current smoking prevalence reductions to 12 percent among persons aged 18 years and older and to 16 percent among youth aged 14 through 17 years will prevent an additional 7.1 million premature deaths after 2010. Without substantially stronger national and state efforts, it is unlikely that this health goal can be achieved. However, even with more modest reductions in tobacco use, significant additional reductions in premature death can be expected.

4. During 1995–1999, estimated annual smoking attributable economic costs in the United States were $157.7 billion, including $75.5 billion for direct medical care (adults), $81.9 billion for lost productivity, and $366 million for neonatal care. In 2001, states alone spent an estimated $12 billion treating smoking attributable diseases.

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Chapter 2
Cancer

Introduction

Since the 1964 Surgeon General's report, the evidence on active smoking and cancer has grown rapidly. In that first report, only cancers of the lung and larynx in men were causally linked to cigarette smoking (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). That list grew with subsequent reports to include more sites and to include cancers in women as well as in men.

The topic of smoking and cancer was last addressed comprehensively in the 1990 Surgeon General's report on smoking cessation (U.S. Department of Health and Human Services [USDHHS] 1990) and in the 1982 report (USDHHS 1982), which focused on cancer. The report on women and smoking (USDHHS 2001) also considered cancer, and this chapter builds from that report for several cancers. This chapter reviews the evidence relating smoking to a range of cancers, some previously associated causally with smoking and some for which substantial new evidence has become available since the 1990 review in the Surgeon General's report on smoking cessation. For some less common cancers, little research has been conducted and these cancer sites are not included in this chapter. Lymphomas and multiple myeloma, skin cancers, bone cancer, and testicular cancer were omitted because they have not been linked to smoking. Pediatric malignancies are also not discussed, since this report concerns active smoking rather than involuntary exposure to cigarette smoke in utero and after birth.

The relationship between smoking and lung cancer in men was the first to be classified as causal, following a review by Surgeon General Luther L. Terry's committee in the landmark 1964 report (USDHEW 1964). The many documented benefits from quitting smoking include a large decline in the risk of lung cancer after cessation compared with the risk from continuing smoking (USDHEW 1979; USDHHS 1989, 1990). There is now equally convincing evidence that smoking causes cancer at a number of other sites for which causal conclusions had not been previously reached.

Previous Surgeon General's reports have concluded that smoking causes cancer in several organ sites. The list of cancers caused by smoking has included cancers of the urinary bladder, esophagus, kidney, larynx, lung, oral cavity, and pancreas. The past conclusions are detailed in the text that follows and

are summarized in Table 2.1. The International Agency for Research on Cancer (IARC) has also reviewed the evidence on tobacco and cancer on two occasions, in 1986 and again in 2002 (IARC 1986, 2002). The system used by IARC differs from that applied in the Surgeon General's reports, but conclusions have generally been similar.

The powerful epidemiologic evidence on smoking and lung cancer reported during the 1950s was one of the first warnings of the strength of smoking as a cause of cancer and other diseases (Doll and Hill 1954, 1956). That warning was soon followed by the rise of lung cancer in women and the epidemic of other chronic diseases caused by smoking. The past decade has seen a rapid expansion of the application of molecular markers to complement traditional epidemiologic approaches to the study of smoking and cancer. This evolving field allows a clearer demonstration of the etiologic pathways from exposure to tobacco smoke to malignant transformation of target cells, and is discussed in relation to lung cancer as a model of the growing insights into the causal pathways from smoking to cancer.

The overall contribution of smoking to disease and death continues to demand attention as excess mortality attributable to smoking maintains its rise. Cancer represents a substantial proportion of this contribution. An analysis of the two American Cancer Society (ACS) prospective cohort studies (Cancer Prevention Study I [CPS-I] and II [CPS-II]) by Thun and colleagues (1995), shows that the risk of premature mortality from smoking (death before 70 years of age) doubled in women and continued to rise in men during the interval (the 1960s to the 1980s) that separates these two cohorts. The contribution of lung cancer and other cancers to this excess in premature mortality was substantial. Annual death rates from lung cancer for women who were current smokers increased from 26.1 to 154.6 per 100,000, and for men the increase was from 187.1 to 341.3 per 100,000. Patterns varied by age. The relative risks (RRs) of lung cancer changed from 11.9 in CPS-I to 23.2 in CPS-II for men, and from 2.7 to 12.8 for women. The percentages of lung cancer deaths attributable to smoking changed from 86 percent in CPS-I to 90 percent in CPS-II for men, and from 40 percent to 79 percent for women (Thun et al. 1997a). Among current cigarette smokers overall, deaths attributable to cigarette smoking increased between CPS-I and

Table 2.1   Conclusions from previous Surgeon General's reports concerning smoking as a cause of cancer*

Disease and statement	Surgeon General's report
Bladder cancer	
"Epidemiological studies have demonstrated a **significant association** between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the **risk** of developing bladder cancer **increases** with inhalation and the number of cigarettes smoked." (p. 75)	1972
"Epidemiological studies have demonstrated a **significant association** between cigarette smoking and bladder cancer in both men and women." (p. 1-17) "Cigarette smoking acts independently and synergistically with other factors, such as occupational exposures, to **increase the risk** of developing cancer of the urinary bladder." (p. 1-17)	1979
"A **dose-response relationship** has been demonstrated between cigarette smoking and cancer of the lung, larynx, oral cavity, and urinary bladder in women." (p. 127)	1980
"Smoking is a **cause** of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking." (p. 178)	1990
Esophageal cancer	
"Epidemiological studies have demonstrated that cigarette smoking is **associated** with the development of cancer of the esophagus." (p. 12)	1971
"Cigarette smoking is a causal factor in the development of cancer of the esophagus, and the **risk increases** with the amount smoked." (p. 1-17)	1979
"Cigarette smoking is **causally associated** with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . ." (p. 126)	1980
"Cigarette smoking is a **major cause** of esophageal cancer in the United States." (p. 7)	1982
Kidney cancer	
"Cigarette smoking is a **contributory factor** in the development of kidney cancer in the United States. The term 'contributory factor' **by no means excludes** the possibility **of a causal role** for smoking in cancers of this site." (p. 7)	1982
Laryngeal cancer	
"Evaluation of the evidence leads to the judgment that cigarette smoking is a **significant factor** in the causation of laryngeal cancer in the male." (p. 37)	1964
"Cigarette smoking is **causally associated** with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . ." (p. 126)	1980

*Words in boldface are for emphasis only and do not indicate emphasis in the original reports.

Table 2.1   Continued

Disease and statement	Surgeon General's report
Lung cancer	
"Cigarette smoking is **causally related to** lung cancer in men; the magnitude of the effect of cigarette smoking **far outweighs all other factors**. The data for women, though less extensive, point in the same direction." (p. 196)	1964
"Additional epidemiological, pathological, and experimental data not only confirm the conclusion of the Surgeon General's 1964 Report regarding lung cancer in men but strengthen the **causal relationship** of smoking to lung cancer in women." (p. 36)	1967
"Cigarette smoking is **causally related** to lung cancer in women. . . ." (p. 4)	1968
"Cigarette smoking is **causally associated** with cancer of the lung. . .in women as well as in men. . . ." (p. 126)	1980
Oral cancer	
"Smoking is a **significant factor**. . .in the development of cancer of the oral cavity." (p. 4)	1968
"Recent epidemiologic data strongly indicate that cigarette smoking plays **an independent role in** the development of oral cancer." (p. 59)	1974
"Epidemiological studies indicate that smoking is **a significant causal factor** in the development of oral cancer." (p. 1-17)	1979
"Cigarette smoking is **causally associated** with cancer of the. . .oral cavity. . .in women as well as in men. . . ." (p. 126)	1980
"Cigarette smoking is a **major cause** of cancers of the oral cavity in the United States." (p. 6)	1982
Pancreatic cancer	
"Epidemiological evidence demonstrates a **significant association** between cigarette smoking and cancer of the pancreas." (p. 75)	1972
"Recent epidemiologic data confirm the **association** between smoking and pancreatic cancer." (p. 59)	1974
"Cigarette smoking is **related** to cancer of the pancreas, and several epidemiological studies have demonstrated a **dose-response relationship**." (p. 1-17)	1979
"Cigarette smoking is a **contributory factor** in the development of pancreatic cancer in the United States. The term 'contributory factor' **by no means excludes** the possibility of a **causal role** for smoking in cancers of this site." (p. 7)	1982

Sources: U.S. Department of Health, Education, and Welfare 1964, 1967, 1968, 1971, 1972, 1974, 1979; U.S. Department of Health and Human Services 1980, 1982, 1990.

CPS-II from 41.2 to 56.5 percent in men and from 16.7 to 47.4 percent in women. Lung cancer accounted for a larger proportion of all-cause mortality in CPS-II, in part reflecting the decline in cardiovascular disease mortality.

In contrast to these changes from the 1960s to the 1980s, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database indicates that the rates of cancer began to decline from 1991 to the present (Ries et al. 2000a, 2003). The decline was observed in large part for smoking-related cancers (stomach, oral cavity, larynx, lung and bronchus, pancreatic, and bladder) (McKean-Cowdin et al. 2000). For each of these cancers, both the incidence and the mortality rates declined. Mortality also declined for cancer of the kidney, while incidence declined for cancer of the esophagus and for leukemia. These changes likely reflect, at least in part, the decline in smoking among men and, to a lesser extent, among women, paralleling the earlier national decline in smoking.

In developing this chapter, the literature review approach was necessarily selective. For cancers for which a causal conclusion had been previously reached, there was no attempt to cover all relevant literature, but rather to focus on key issues or particularly important new studies for the site. For sites for which a causal conclusion had not been previously reached, a comprehensive search strategy was used.

Lung Cancer

Lung cancer was one of the first diseases to be causally linked to tobacco smoking. Although there are causes of lung cancer other than tobacco smoking, lung cancer occurrence rates have served as a sentinel for the epidemic of tobacco-caused diseases that began during the twentieth century because of the predominant causal role of smoking in these diseases. Across the early decades of the last century, clinicians noted the increase in lung cancer among their patients, and Ochsner and DeBakey (1939) speculated that cigarette smoking might be the cause in a case series reported in 1939. Although the possibility of an artifactual increase reflecting diagnostic bias was considered, by midcentury there was no doubt as to the presence of an epidemic (Macklin and Macklin 1940). Lung cancer was therefore the focus of many early epidemiologic studies on smoking (White 1990; Doll et al. 1994) and one of the principal topics of the 1964 Surgeon General's report (USDHEW 1964), which reached the momentous conclusion that smoking was a cause of lung cancer (in men). Lung cancer mortality, which closely parallels incidence because of the extremely high case-fatality rate, is tracked in countries throughout the world and has provided a useful anchoring and index point for estimating the burden of tobacco-caused diseases (Peto et al. 1994). A decrease in lung cancer incidence and mortality rates has become evident among younger men in the United States and in other countries in the last 20 years, reflecting the impact of efforts over decades to reduce smoking (Gilliland and Samet 1994; Wingo et al. 1999).

However, 40 years after smoking was first identified as a cause of lung cancer, it remains a leading cause of cancer and of death from cancer. Lung cancer accounts for 28 percent of all cancer deaths in the United States (ACS 2003). In 2003, an estimated 171,900 new cases of lung cancer were expected to be diagnosed in the United States, accounting for 13 percent of all cancer diagnoses, and an estimated 157,200 deaths attributable to lung cancer were expected to occur. In spite of vigorous research on therapy, survival remains poor with five-year survival of only 15 percent for all stages of lung cancer combined (ACS 2003). The age-adjusted annual incidence rate is declining steadily in men, from a high of 102.1 per 100,000 in 1984 to 80.8 per 100,000 in 2000 (ACS 2003; Ries et al. 2003). In the 1990s, the rate of increase began to slow for women, but by 2000 the incidence rate among women was 49.6 per 100,000 (Thun et al. 1997b; Wingo et al. 1999; Ries et al. 2003). During the 1990s deaths attributable to lung cancer declined significantly in men, while mortality rates in women continued to increase. These changing patterns of incidence and mortality reflect temporal changes in smoking behaviors among U.S. adults that occurred decades ago (National Cancer Institute [NCI] 1997). Smoking declined more precipitously among men than among women beginning in the 1950s, and the recent patterns of change in lung cancer rates reflect these earlier prevalence rates.

Lung cancer refers to a histologically and clinically diverse group of malignancies arising in the respiratory tract, primarily but not exclusively in cells

lining the airways of the lung. The four principal types, classified by light microscopy and special stains, are squamous cell carcinoma, small cell undifferentiated carcinoma, adenocarcinoma, and large cell carcinoma. Beginning at the trachea, the airways branch 20 or more times. Until recently, most cancers were believed to originate in the larger airways of the lung, typically at the fourth through the eighth branches. However, there has been a rise in the frequency of adenocarcinomas since the 1960s, which tend to develop in the peripheral lung (Churg 1994). The specific cells of origin of the different types of lung cancer are still unknown; candidates include the secretory cells, pluripotential basal cells, and the neuroepithelial cells (National Research Council [NRC] 1991, 1999).

The rising incidence of lung cancer through the first half of the twentieth century prompted intensive epidemiologic investigations of the disease, resulting in the identification of a number of causal agents (Samet 1994; Blot and Fraumeni 1996). Cigarette smoking is by far the largest cause of lung cancer, and the worldwide epidemic of lung cancer is attributable largely to smoking. However, occupational exposures have placed a number of worker groups at high risk, and some of these occupational agents are synergistic with smoking in increasing lung cancer risks (Saracci and Boffetta 1994; IARC 2002). There is some evidence that both indoor and outdoor air pollution also increase lung cancer risks generally (Samet and Cohen 1999). Observational evidence showing a familial aggregation of lung cancer has suggested that genetic factors also may determine risks in smokers, but the specific genes remain under active investigation.

Prior reports have fully described the variation of lung cancer risk with aspects of smoking (USDHHS 1982, 1989, 1990, 2001). In smokers, the risk of lung cancer depends largely on the duration of smoking and the number of cigarettes smoked (Samet 1996). The excess risks for smokers, compared with persons who have never smoked, are remarkably high. Many studies provide RR estimates for developing lung cancer of 20 or higher for smokers compared with lifetime nonsmokers (USDHHS 1990; Wu-Williams and Samet 1994). A risk-free level of smoking has not been identified, and even involuntary exposure to tobacco smoke increases lung cancer risks for nonsmokers (USDHHS 1986). Lung cancer risk decreases with successful cessation and maintained abstinence, but not to the level of risk for those who have never smoked, even after 15 to 20 years of not smoking (USDHHS 1990; NCI 1997). Other aspects of smoking—depth of inhalation and the type of cigarettes smoked—have relatively small effects on risk once duration of smoking and the number of cigarettes smoked are considered.

Conclusions of Previous Surgeon General's Reports

By 1964, epidemiologic evidence was considered sufficiently complete to support a conclusion by the Surgeon General's Advisory Committee that smoking causes lung cancer in men (USDHEW 1964). Conclusions followed for women in 1967 as the evidence for a causal relationship strengthened, and in 1968 the Surgeon General concluded that smoking caused lung cancer in women (USDHEW 1967, 1968). In 1986, the Surgeon General's report concluded that involuntarily inhaled tobacco smoke increased the risk of lung cancer in nonsmokers (USDHHS 1986). The 1990 report (USDHHS 1990) concluded that smoking cessation reduces the risk of lung cancer compared with continued smoking. The 1998 report on racial and ethnic minority groups noted that ". . . lung cancer is the leading cause of cancer death for each of the racial/ethnic groups studied in this report" (USDHHS 1998, p. 12). The 2001 Surgeon General's report on women and smoking concluded that "About 90 percent of all lung cancer deaths among U.S. women smokers are attributable to smoking" (USDHHS 2001, p. 13).

Biologic Basis

In the most general conceptual model, the development of cancer is considered a result of heritable alterations in a single cell, as demonstrated by Furth and Kahn (1937) more than 60 years ago. They showed that the progeny of multiple single-cell clones from a tumor could reproduce the original disease on re-injection of the cells into a suitable host. This observation established that cancer was a disease with a molecular basis and a heritable and stable cellular phenotype. This discovery set in motion the development of experimental models of carcinogenesis, for example, the mouse skin model (Berenblum and Shubik 1947). This experimental model led to the development of a multistage concept of carcinogenesis in which some agents are termed "initiators" and others "promoters," depending on their pattern of action in the model. The initiators are causal agents that exert their effects by inducing genetic changes at the start of carcinogenesis. These genetic changes are hypothesized to be "promoted" by substances that are required for inducing the subsequent, still not fully defined, events that give rise to tumors. This model has been refined, updated, and reproduced in the rat liver (Peraino et al. 1973) and urinary bladder (Fukushima et al. 1983). Farber (1984) provides a comprehensive review of these experimental approaches.

These models had a counterpart in the multistage model of carcinogenesis that was proposed initially by Armitage and Doll (1954), based on their insightful interpretation of the increase in cancer risks with age. Armitage and Doll proposed that "k" stages are required for the transformation of a normal cell to a malignant cell, and that these stages occurred in a fixed order. Their model did not include a requirement that the cell "age" at any one of the "k" stages. With this model, the age-cancer incidence curve for a tissue containing a fixed number of cells would follow a log-log relationship, consistent with the empirical observations.

These risk models have proved useful in guiding tobacco control approaches for the prevention of cancer. They indicate that the risk will increase with the duration of smoking, and that risks can be expected to decrease with quitting and maintained abstinence if the full set of cellular changes has not yet occurred at the time of quitting. The multistage model also implies that risk depends on the duration of the exposure to tobacco smoke and not on the age at which the person started to smoke, unless there is some special susceptibility for target cells in younger smokers, an unresolved question at present. Beginning to smoke at a younger age increases the duration of smoking at any particular age and is predicted to increase the lung cancer risk. The shift across the twentieth century toward smoking initiation at younger ages is expected to increase the risk of lung cancer and other tobacco-caused cancers. These models can be used to predict the outcomes of strategies to control smoking, such as delaying initiation until later ages, reducing the number of cigarettes smoked, or quitting at different ages.

The epidemiologic evidence is limited and mixed as to whether age at onset of smoking may be an independent risk factor for lung cancer, beyond the inherently longer duration of smoking by those starting to smoke at younger ages (Hegmann et al. 1993; Benhamou and Benhamou 1994). Some recent molecular epidemiologic evidence is consistent with an early age of onset of smoking producing biologic changes that enhance susceptibility to the effects of exposures to tobacco carcinogens (Wiencke et al. 1999).

In Figure 2.1, Hecht (1999) proposes a general schema for carcinogenesis by tobacco smoke. Viewed in the framework of this model, research findings are consistent with the predictions of the multistage model in many respects, and are enhancing an understanding of the mechanisms by which smoking causes cancers of the lung and other organs. A rapidly expanding body of literature addresses dosimetry and the metabolism of tobacco carcinogens at the cellular and molecular levels, genetic determinants of susceptibility, and patterns of genetic changes in the tissues of smokers and in the cancers that develop (Vineis and Caporaso 1995; Hecht 1999). Whereas much of this literature has focused on carcinogenesis in the respiratory system, the findings are likely to have implications for the causation of cancer by tobacco smoke at other organ sites.

In general, the risk of cancer depends on exposures to carcinogens and factors that influence host susceptibility, including a genetic predisposition (Hussain and Harris 1998). The elements of this paradigm are all topics of inquiry for tobacco smoking and lung and other cancers. Central to the molecular epidemiology approach to the problem is identifying biomarkers, which measure indicators of exposure, dose, susceptibility, and response in biologic materials, including tissue and cell samples, blood, urine, and saliva (IARC 1987, 1992; Schulte and Perera 1993). Research findings under the new paradigm will ultimately lay out the process that begins with exposures to carcinogens in tobacco smoke and ends with malignancy.

Biomarkers have already helped characterize the dosimetry of tobacco-smoke carcinogens. Adducts formed by the binding of carcinogens or metabolites to DNA and proteins have been measured in the blood and tissues of current smokers, former smokers, and persons who have never smoked (Hecht 1999). A significant advance in the detection of the biologically effective carcinogenic dose is the measurement of DNA adducts associated with tobacco in the lung and blood. More than 50 known carcinogens, including poly-aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines, have been identified in tobacco smoke (Hecht et al. 1993; IARC 2002). Experimental research has further shown that adducts formed by PAHs that exert their carcinogenic effects by binding to DNA may lead to mutations and ultimately to cancer. Adducts of PAHs bound to DNA (PAH-DNA adducts) were first measured in the early 1980s in white blood cells (Perera et al. 1982). Subsequently, PAH-DNA adducts have been measured in lung and other tissues as well as in blood, as markers of exposures to tobacco carcinogens (Chacko and Gupta 1988; Phillips et al. 1988; Foiles et al. 1989; Randerath et al. 1989; Garner et al. 1990; van Schooten et al. 1990; Routledge et al. 1992; Bartsch et al. 1993; Shields et al. 1993; Weston et al. 1993; Degawa et al. 1994; Wiencke et al. 1995a). Levels of these adducts in lung tissue are correlated with those in blood and differ across groups defined by their smoking status: current smokers, former smokers, and those who had never smoked. Strong, statistically significant

Figure 2.1   Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes
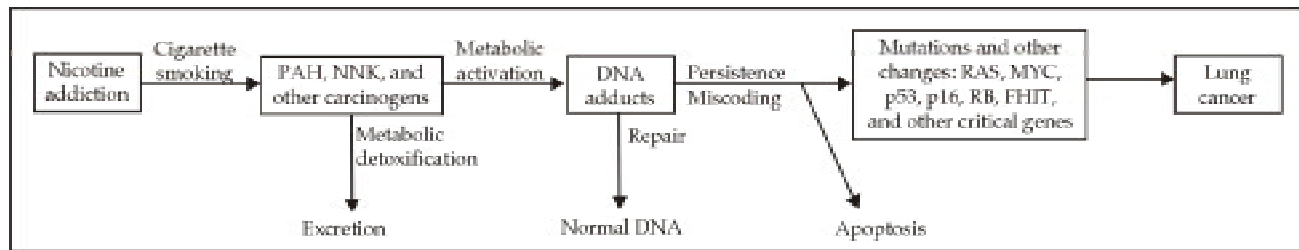
relationships have been shown (Wiencke et al. 1995a). Hence, current smokers have significantly elevated PAH-DNA adducts in their lungs. As smokers quit, it is believed that the amount of adducts declines rapidly. This notion is based on cross-sectional studies in former smokers that have shown significant differences in the adduct burdens of current compared with former smokers (Wiencke et al. 1995a, 1999).

Investigations of adducts and lung cancer risk have been limited. Several studies indicate that PHA-DNA adducts may be related to lung cancer risk (Rudiger et al. 1985; Cheng et al. 2000b; Vulimiri et al. 2000). Work examining PAH-DNA adducts in the lungs of cancer patients has also suggested that age at the initiation of smoking is a significant independent predictor of the overall DNA adduct burden measured at the time of surgery for lung cancer (Wiencke et al. 1999).

Studies in molecular carcinogenesis have produced an expanded understanding of the growth signaling circuit of the cell (Hanahan and Weinberg 2000). In addition, Shields and Harris (2000) have articulated a new paradigm, calling for epidemiologic analyses to categorize genes as caretakers or gatekeepers. The gatekeepers represent genes that limit tumor growth and that, of necessity, must be inactivated in carcinogenesis (Vogelstein and Kinzler 1998). The caretakers do not directly regulate growth, but act to prevent genomic instability; thus their mutation leads to accelerated conversion of a normal cell to a neoplastic cell (Levitt and Hickson 2002). The approach of molecular epidemiology to the understanding of the nature of tobacco smoke-induced lung cancer should now move to integrate these concepts, and to include analyses of the components of this circuitry as part of the overall framework for addressing the underlying biologic phenomena.

Biomarkers have also been used to investigate the specific molecular changes in DNA caused by tobacco carcinogens. Lung cancers have been estimated to have more than 10 and perhaps as many as 20 genetic changes before any individual clonal tumor emerges (Harlow 1994). Thus, some 10 to 20 individual alterations may have to take place in a sequence before any individual clone becomes truly malignant. This process of mutational selection (the process whereby individual somatic changes in the clone occur) is one of the most basic issues being investigated in cancer biology. Research using the tool of molecular epidemiology is examining the relationship of carcinogenic exposures to the genesis of mutation for each of these individual events. This research has addressed both oncogenes and tumor suppressor genes relevant to tobacco smoke carcinogenesis.

Substantial data are now available on the relationship between exposures to tobacco carcinogens and mutations in one oncogene, the *K-ras* gene. The *K-ras* gene is known to be mutated at codons 12, 13, and 61 in adenocarcinomas of the lung, and mutations arise almost overwhelmingly in persons who smoke cigarettes (Slebos et al. 1990; Sugio et al. 1992; Rosell et al. 1993; Silini et al. 1994; Rosell et al. 1995; Cho et al. 1997; Fukuyama et al. 1997; De Gregorio et al. 1998; Kwiatkowski et al. 1998; Nelson et al. 1999). However, mutations are not associated with the duration or intensity of smoking (Nelson et al. 1999). Thus, *K-ras* mutations may occur early in the lifetime of the smoker, and the mutated clones of the gene may be subsequently selected for continued growth by tobacco carcinogens. If *K-ras* mutations occurred later in the process of tumor generation, one would expect to find an association in the epidemiologic data between mutation frequency and the duration or intensity of smoking.

The deletion of one copy of the short arm of chromosome 3(3p) is an additional example of a possible early molecular change. This type of loss of heterozygosity (LOH) has been documented relatively early in lung carcinogenesis (Whang-Peng et al. 1982; Sundaresan et al. 1992; Hung et al. 1995; Thiberville et al. 1995; Kohno et al. 1999; Wistuba et al. 1999) and has been detected in preneoplastic epithelial cells in the lung. The frequency of any 3p LOH in persons with lung cancer has been reported to be 49 to 86 percent (Wistuba et al. 1997). The prevalence of LOH of 3p at region 2, band 1 (3p21) also has been observed to be higher in squamous cell carcinoma than in adenocarcinoma. Thus, LOH of 3p21 is perhaps one of the earliest genetic events involved in tobacco smoke-induced lung carcinogenesis. LOH at this locus has not been associated with duration of smoking or cumulative amount smoked.

The *p53* tumor suppressor gene has been studied extensively in smokers, with some researchers concluding that there is a specific pattern of mutation associated with this gene in cancers in smokers. The *p53* tumor suppressor gene shows an unusual spectrum of mutations that is predominantly of the missense type. These *p53* mutations are quite common in lung cancer, and a large number of tumors have been examined and categorized in the IARC database (Hainaut et al. 1998). Examinations of the spectrum of *p53* mutations in different human cancers have suggested that the mutations may be particular molecular lesions associated with particular exposures (Greenblatt et al. 1994). For example, in hepatocellular carcinoma, unique mutations in codon 249 have been associated with a dietary exposure to aflatoxin B1 (Bressac et al. 1991; Hsu et al. 1991). Sunlight exposure-associated skin cancer has been strongly associated with the occurrence of dipyrimidine mutations (CC to TT) in the *p53* gene (Brash et al. 1991; Nakazawa et al. 1994; Ziegler et al. 1994). For lung cancer, tobacco carcinogens have been associated with particular *p53* mutations at codons 157, 248, and 273 (Bennett et al. 1999). Further, there is evidence that the frequency of *p53* mutations increases with the extent of smoking (Kondo et al. 1996; Bennett et al. 1999). Finally, transversion mutations that occur frequently in lung cancers of smokers are of the same type as those observed in vitro after growing cells are exposed to benzo[*a*]pyrene diol epoxide. Denissenko and colleagues (1996, 1997) demonstrated that cytosine methylation greatly enhances guanine alkylation at all the sites in the *p53* gene that have the sequence "... cg ..." and that are known to

be preferentially methylated. These sites are also where mutations are commonly found in persons with lung tumors. The PAH intermediate benzo[*a*]pyrene binds preferentially to the *p53* gene at these sites (Denissenko et al. 1996, 1997), suggesting that benzo[*a*]pyrene contributes to the common mutations in the *p53* gene found in persons with lung cancer.

Recent work also has demonstrated that silencing of the transcriptional promoters of tumor suppressor genes by DNA methylation occurs frequently in tobacco smoke-related cancers. For example, in approximately 15 to 35 percent of lung cancer tumors, methylation of the promoter of the *p16* gene essentially halts transcription and inactivates this tumor suppressor gene (Kashiwabara et al. 1998). Inactivation of the *p16* gene has been detected in more than 70 percent of cell lines derived from human non-small cell lung cancers (Kamb et al. 1994). In addition, *p16* inactivation (by multiple mechanisms) has been detected in approximately 50 percent of primary non-small cell lung cancers (Kratzke et al. 1996; Vonlanthen et al. 1998; Sanchez-Cespedes et al. 1999). The frequency of other types of *p16* inactivation in non-small cell lung cancers has been highly variable, such as homozygous deletions (9 to 25 percent) (Nobori et al. 1994; de Vos et al. 1995; Washimi et al. 1995) and *p16* mutations (0 to 8 percent) (Okamoto et al. 1995; Rusin et al. 1996; Betticher et al. 1997; Marchetti et al. 1997). Further, methylated tumor DNA (at the *p16* gene, but probably at other important loci as well) can be detected in the serum of affected patients (Esteller et al. 1999). The relationship of tobacco smoke exposure to the many types of *p16* inactivation remains under investigation. Similarly, the nature of the relationships of all of these tumor suppressor gene alterations with one another is also under study.

Since the epidemiologic study by Tokuhata and Lilienfeld (1963), subsequent epidemiologic studies have shown that a family history of lung cancer is associated with an increased risk of lung cancer in smokers (Economou et al. 1994). Numerous epidemiologic studies, primarily using the case-control design, have been directed at identifying phenotypes and genotypes for carcinogen metabolism that may contribute to this familial aggregation.

In the search to identify candidate genes that can explain the observed familial excess, genes involved in the activation or elimination of tobacco carcinogens were the earliest studied. The metabolism of toxic agents, including carcinogens, generally proceeds through two phases (Garte and Kneip 1988). In phase

1, unreactive nonpolar compounds are converted, usually by oxidative reactions, to highly reactive intermediates. These intermediates are then able to form complexes with conjugating molecules in phase 2 conjugation reactions, which are usually less reactive and more easily excreted. However, the intermediate metabolite may react with other cellular components, such as DNA, before conjugation occurs. This binding to DNA may be the first step in the initiation of a carcinogenic process (Garte et al. 1997).

The cytochrome P-450 enzymes are a large multigene family that is important in phase 1 reactions. *CYP1A1*, *CYP2E1*, and *CYP2A6* are phase 1 genes that activate carcinogens and have been investigated in relation to lung cancer risk. Three phase 2 genes have received wide attention as metabolic markers: *GSTM1*, *NAT1*, and *NAT2* (Garte et al. 1997). A growing body of work has examined differences in genotypes for these and many other genes thought to alter risks for lung and other tobacco-related cancers.

The genetic basis for this variation has been investigated in many individual studies and summarized through a number of systematic meta-analyses (e.g., d'Errico et al. 1999, Marcus et al. 2000, Benhamou et al. 2002, and Vineis et al. 2003). Underlying this research is the hypothesis that variations in the metabolism of carcinogens result in variations in the biologically effective carcinogenic dose. The biologically effective doses of carcinogenic and mutagenic intermediates might be enhanced by an inherited variation that causes (1) a relatively higher rate of activation of the carcinogen than other variations, (2) a relatively lower rate of detoxification via conjugation than other variants, or (3) the complementary action of both of these mechanisms. Some genetic variations in the metabolism of carcinogens could generate detectable interactions among the variant genetic exposures to tobacco carcinogens.

Initial research in this area focused on the normal polymorphic variants of the cytochrome P-450 system, which is responsible for the oxidative activation of many PAHs (phase 1 metabolism). In Japanese and other Asian populations, polymorphic variants of the *CYP1A1* gene are highly prevalent and have been associated repeatedly with higher risks for smoking-related lung cancers (Kawajiri et al. 1990; Hayashi et al. 1991; Nakachi et al. 1991, 1995; Okada et al. 1994; Kawajiri et al. 1996). This susceptibility is less apparent in other racial groups, which may be attributable to inadequate statistical power to detect associations because of a lower prevalence of gene variants (Ishibe et al. 1997).

Polymorphic variants in phase 2 metabolic systems also have been studied and associated with lung cancer (Zhong et al. 1991; Brockmoller et al. 1993; Hirvonen et al. 1993; Nakachi et al. 1993; Nazar-Stewart et al. 1993; Alexandrie et al. 1994; Kihara et al. 1994; Anttila et al. 1995; London et al. 1995; Nakajima et al. 1995; Vaury et al. 1995). Predominant among the variants studied have been several classes of the glutathione transferases. The glutathione transferase classes mu (the *GSTM1* null genotype) and theta (*GSTT1* gene) enhance susceptibility of cellular genetic material to the action of carcinogens in vitro (Wiencke et al. 1990; Rebbeck 1997). A meta-analysis of investigations of the association of the *GSTM1* null genotype with susceptibility to tobacco-associated lung cancer has shown significant, albeit small, increases in risk compared with other genotypes (Wiencke et al. 1995b).

An emerging area of similar research is directed at an understanding of the role of individual variations in DNA repair and lung cancer risks. Since Cleaver (1968) demonstrated that defective DNA repair was responsible for multiple skin cancers in xerodema pigmentosum, there have been further reports suggesting that DNA repair capacity is a determinant of susceptibility to cancer (reviewed in Oesch et al. 1987). Cheng and colleagues (2000a) reported reduced expression levels of nucleotide excision repair genes in lung cancer patients compared with controls. They suggest that this reduced expression level fosters a gene-environment interaction and enhances the risk of lung cancer. Considerable work is being done to find the precise gene alterations responsible for these interactions. Many novel DNA repair gene polymorphisms have been reported, but their phenotypic expression remains unclear (Marcus et al. 2000a,b).

In summary, laboratory and molecular epidemiologic studies have provided substantial new insights into respiratory carcinogenesis by tobacco smoke, closing some of the gaps noted in the 1964 Surgeon General's report (USDHEW 1964). Components of tobacco smoke are potent mutagens and carcinogens in animals. The paradigm developed for examining molecular biomarkers is consistent with longstanding models of disease occurrence. DNA adduct measurements now offer useful biomarkers of effective carcinogenic doses. Evaluations of somatic mutations in tumors also provide evidence that tobacco smoke components and their metabolites directly interact with DNA, and produce characteristic lesions in genes that are in the causal pathway for the changes that lead to the development of lung cancer. In addition, normal variants of genes that code for enzymes known to

metabolize constituents of tobacco smoke significantly affect susceptibility to lung cancer.

Epidemiologic Evidence

Although smoking was identified as a cause of lung cancer 40 years ago in the 1964 Surgeon General's report (USDHEW 1964), changing epidemiologic characteristics of the disease have motivated numerous further epidemiologic studies. These studies have been primarily case-control studies comparing smokers who have lung cancer with appropriate controls, or prospective cohort studies that follow smokers and nonsmokers over time and observe lung cancer incidence or deaths. These studies have also tested additional hypotheses related to the causation of lung cancer by cigarette smoking, and have provided abundant evidence consistent with the 1964 conclusion.

Among the principal issues addressed have been

- the characterization of the dose-response relationship for lung cancer risk with smoking;

- the consequences of changing the characteristics of cigarettes, including the addition of filters and the reduction of machine-measured tar and nicotine yields;

- changes in lung cancer occurrence following smoking cessation; and

- factors influencing the shift in lung cancer histopathology in recent decades.

Extensive reviews of the epidemiologic evidence on smoking and lung cancer have been published covering the key findings (USDHHS 1990; Samet 1994; NCI 1997). Variations in lung cancer risks among racial and ethnic minority groups in the United States were covered in the 1998 Surgeon General's report (USDHHS 1998), and lung cancer in women was addressed in the 2001 report (USDHHS 2001).

This section emphasizes two of the more critical issues that have arisen since the topic of lung cancer was last covered in the 1981, 1982, and 1990 reports (USDHHS 1981, 1982, 1990): the risk of lung cancer as a consequence of changes in the characteristics of cigarettes, and the emergence of adenocarcinoma as the most frequent histologic type of lung cancer. This chapter also addresses newer evidence on changing risks of lung cancer following smoking cessation, as data

Figure 2.2   Effects of smoking cessation at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990
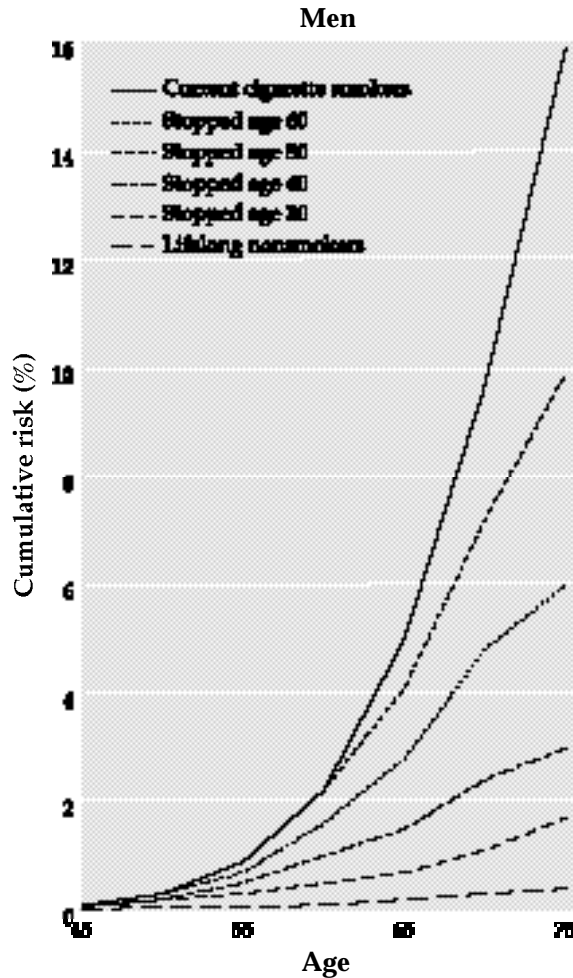
Note: Nonsmoker risks are taken from a U.S. prospective study of mortality.
Source: Peto et al. 2000, p. 326. Reprinted with permission.

have become available from increasing numbers of former smokers.

Changes in Relative Risks Following Smoking Cessation

Substantial epidemiologic evidence exists regarding the decline of lung cancer risks following successful cessation (USDHHS 1990; Wu-Williams and Samet 1994; NCI 1997). As the follow-up of participants in

the major prospective cohort studies has been maintained, data have become available on patterns of lung cancer risks with increasing durations of not smoking. The findings from the principal studies conducted in the United States were summarized in Monograph 8 from the NCI series on smoking and tobacco control (NCI 1997). The data show that the RR for lung cancer among former smokers (persons who responded "yes" to ever smoking cigarettes at least 2 years before completing the study questionnaire) continues to decline as the duration of not smoking increases in comparison with the risk among continuing smokers.

Extensive data convincingly show how smoking cessation lowers lung cancer risks (NCI 1997; Peto et al. 2000). Using data from a 1990 case-control study, Peto and colleagues (2000) estimated cumulative lung cancer risks for persons up to 75 years of age (Figure 2.2). The estimated lifetime risk of lung cancer deaths for men who continue to smoke, absent death from another cause, was 16 percent. Substantial reductions in this risk can be achieved by cessation at younger ages; even cessation at 60 years of age lowered the cumulative risk from 16 percent to about 10 percent.

Even with the longest durations of quitting that have been studied, however, the risks for lung cancer remain greater in former smokers compared with lifetime nonsmokers (NCI 1997). The absolute risk of lung cancer does not decline following cessation, but the additional risk that comes with continued smoking is avoided. The study of veterans in the United States that was initiated in the early 1950s provides some of the lengthiest follow-up data. Although smoking was assessed only at the beginning of the study, those who reported having quit were assumed to have remained nonsmokers during the follow-up period. With this assumption, the veterans study provides a picture of risks for lung cancer up to 40 years after smoking cessation. Even for this duration, former smokers have a 50 percent increased risk of death from lung cancer compared with lifetime nonsmokers. The 1990 Surgeon General's report (USDHHS 1990) reviewed findings of additional cohort and case-control studies. The results consistently showed declining RRs, compared with continuing smoking, with increasing duration of not smoking. The general pattern of this decline was the same for men and women, for smokers of filter-tipped and unfiltered cigarettes, and for all major histologic types of lung cancer. However, lung cancer incidence in former smokers, even decades after quitting, has not been shown to return to the rate seen in persons who have never smoked.

Studies of biopsy specimens of nonmalignant tissues have documented persistent molecular damage in the respiratory epithelium of former smokers. Wistuba and colleagues (1997) examined microsatellite markers of heterozygosity in current and former smokers and found similar rates of abnormality in the two groups; the former smokers had stopped for an average of 11 years. Wiencke and colleagues (1995a, 1999) assessed levels of aromatic hydrophobic DNA adducts in nontumorous tissues of persons having surgery for lung cancer. Levels of adducts were lower in former smokers compared with current smokers, and were very low in the seven patients in the series who had never smoked. In a predictive model for adduct levels in former smokers, initiating smoking at a younger age was associated with higher adduct levels.

Changing Characteristics of Cigarettes

Since the first research reports linking smoking to lung cancer and other diseases, the tobacco industry has continually changed the characteristics of the cigarette (USDHHS 1981; NCI 1996; Hoffmann and Hoffmann 1997). These changes have included the addition of filter tips, perforation of the filter tips, use of reconstituted tobacco, and changes in the paper and in additives (Hoffmann and Hoffmann 2001; NCI 2001; Stratton et al. 2001). During the nearly 50 years that these changes have been made in the United States, there have been substantial declines in the sales-weighted average tar and nicotine yields of cigarettes, as measured by the Federal Trade Commission (FTC) protocol (Figure 2.3) (Hoffmann and Hoffmann 1997, 2001). Limitations of this protocol for assessing actual yields to smokers have been widely acknowledged (NCI 1996; Hoffmann and Hoffmann 1997, 2001). For example, tar and nicotine yields are lowered by perforation of the filter with small holes to increase dilution during machine smoking in the FTC protocol; unlike the machines, smokers tend to cover these holes with their fingers, thereby increasing the yield beyond that measured by the machine (Hoffmann and Hoffmann 1997). The changing cigarette was the focus of the 1981 report of the Surgeon General (USDHHS 1981). The major conclusions from that report were as follows:

1. There is no safe cigarette and no safe level of consumption.

2. Smoking cigarettes with lower yields of "tar" and nicotine reduces the risk of lung cancer and, to some extent, improves the smoker's chance for longer life, provided there is no compensatory increase in the

Figure 2.3 Sales-weighted tar and nicotine values for U.S. cigarettes as measured by machine using the Federal Trade Commission (FTC) method, 1954–1998*
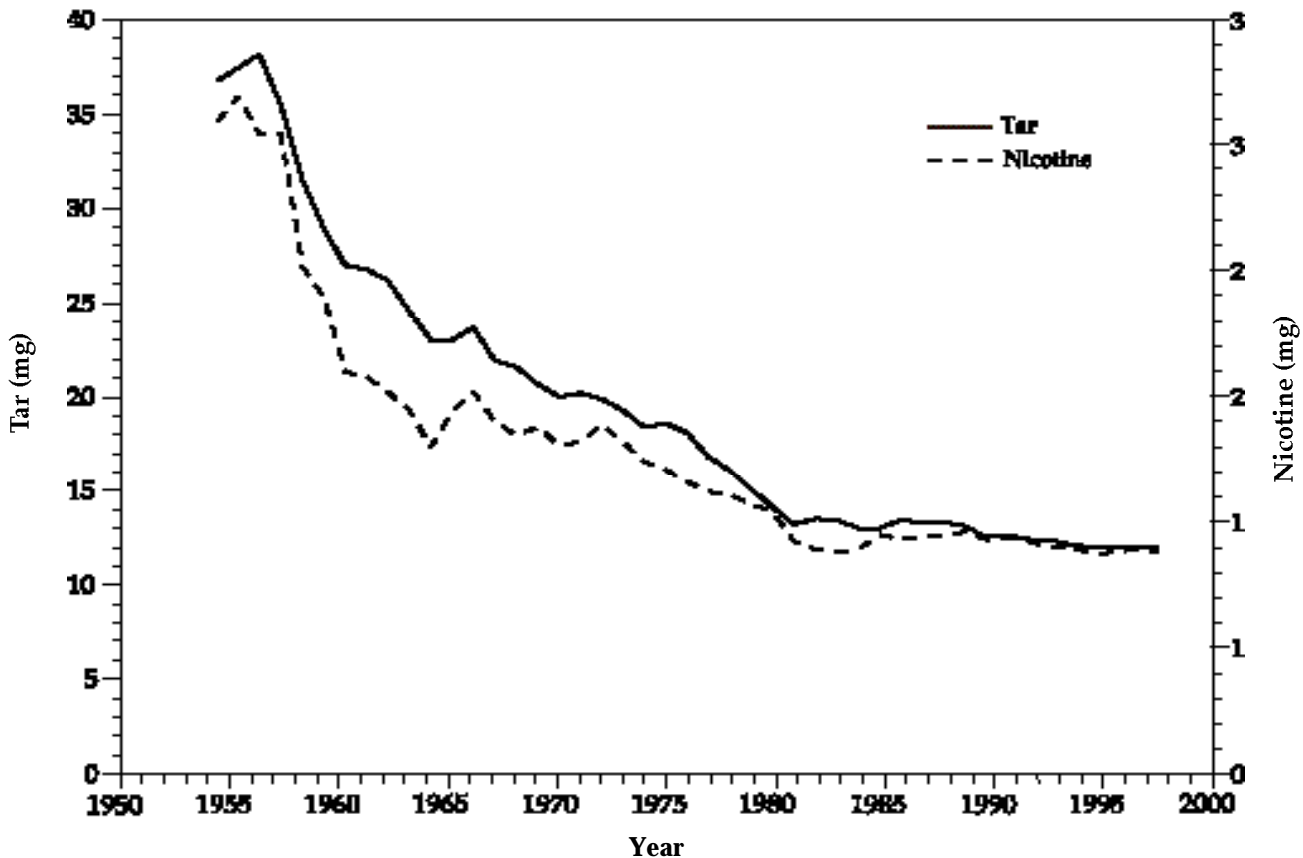
*Values before 1968 are estimated from available data.
Source: Hoffmann and Hoffmann 2001, p. 167.

amount smoked. However, the benefits are minimal in comparison with giving up cigarettes entirely. The single most effective way to reduce hazards of smoking continues to be that of quitting entirely.

3. It is not clear what reductions in risk may occur in the case of diseases other than lung cancer. The evidence in the case of cardiovascular disease is too limited to warrant a conclusion, nor is there enough information on which to base a judgment in the case of chronic obstructive lung disease. In the case of smoking's effects on the fetus and newborn, there is no evidence that changing to a lower "tar" and nicotine cigarette has any effect at all on reducing risk.

4. Carbon monoxide has been impugned as a harmful constituent of cigarette smoke. There is no evidence available, however, that permits a determination of changes in the risk of diseases due to variations in carbon monoxide levels.

5. Smokers may increase the number of cigarettes they smoke and inhale more deeply when they switch to lower yield cigarettes. Compensatory behavior may negate any advantage of the lower yield product or even increase the health risk.

6. The "tar" and nicotine yields obtained by present testing methods do not correspond to the dosages that the individual

smokers receive: in some cases they may seriously underestimate these dosages.

7. A final question is unresolved, whether the new cigarettes being produced today introduce new risks through their design, filtering mechanisms, tobacco ingredients, or additives. The chief concern is additives. The Public Health Service has been unable to assess the relative risks of cigarette additives because information was not available from manufacturers as to what these additives are (p. vi).

Subsequently, this topic has been the focus of several reviews including NCI Monograph 7, *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes* (NCI 1996); the Institute of Medicine (IOM) report, *Clearing the Smoke* (IOM 2001); and NCI Monograph 13, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine* (NCI 2001). The IARC monograph addressed this topic in relation to lung cancer (IARC 2002). These reports provide comprehensive reviews of changes in cigarettes and the ways that they are smoked, related changes in doses of tobacco smoke components, and evidence on changes in health risks associated with changes in cigarettes. Each of these lines of evidence is relevant to interpreting the public health implications of changes in cigarette characteristics and machine-measured yields.

Studies using biomarkers of exposures to and doses of tobacco smoke components show little relationship between the biomarkers and tar or nicotine yields as measured by the FTC protocol (Hoffmann and Hoffmann 1997; NCI 2001). These studies have been conducted in both population samples and during smoking in the laboratory setting. For example, Coultas and colleagues (1988) collected saliva to analyze the cotinine levels and end-tidal breath samples for carbon monoxide levels in a population sample of Hispanics in New Mexico. Levels of the biomarkers in smokers were not associated with the tar and nicotine yields of those brands smoked by individual participants. Djordjevic and colleagues (2000) evaluated smoking patterns and biomarkers in the laboratory setting, comparing smokers of medium-yield cigarettes with smokers of low-yield cigarettes. The smokers averaged greater puff volumes and frequencies than those specified in the FTC protocol, and had substantially greater intakes of tar and nicotine than implied by the brand listings.

Epidemiologic studies assessed whether the seemingly substantial changes in tar and nicotine yields, as measured in the FTC protocol, have resulted in parallel changes in risks from smoking. These studies have been one of the key sources of information because they provide direct evidence about the risks from cigarettes as people actually use them. Some of the earliest studies were considered in the 1981 Surgeon General's report (USDHHS 1981); the principal studies on cigarette type or tar yield and lung cancer are summarized in Table 2.2. For lung cancer and other diseases, three types of epidemiologic data have been available. The first comes from case-control studies that compared the smoking history profiles of persons developing lung cancer with those of controls. The second comes from cohort studies that tracked the risks of lung cancer over time as the products smoked changed. The third involves ecologic assessment of age-specific patterns of change in disease mortality (e.g., lung cancer) across the decades over which cigarette characteristics were changing.

The initial epidemiologic evidence came primarily from case-control studies of lung cancer that compared the risks between filter-tipped cigarette smokers and unfiltered cigarette smokers exclusively (Bross and Gibson 1968; Wynder et al. 1970). This comparison could be made in the 1960s because there were still a substantial number of smokers who had not used filter-tipped cigarettes at all. Bross and Gibson (1968) were able to make this comparison using patients seen at Roswell Park Cancer Institute in Buffalo, New York; persons were classified as filter-tipped cigarette smokers if they had used these products for at least 10 years. These initial studies indicate that filter-tipped cigarettes provided some reduction in lung cancer risks. Subsequent case-control studies that have compared the use of either filter-tipped or lower-yield products with unfiltered or higher-yield products across a cumulative smoking history have had generally similar findings.

The case-control studies provide an assessment of risk from smoking different types of cigarettes that is inherently static in time; that is, risks are assessed for the particular birth cohorts that are included in a study. For example, Bross and Gibson (1968) compared risk for lung cancer in people who switched to the initial filter-tipped cigarettes with those who continued to smoke unfiltered cigarettes. Later studies made comparisons between risks for those smoking higher-versus lower-yield cigarettes (Table 2.2). Thus, the case-control studies provide a longitudinal perspective on the comparative risks of changing types of cigarettes

Table 2.2   Studies on the association between cigarette characteristics and lung cancer

Study	Design/population	Exposure
Bross and Gibson 1968	Case-control study; 974 white male lung cancer patients and matched controls	Cigarette smoking habits and tar content
Wynder et al. 1970	Case-control study; 350 lung cancer patients and controls	Cigarette smoking habits and type of cigarette
Hammond et al. 1976	Cohort study; 1 million volunteers in the American Cancer Society Cancer Prevention Study followed from 1959–1972	Tar content (low: <17.6 mg/cigarette, high: 25.8–35.7 mg/cigarette, medium: intermediate)
Wynder and Stellman 1979	Case-control study; 1,034 male and female larynx and lung cancer patients (Kreyberg type I) or larynx cancer patients; 9,547 cancer controls with no tobacco-related diseases	Cigarette smoking habits and tar content
Rimington 1981	Cohort study; 5,348 current smokers (3,045 filter-tipped, 2,303 plain)	Cigarette smoking habits and type of cigarette
Higenbottam et al. 1982	Cohort study; 17,475 male civil servants aged 40–64 years and 8,089 male British residents aged 35–69 years	Cigarette smoking habits
Vutuc and Kunze 1982	Case-control study; 297 female lung cancer patients and 580 controls (50% hospital-based and 50% neighborhood-based) matched for tobacco-related disease and 5-year age group	Cigarette tar content
Lubin et al. 1984	European case-control study; 7,804 lung cancer patients and 15,207 hospital-based controls	Cigarette smoking habits and type of cigarette smoked
Pathak et al. 1986	Population-based case-control study from 1980–1982 in New Mexico; 521 cases and 769 controls matched for age, gender, and ethnicity	Cigarette smoking

*RR = Relative risk.
†SMR = Standardized mortality ratio.
‡OR = Odds ratio.
§CI = Confidence interval.

Outcome	Results
Lung cancer	• Current smokers of filter-tipped cigarettes have a RR* approximately 40 % lower than smokers of unfiltered cigarettes
Lung cancer	• There was a lower RR for those who smoked filter-tipped cigarettes for 10 years compared with those who smoked plain cigarettes
Mortality (1967–1972) for all deaths, lung cancer, and coronary heart disease (CHD)	• Compared with high-tar smokers: total mortality SMR† = 0.98 and 0.81 for medium- and low-tar smokers, respectively; lung cancer SMR = 1.03 and 0.82 for medium- and low-tar smokers
Lung or larynx cancer	• Risks of developing lung or larynx cancer were lower among long-term filter-tipped cigarette smokers vs. plain cigarette smokers, regardless of the number smoked
Lung cancer	• 104 lung cancers were diagnosed and followed for 69–81 months; incidence among plain cigarette smokers was 50% higher than among filter-tipped smokers
Lung cancer	• Tar yield was associated with the risk of lung cancer in noninhalers but less so in inhalers • Effects of tar/nicotine yields were confined to inhalers • Interactions were found between the amount smoked, tar yields, and smoking styles (i.e., inhaling)
Lung cancer	• Compared with never smokers, OR‡ for cigarette smokers of <15 mg tar/cigarette = 1.5 (95% CI§, 0.1–14.2); 15–24 mg tar/cigarette = 2.7 (95% CI, 1.5–4.7); and 25 mg tar/cigarette = 6.3 (95% CI, 3.5–11.3)
Lung cancer	• Long-term unfiltered smokers were at nearly twice the risk of developing lung cancer compared with long-term filter-tipped smokers, after controlling for duration of cigarette use and the number of cigarettes smoked/day (RR = 1.7 for men and 2.0 for women)
Lung cancer	• There was a higher risk among unfiltered cigarette smokers, but no evidence of a decreasing risk with more filter-tipped cigarette smoking • Long-term filter-tipped smokers and smokers of both filter-tipped and unfiltered cigarettes had a lower risk than long-term unfiltered smokers only

Table 2.2   Continued

Study	Design/population	Exposure
Gillis et al. 1988	Case-control study; 656 male lung cancer patients and 1,312 age- and gender-matched controls, interviewed from 1976–1981 in Glasgow and West Scotland	Cigarette smoking habits
Wilcox et al. 1988	Population-based case-control study; New Jersey white male lung cancer patients who smoked cigarettes from 1973–1980; 900 controls from a random sample of men with New Jersey motor vehicle licenses; frequency was matched to cases by geographic area, race, and 5-year age group	Time-weighted average tar levels of cigarettes
Augustine et al. 1989	Case-control study; 1,242 histologically confirmed lung cancer cases, and 2,300 gender- and age-matched hospital controls in 9 U.S. cities from 1969–1984	Switching from plain to filter-tipped cigarettes
Kaufman et al. 1989	Case-control study; 881 lung cancer cases and 2,570 hospital controls; aged 40–69 years; from 1981–1986 in the United States and Canada	Tar content, by the Federal Trade Commission (1967–1985) and *Reader's Digest* (1957–1966)
Stellman and Garfinkel 1989	Prospective cohort study; 120,000 male current cigarette smokers in the American Cancer Society 1959–1972 Cancer Prevention Survey	Cigarette smoking habits and tar yield
Giles et al. 1991	Cohort study; lung cancer cases in Australia from 1985–1989	Cigarette smoking habits
Zang and Wynder 1992; Wynder and Kabat 1988	Case-control study; 2,296 lung cancer cases (1,274 Kreyberg type I [KI] and 1,022 Kreyberg type II [KII]) and 4,667 controls	Long-term tar exposure

[†]SMR = Standardized mortality ratio.
 Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Outcome	Results
Lung cancer	• Smokers of <15 cigarettes/day had reductions in risks from smoking lower-tar cigarettes than those who smoked 15 lower-tar cigarettes • RRs increased for smokers of <20 cigarettes/day but not for those who smoked >20/day; tar yields of brands did not explain this finding
Primary lung cancer patients	• Unadjusted RR = 0.53 (95% CI, 0.29–0.97), significantly lower for the lowest-tar smokers (<14 mg/cigarette) compared with highest-tar smokers (21.1–28 mg/cigarette) • After adjusting for age and total pack-years the difference in risks was insignificant • Low-tar smokers compensated by smoking almost half a pack more per day
Lung cancer incidence	• Mean increase in cigarettes/day was 2 times higher for cancer cases than for controls • Linear dose-response relationship between risk and increased compensation; OR = 1.19–2.37 in men and 1.66–3.83 in women for increases of 1–10 and 21 cigarettes/day, respectively
Lung cancer	• Compared with low-tar smokers (<22 mg/cigarette), adjusted RRs = 3.0 and 4.0 for medium- (22–28 mg/cigarette) and high-tar (>29 mg/cigarette) smokers, respectively, for both genders, based on smoking 10 years; significant trend (p = 0.002); there were few low-tar smokers in the study
Lung cancer	• Risks increased with higher-tar yields at each quantity level, and risks increased with more cigarettes smoked daily at each tar level • Excess lung cancer risks for current smokers were proportional to the estimated mg of tar inhaled daily (SMR[†] = 100 + 1.731 x mg tar/day)
Lung cancer incidence	• Age-standardized mortality rate decreased from 49/100,000 in 1980–1984 to 46.4/100,000 in 1985–1989 in men, likely due to lowered-tar content of brands, and trends in smoking cessation
Lung cancer KI and KII	• For KI: OR = 0.69 (95% CI, 0.37–1.27) in men and 0.64 (95% CI, 0.30–1.35) in women who smoked filter-tipped cigarettes only • Among long-term switchers to and smokers of filter-tipped cigarettes for 10 years, OR for men = 0.66 (95% CI, 0.49–0.90) and 0.74 (95% CI, 0.40–1.36) for women • Among short-term switchers to and smokers of filter-tipped cigarettes for 1–9 years, OR = 0.83 (95% CI, 0.59–1.17) in men and 0.99 (95% CI, 0.49–2.03) in women • Evidence for reductions in risk of KII was weaker in men and undetectable in women

Table 2.2   Continued

Study	Design/population	Exposure
Sidney et al. 1993	Cohort study; 79,946 Kaiser Permanente Medical Care Program members, aged 30–89 years, who completed a detailed, self-administered smoking habit questionnaire between 1979 and 1985	Cigarette tar yield and other cigarette use characteristics
Benhamou et al. 1994	Case-control study; 1,114 persons with histologically confirmed cases of lung cancer and 1,466 hospital controls, interviewed in hospitals in France from 1976–1980	Past tar content of cigarettes manufactured by the French Tobacco Monopoly
Tang et al. 1995	4 cohort studies; 56,255 men studied between 1967 and 1982 from the British United Provident Association Study (London), Whitehall Study (London), Paisley-Renfrew Study (Scotland), and United Kingdom Heart Disease Prevention Project (England and Wales)	Tar yield of manufactured cigarettes
Stellman et al. 1997	Case-control study; 2,292 lung carcinoma patients and 1,343 currently smoking hospital controls, between 1977 and 1995	Long-term filter-tipped cigarette smoking

over time, as results are compared from the earliest to the most recent study. The studies use differing designs and populations, however, and provide only a relative rather than an absolute comparison of the risks associated with cigarettes of different designs and yields.

The relevant cohort data come from the ACS CPS-I and CPS-II studies and the British physicians cohort. In a 1976 publication, Hammond and colleagues (1976) used tar yields of products smoked by CPS-I participants to compare mortality risks from lung cancer and other diseases. The 12-year follow-up interval spanned 1960–1972. Smokers were placed into three categories of products smoked: low yield (<17.6 mg/cigarette), high yield (25.8–35.7 mg/cigarette), and medium yield (intermediate). The standardized mortality rate for lung cancer in smokers of low-yield cigarettes was approximately 80 percent of the rate found in high-yield smokers. A further analysis of tar yields using

the same data set confirmed that risks for lung cancer deaths increased with tar yield (Stellman and Garfinkel 1989).

Further insights have been gained by comparing the risks found in the two ACS studies; this comparison addresses whether risks have changed, by comparing smokers developing disease during 1960–1972 with a similar group developing disease during the 1980–1986 follow-up of CPS-II (Thun et al. 1995, 1997a). If newer cigarettes are increasingly associated with a lower risk for lung cancer, the expectation would be that risks for smokers would be less in CPS-II than in CPS-I. In fact, the opposite was observed, with increasing lung cancer mortality in male and female smokers in CPS-II compared with CPS-I (Figure 2.4) (Thun et al. 1997a). Whereas differences in smoking patterns, including amount smoked and age at starting, may partially explain this increase, male smokers

Outcome	Results
Lung cancer incidence	• Tar yield of current cigarette brand was not associated with lung cancer incidence (RR = 1.02/1 mg tar yield in men and 0.99/1 mg tar yield in women)
Lung cancer	• Increased RR for smokers of both plain and filter-tipped cigarettes (RR = 1.6 [95% CI, 0.9–2.7]) • Long-term smokers of plain cigarettes had higher risks than long-term smokers of filter-tipped cigarettes (RR = 1.6 [95% CI, 0.9–2.8]) • No significant difference in risk was associated with the proportion of years smoking high-tar cigarettes
Lung cancer mortality	• Relative mortality per 15 mg decrease in tar yield/cigarette was 0.75 (95% CI, 0.52–1.09)
Lung cancer (squamous cell carcinoma [SCC] and adenocarcinoma [AC])	• ORs for long-term filter-tipped cigarette smokers compared with long-term plain cigarette smokers = 0.8 (95% CI, 0.5–1.2) for SCC for men and 0.4 (95% CI, 0.2–0.8) for women • No reduction for AC was observed

in CPS-II had substantially higher lung cancer mortality rates than their counterparts in CPS-I (Thun et al. 1997a).

In an analysis with a similar pattern of findings, Doll and colleagues (1994) compared the risks of death from lung cancer and other causes during the first and second 20 years of the 40-year follow-up of the British physicians cohort. Lung cancer mortality increased among smokers in the second 20 years (1971–1991), even though products smoked during that time period would have had substantially lower tar and nicotine yields than those smoked during the first 20 years (1951–1971). For the first 20 years, the annual lung cancer mortality rate for current smokers was 264 per 100,000 and for the second 20 years it was 314 per 100,000. Of course, the cohort had aged substantially from the first to the second 20 years. The comparison took age into account, although some residual confounding by age is possible.

The third line of observational evidence comes from descriptive analyses of age-specific trends of lung cancer mortality (IARC 1986; Peto et al. 2000; NCI 2001). Successive birth cohorts have had differing patterns of exposure to cigarettes of different characteristics and yields. For example, the cohort of persons born between 1930 and 1940 who started to smoke during the 1950s was one of the first to have the opportunity to smoke primarily filter-tipped cigarettes. Subsequent birth cohorts would have had access to the increasingly lower-yield products while earlier cohorts had access initially only to unfiltered cigarettes. Patterns of temporal change in age-specific rates of lung cancer mortality in younger men have been examined to assess if there has been a decline greater than expected from changing prevalence, duration, and amount of smoking, hence indicating a possible effect of cigarette yield.

Figure 2.4 **Age-specific death rates from lung cancer among current cigarette smokers and never smokers, based on smoking status at enrollment in Cancer Prevention Study I (CPS-I) or Cancer Prevention Study II (CPS-II), according to attained age**

Men

Women
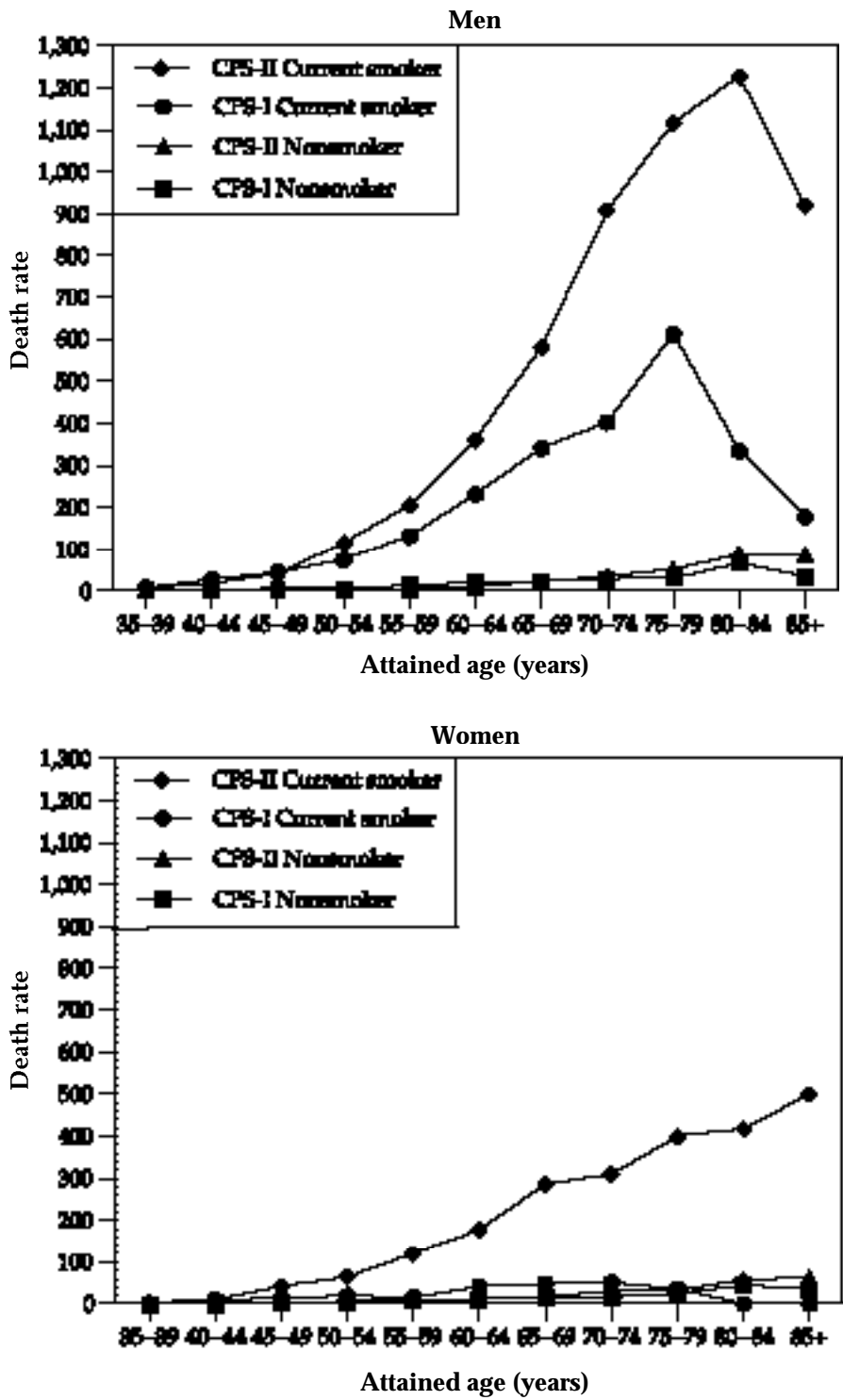
Note: **Rate per 100,000 person-years.**
Source: Thun et al. 1997a, p. 317.

Data on lung cancer mortality in younger men in the United Kingdom have been interpreted as indicating a possible reduction in lung cancer risk associated with changes in cigarettes (Peto et al. 2000; NCI 2001). A sharp decline in lung cancer mortality has occurred across recent decades in United Kingdom men under 50 years of age. The decline seems greater than anticipated from trends in prevalence and other aspects of smoking—age starting and number of cigarettes smoked. A similarly steep decline has not taken place in the United States. Given the ecologic nature of the data under consideration, uncertainty remains with regard to their interpretation and alternative explanations have been proposed, including less intense smoking at younger ages in more recent birth cohorts (NCI 2001).

Three monographs have recently reviewed epidemiologic and other evidence on cigarette yields and lung cancer risk. IOM found the evidence on yield to be mixed but did conclude that unfiltered cigarettes probably posed a greater risk than filtered cigarettes (IOM 2001). NCI Monograph 13 also judged the evidence on yield and lung cancer risk to be mixed and noted that lung cancer rates have increased steadily in older smokers (NCI 2001). Monograph 13 also noted that consideration of the public health consequences of lower-yield products needs to go beyond risks to individual smokers to consider the impact of their availability on decisions to start smoking and to quit smoking. The availability of products that seemingly convey less risk may increase rates of smoking initiation and possibly lead current smokers to switch rather than quit. Finally, the 2002 IARC monograph reviewed the same body of evidence, reaching the conclusion that any reduction in lung cancer risk associated with changes in the cigarette had probably been small (IARC 2002).

These prior analyses have highlighted the complexity of isolating the effect on lung cancer risk of the continually changing cigarette. The available data have limitations, particularly in systematically capturing the experience of successive birth cohorts in either case-control or cohort studies that were appropriately designed. The United Kingdom mortality data are consistent with a greater effect of changes in cigarettes than is found in the case-control and cohort studies. Regardless of changes in cigarettes, many countries around the world, including the United States, have epidemics of lung cancer in progress that are largely caused by cigarette smoking and other forms of tobacco use. As recommended by IOM (2001), surveillance is needed to track the health consequences of the changing cigarette.

Lung Cancer Histopathology

Conventional light microscopy is used to classify the many histologic types of lung cancer. Again, the four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma. These four types of lung cancer together account for more than 90 percent of lung cancer cases in the United States (Churg 1994). In spite of extensive research, the mechanisms leading to these different types of lung cancer remain uncertain. Hypotheses have focused on the cells of origin of lung cancers and on the pathways of differentiation of malignant cells (NRC 1991; Churg 1994). There are few environmental or occupational exposures associated with specific histologic types of lung cancer. Although adenocarcinoma now predominates and small cell carcinoma is quite unusual in persons who have never smoked, specific types of lung cancer have been associated with a few occupational exposures (e.g., chloromethyl ethers and small cell undifferentiated carcinomas) (NRC 1991, 1999; Churg 1994). Smoking has been shown to cause each of the major histologic types, although a dose-response relationship with the number of cigarettes smoked varies across types, being steepest for small cell carcinoma (Morabia and Wynder 1991; Wu-Williams and Samet 1994).

In the initial decades of the smoking-induced lung cancer epidemic, squamous cell carcinoma was most frequently observed in smokers, followed by small cell carcinoma. In the late 1970s, the first evidence of a shift toward a predominance of adenocarcinoma was noted (Vincent et al. 1977; Churg 1994), and now adenocarcinoma of the lung is the most common histologic type (Travis et al. 1995; Wingo et al. 1999). Among men, the decline in lung cancer incidence and mortality rates in the United States has been more rapid for squamous cell and small cell carcinomas than for adenocarcinoma, which is just beginning to show a lower incidence (Figure 2.5) (Wingo et al. 1999). Among women, the SEER data for 1973–1996 indicate that the incidence of squamous cell, small cell, and large cell carcinomas has plateaued, while the rate for adenocarcinoma is still rising (Wingo et al. 1999).

Although changing patterns of diagnosing and classifying lung cancers could have led to these alterations over time, most observers have set aside such an artifactual change (Churg 1994; Thun et al. 1997a). Beginning in the 1970s, new techniques for diagnosing lung cancer became available, including the fiberoptic bronchoscope and thin-needle aspiration (Thun et al. 1997b); improved stains for mucin, the hallmark of adenocarcinoma, were also introduced.

Figure 2.5   Cancer of the lung and bronchus: Surveillance, Epidemiology, and End Results (SEER) incidence rates by histologic type, gender, race, and ethnicity, all ages, 1973–1996
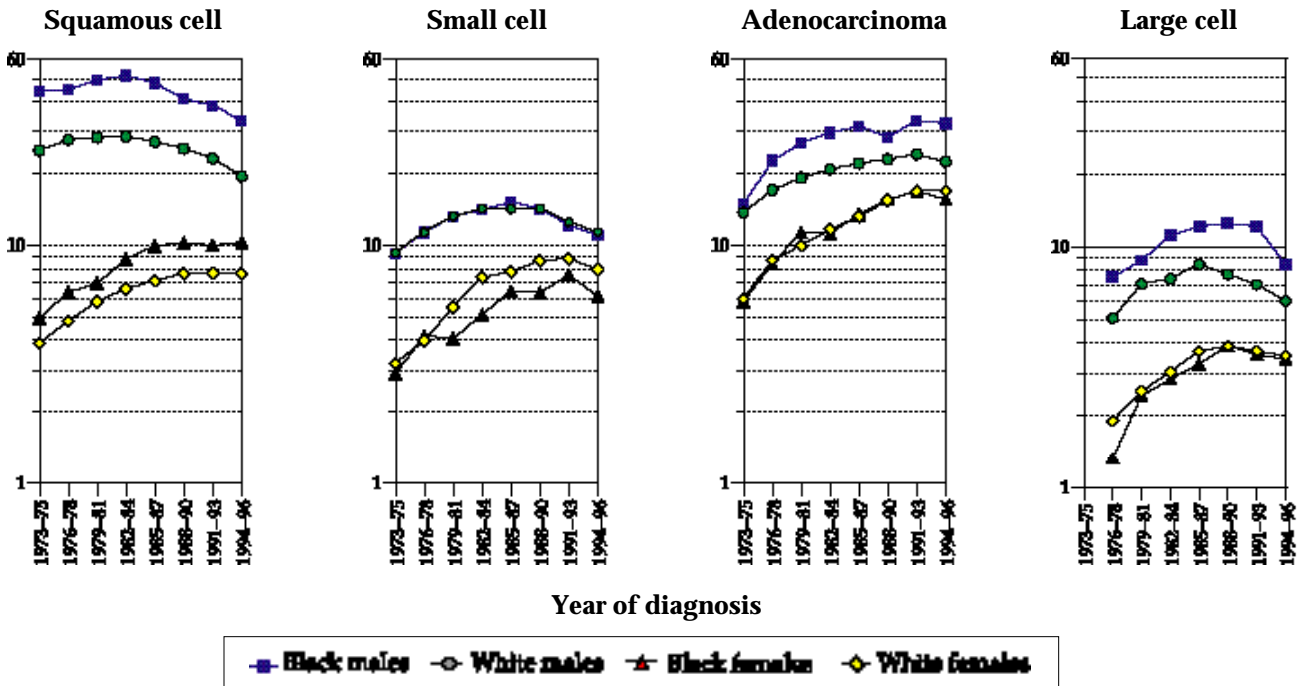
Note: Rates are per 100,000 (log scale) and are age-adjusted to 1970 U.S. standard million population.
Source: Wingo et al. 1999, p. 681. Reprinted with permission.

Using data from the Connecticut Tumor Registry, Thun and colleagues (1997b) showed that the increase in adenocarcinoma antedated these diagnostic innovations.

Hypotheses concerning the shift in histopathology have focused on the potential role of changes in the characteristics of cigarettes and consequent changes in the inhaled doses of carcinogens (Wynder and Muscat 1995; NCI 1996; Hoffmann and Hoffmann 1997). Puff volume may have increased over the decades with the possibility that patterns of deposition in the lung have changed, tending toward enhanced deposition of tobacco smoke in the peripheral airways and alveoli (Hoffmann and Hoffmann 1997). Nitrate levels, which enhance the combustion of tobacco, also may have increased. Although more complete combustion decreases the concentrations of polycyclic aromatic hydrocarbons, the increased production of nitrogen oxides contributes to increases in the formation of tobacco-specific nitrosamines. An increase in the dose of the potent tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) has been postulated as one factor leading to the increase in adenocarcinomas (Hoffmann and Hoffmann 1997; Hecht 1999). NNK induces lung carcinomas in mice, predominantly adenomas and adenocarcinomas, regardless of the route of administration (Hecht 1999).

Few studies can provide data to test these hypotheses because of the need for longitudinal observations of lung cancer risks in relation to the characteristics of the cigarettes smoked over time. Thun and colleagues (1997b) compared risks for lung cancers of the different histologic types among CPS-I and CPS-II participants. They found markedly increasing risks associated with smoking for adenocarcinoma of the lung in both men and women over the approximately 20 years separating the two studies. The authors concluded that "The increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances" (p. 1580).

Evidence Synthesis

There is now a massive body of evidence on lung cancer and smoking, with repeated confirmation of the causal link between smoking and lung cancer. The quickly expanding body of evidence at the molecular level exemplifies the growing understanding of the changes in cells as they transform from normal to malignant. Carcinogenesis caused by tobacco smoke has been extensively investigated at the molecular and cellular levels; substantial investigative efforts have been directed at lung cancer and cancers of the oropharynx, esophagus, and larynx ("aerodigestive cancers"). Smokers are at substantially increased risks for cancers at these sites, and tissues can be accessed for investigation without difficulty. The findings of this research show that the effects of tobacco smoke on cellular DNA are quite consistent with the current conceptual model of carcinogenesis—a multistep process of genetic change.

Although the conclusion of the 1964 Surgeon General's report (USDHEW 1964) that smoking causes lung cancer was solidly grounded in epidemiologic and toxicologic data, this new evidence is completing the mechanistic foundation of that conclusion. Comparable investigations of other smoking-caused cancers show similar patterns of genetic changes in organs of smokers.

The risk of lung cancer varies strongly with duration of smoking and with the number of cigarettes smoked. For those who successfully quit, the RR declines as the interval of not smoking lengthens, in comparison with those who continue to smoke. By comparison, the characteristics of the cigarettes smoked, primarily indicated by the presence or absence of a filter and machine-measured tar and nicotine yields, have at most a small effect on risk. The net consequence of products with lower yields may be a detriment to public health, if their availability unfavorably affects decisions to start or stop smoking.

Conclusions

The scope of the evidence on cigarette smoking and lung cancer is extraordinary. Epidemiologists continue to refine the characterization of the risks from smoking, rapidly gaining new insights concerning respiratory carcinogenesis from the application of increasingly informative modern cellular and molecular biology techniques. This chapter has not covered the full sweep of this extensive evidence. Even the

selected review presented here, however, is sufficient to support additional conclusions about smoking and lung cancer, particularly in relation to key issues that have emerged since prior reviews. These conclusions are as follows:

1. The evidence is sufficient to infer a causal relationship between smoking and lung cancer.

2. Smoking causes genetic changes in cells of the lung that ultimately lead to the development of lung cancer.

3. Although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined.

4. Adenocarcinoma has now become the most common type of lung cancer in smokers. The basis for this shift is unclear but may reflect changes in the carcinogens in cigarette smoke.

5. Even after many years of not smoking, the risk of lung cancer in former smokers remains higher than in persons who have never smoked.

6. Lung cancer incidence and mortality rates in men are now declining, reflecting past patterns of cigarette use, while rates in women are still rising.

Implications

Lung cancer is the leading cause of cancer death in the United States, and cigarette smoking causes most cases. In spite of gains in understanding respiratory carcinogenesis and the potential of molecular and imaging techniques to screen for lung cancer, smoking prevention and cessation remain the fundamental strategies for controlling the lung cancer epidemic. The evidence shows that changes in the design of cigarettes intended to reduce tar and nicotine yields have had no significant beneficial consequences for lung cancer risks in smokers. Although sustained smoking cessation does reduce the risk in former smokers, the level of risk never declines to that of persons who have never smoked. Only the prevention of smoking can stop the epidemic of lung cancer.

Laryngeal Cancer

Unlike lung cancer, the majority of laryngeal cancer cases can be successfully treated and the current five-year survival rate is 65 percent (Ries et al. 2003). Nonetheless, in 2003 an estimated 3,800 deaths were expected to occur from laryngeal cancer among an estimated 9,500 incident cases (ACS 2003).

Conclusions of Previous Surgeon General's Reports

As early as the 1964 Surgeon General's report, smoking was identified as a cause of lung cancer and cancer of the larynx (USDHEW 1964). Since 1964, other reports of the Surgeon General have covered the extensive evidence supporting the conclusion that smoking causes cancer of the larynx (USDHHS 1980, 1982, 1990).

Biologic Basis

The larynx is directly exposed to carcinogens in tobacco smoke as inhaled smoke passes through the glottis, the space between the vocal chords. Most laryngeal cancers are of the squamous cell type.

Epidemiologic Evidence

Many recent studies have grouped laryngeal cancers, along with cancer of the oral cavity and pharynx, in an umbrella category of "upper aerodigestive cancers." From an epidemiologic perspective, these cancers have a comparable relationship with cigarette smoking.

Table 2.3 includes selected recent studies that provide findings for laryngeal cancer alone. These results show that smoking remains a strong cause of laryngeal cancer. As with lung cancer, the RR rises sharply with the duration of smoking and number of cigarettes smoked, and falls after successful cessation. In some studies, for the strata with the greatest number of cigarettes smoked the RRs are 20 or more, compared with lifetime nonsmokers.

Evidence Synthesis

For laryngeal cancer, alcohol consumption is also an independent risk factor that acts synergistically with cigarette smoking. The synergism between smoking and alcohol consumption as a cause of laryngeal cancer has been well documented in many earlier studies (Table 2.4) (IARC 2002). The case-control study carried out in Brazil by Schlecht and colleagues (1999b) shows this synergism, with the RRs for cigarette consumption increasing with increasing levels of ethanol intake.

There is a long-standing conclusion that smoking causes laryngeal cancer. The evidence remains consistent with this conclusion.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and cancer of the larynx.

2. Together, smoking and alcohol cause most cases of laryngeal cancer in the United States.

Implications

Fortunately, therapeutic advances provide the possibility of cure to many people with laryngeal cancer. Nonetheless, almost all cases reflect the use of tobacco and alcohol and could be prevented.

Oral Cavity and Pharyngeal Cancers

An estimated 27,700 new cases and 7,200 deaths from cancers of the oral cavity and pharynx were expected to occur in the United States in 2003 (ACS 2003). Incidence rates are more than twice as high in men as in women. Age-adjusted incidence rates per 100,000 for 1996–2000 in areas of the SEER Program were highest among black men (20.5), intermediate among white men (16.0), and lowest among black (6.4) and white (6.5) women (Ries et al. 2003). Internationally, death rates from cancers of the oral cavity and pharynx vary more than 100-fold across countries (IARC 2003). The highest rates occur among men in the western Pacific region and Sri Lanka, where tobacco is chewed in combination with betel. In these regions, mortality rates exceed incidence rates among black men in the United States. The type of tobacco used and whether there is also regular alcohol intake influence the location of cancers within the oral cavity and pharynx. In New Guinea, Sri Lanka, and India, tumors occur predominantly in the oral cavity where the betel quid is held. In France, men who smoke cigarettes and drink alcohol develop mostly cancers of the pharynx (Blot et al. 1996).

Conclusions of Previous Surgeon General's Reports

Many Surgeon General's reports on smoking and health since 1964 have considered the role of tobacco smoking and/or smokeless tobacco as a cause of cancers of the oral cavity and pharynx. The conclusions of these reports have become progressively more definite over time. The conclusion has been reached that all forms of tobacco use cause these cancers, and malignancies from tobacco use can involve any part of the oral cavity and pharynx except the salivary glands. Key conclusions from the reports are chronologically presented below:

> The causal relationship of the smoking of pipes to the development of cancer of the lip appears to be established. Although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their causal implications cannot at present be stated (USDHEW 1964, pp. 204–5).

> With the exception of the pipe-lip cancer relations there are too few cases related to the individual parts of the buccal cavity to evaluate each independently, and data are inadequate on the interaction of smoking with other factors (USDHEW 1967, p. 35).

> It is clear that people who use tobacco have higher rates of oral cancer than those who do not. Research is needed to identify the dose relationships, to determine whether or not there are dosage thresholds, and to clarify the relationships between dosage, style of tobacco use, and part of the mouth affected. . . .For patients with oral cancer. . . .cessation of tobacco use can make an important contribution to reducing the risk of a new primary cancer (USDHEW 1968, p. 101).

> Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity (USDHEW 1972, p. 67).

> Prospective and retrospective studies have shown an association between mortality for oral cancer and tobacco usage in men and women. This association has been demonstrated for all different modes of tobacco usage—cigarette and pipe/cigar smoking, tobacco and snuff chewing, reverse smoking, and "pan" chewing. Several studies have

shown that the development of recurrent oral cancers has a highly significant correlation with continued smoking. Tobacco usage may act in concert with alcohol consumption to increase the risk of development of oral cancer. The association between tobacco use and oral cancer in both men and women has been demonstrated for Caucasian, Indian, and Asian populations. Epidemiologic data suggest that premalignant lesions in the oral cavity (e.g., leukoplakia) are associated with tobacco usage. Results from experimental studies indicate that cigarette smoke may contain tumor promoters active in oral carcinogenesis and is a promoting agent in the hamster cheek pouch (USDHEW 1974, pp. 52–3).

Epidemiological studies indicate that smoking is a significant causal factor in the development of cancer of the oral cavity. Dose-response relationships with the number of cigarettes smoked per day have been described. The use of pipes, cigars, and chewing tobacco is associated with the development of cancer of the oral cavity. The risk of using these forms is of the same general magnitude as that of using cigarettes. There is a synergism between cigarette smoking and alcohol use and the development of cancer of the oral cavity. The use of alcohol and tobacco results in a higher risk of developing cancer than that resulting from the use of either substance alone (USDHEW 1979, p. 5-42).

Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker. Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking. Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers. Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum (USDHHS 1982, pp. 89–90).

Tobacco use is a major cause of oral cancer. An exposure-response relationship has been identified between the amount of tobacco consumed and the risk of cancer of the oral cavity after considering the effects of alcohol consumption. The proportion of 1985 oral cancer deaths attributable to cigarette smoking in the United States has been estimated to be 92 percent for men and 61 percent for women (USDHHS 1990, p. 147).

Biologic Basis

Cancers of the oral cavity and pharynx predominantly are epithelial in origin, and approximately 90 percent are classified as squamous cell carcinomas (Silverman 1998). Most oral cancers are preceded by the progressive development of premalignant changes and dysplasia, as normal mucosa is transformed into in situ and ultimately invasive carcinoma. Classic precursor lesions include leukoplakia (raised white patches on the oral mucosa that measure at least 5 mm and cannot be scraped off) and erythroplasia (leukoplakia with an erythematous, or red, component) (Silverman 1998). Areas of leukoplakia and carcinoma in situ often surround invasive carcinomas.

Among tobacco users, premalignant lesions may regress after the discontinuation of smoking or stopping smokeless tobacco use (Martin et al. 1999), but can become more dysplastic with continued exposures. Smoking cessation decreases the risk of second or multiple primary tumors in patients with a previous cancer of the oral cavity or pharynx (Moore 1965). The leukoplakia that occurs in cigarette smokers differs morphologically from the keratoses caused by smokeless tobacco; although less common, the leukoplakia induced by cigarettes is more susceptible to malignant transformations (Bouquot 1994).

Underlying the progression from healthy mucosa to invasive and metastatic carcinoma is the accumulation of genetic mutations that disrupt the normal control of cell growth (Califano et al. 1996). Chromosomal loss at 9p21 is the most common genetic change in oral cavity cancers and in other head and neck tumors. This loss is accompanied by the inactivation of the *p16INK4a* gene caused by various mechanisms including promoter methylation, point mutation, and

homozygous deletion (Reed et al. 1996). A second critical tumor suppressor gene also resides at 9p21 ($p14^{ARF}$), and functional studies have suggested that ARF binds to MDM2, leading to a decrease in $p53$ degradation and a subsequent increase in $p53$ levels. The 3p21 region is frequently lost in oral cancer, with the exact target of this loss yet to be identified. Approximately 50 percent of all primary head and neck squamous cell carcinomas harbor $p53$ mutations and have diminished $p53$ tumor suppressor activity. Amplification of the *cyclin D1* gene on chromosome 11q13 occurs in about 30 percent of these tumors, resulting in increased activity of the gene. Abnormal cell cycling through p16 inactivation or *cyclin D1* overexpression may be a consistent genetic alteration in a majority of head and neck squamous cell carcinomas.

Several of these genetic alterations correlate with the malignant progression in oral leukoplakia. Loss of heterozygosity at the genetic loci 3p14-21 or 9p21 is virtually essential for this progression (Mao et al. 1996; Lee et al. 2000; Partridge et al. 2000; Rosin et al. 2000). Moreover, inactivation of the $p53$ gene, multiple chromosomal losses, and chromosomal polysomy are associated with a high likelihood of progression to invasive cancer. Mutations of the $p53$ gene occur commonly in leukoplakia among tobacco users, but not in premalignant oral lesions in nontobacco users (Lazarus et al. 1995). Several genetic changes appear to be more common in tumors from smokers compared with those from nonsmokers; $p53$ mutations appear to increase with the number of cigarettes smoked and are augmented by alcohol intake (Brennan et al. 1995). Moreover, several chromosomal losses described in the progression of head and neck cancers appear to be more common in the tumors of smokers compared with those of nonsmokers (Brennan et al. 1995; Koch et al. 1999).

Clones of genetically damaged cells can extend beyond the microscopically visible premalignant or malignant lesions in head and neck cancers (Sidransky 2001). These clones are probably responsible for the high frequency of second primary tumors in this disease and the high incidence of local regional recurrence. Westra and Sidransky (1998) have proposed that molecular tests be used to identify genetically abnormal but phenotypically normal cells at the margins of surgically resected head and neck cancers to reduce tumor recurrence.

Several carcinogens and metabolites from tobacco have been measured in saliva and oral mucosa as well as in the urine and blood of smokers and smokeless tobacco users. In male university students who used smokeless tobacco, urinary excretion of metabolites of tobacco-specific nitrosamines correlated with the presence of leukoplakia (Kresty et al. 1996). Similar compounds have been documented in the saliva of smokeless tobacco users (Hoffmann and Adams 1981; Brunnemann and Hornby 1987; Osterdahl and Slorach 1988; Idris et al. 1992; Stich et al. 1992) and as hemoglobin adducts in this population (Carmella et al. 1990; Falter et al. 1994; Murphy et al. 1994). Abnormal methylation of DNA occurred in rat oral tissue incubated with tobacco-specific nitrosamines (Hecht and Hoffmann 1988). The reduced capacity to repair DNA damage caused by benzo[*a*]pyrene diol epoxide (Cheng et al. 1998; Wang et al. 1998) and genetic polymorphisms of glutathione *S*-transferase have been proposed as potential markers of susceptibility to tobacco-induced carcinogenicity.

Animal models of tobacco carcinogenicity for the oral cavity and pharynx are limited. In experiments on hamsters, topical application of benzo[*a*]pyrene to the cheek pouch mucosa induced cancers of the oral cavity (Chen et al. 1994). Injecting tobacco smoke condensates into the gingiva of rabbits induced leukoplakia (USDHEW 1964).

Epidemiologic Evidence

This section includes published studies (in English), identified with a comprehensive search strategy, that provide separate data for lifetime nonsmokers and current and former cigarette smokers. If multiple follow-ups have been reported on the same cohort, data from the longest follow-up are presented unless otherwise stated. To identify studies, the MEDLINE database was searched (from January 1966 to July 2000) using the medical subject headings "tobacco," "smoking," "head and neck neoplasms," "mouth neoplasms," "lip neoplasms," "pharyngeal neoplasms," "oropharyngeal neoplasms," and "stomatognathic system." References cited in published original and review articles were also examined.

Nine cohort studies (Hammond 1966; Weir and Dunn 1970; Carstensen et al. 1987; Hirayama 1990; Doll et al. 1994; McLaughlin et al. 1995a; Engeland et al. 1996; Knekt et al. 1999; ACS, unpublished data) and 10 case-control studies (Vincent and Marchetta 1963; Keller and Terris 1965; Kono et al. 1987; Blot et al. 1988; Franceschi et al. 1992; Mashberg et al. 1993; Muscat et al. 1996; Levi et al. 1998; Schildt et al. 1998; La Vecchia et al. 1999) have measured the association between current and former cigarette smoking and the incidence of or death from cancers of the oral cavity or pharynx. Not all of these studies separated pipe and cigar smoking from cigarette smoking (Vincent and Marchetta 1963; Hammond 1966; Weir and Dunn 1970; Carstensen et al. 1987; Hirayama 1990; Engeland et al. 1996; Schildt et al. 1998) or distinguished between current and former smokers (Keller and Terris 1965; Hammond 1966; Weir and Dunn 1970; Kono et al. 1987; Blot et al. 1988; La Vecchia and Negri 1989; Hirayama 1990). Because of the rarity of these cancers among lifetime nonsmokers, some studies include "occasional" or "light" cigarette smokers in the referent group (Mashberg et al. 1993) or combine cancers of the oral cavity, pharynx, larynx, and esophagus (Hammond 1966; Carstensen et al. 1987; Doll et al. 1994; Engeland et al. 1996; Knekt et al. 1999). Tables 2.5 through 2.8 include only studies that reported data separately for current or former cigarette smokers or lifetime nonsmokers, and that included only cancers of the oral cavity or pharynx.

Table 2.5 shows the results of two cohorts, the United States veterans study (McLaughlin et al. 1995a) and CPS-II (ACS, unpublished data), and four case-control studies (Franceschi et al. 1992; Muscat et al. 1996; Levi et al. 1998; La Vecchia et al. 1999) that met the above criteria for inclusion and provided results by smoking status. The RR estimates among male current smokers compared with lifetime nonsmokers ranged from 3.6 to 11.8 (Franceschi et al. 1992) for cancers within the oral cavity, and up to 14.1 (McLaughlin et al. 1995a) for cancers of the pharynx. Risk was higher among current than former smokers in all studies. The RR of death from any cancer of the oral cavity or pharynx in CPS-II was 9.3 (95 percent confidence interval

[CI], 6.4–13.5) among male current smokers and 4.9 (95 percent CI, 3.5–6.8) among female current smokers who were followed from 1982–1996 (ACS, unpublished data). These numbers are likely to be underestimates of the true risk of continuing to smoke, because many persons classified as current smokers at enrollment into the study will have quit during the 14-year follow-up period.

Table 2.6 shows the increase in RR associated with the number of cigarettes smoked per day among current smokers. Relative risk estimates increased with the amount smoked in all of the studies, although the magnitude of the estimates varied almost 20-fold according to the cancer subsite and the number of cigarettes smoked. In general, the risk was associated more strongly with the number of cigarettes smoked daily by current smokers (Table 2.6) than with cumulative tar exposures or pack-years[1] of smoking (Muscat et al. 1996).

In most studies, the risk of cancer of the oral cavity and pharynx among former smokers decreases rapidly after smoking cessation compared with the risk among continuing smokers (Table 2.7). A substantial decrease in risk occurs in the first 10 years after quitting. Two of the largest case-control studies (La Vecchia et al. 1999; Schlecht et al. 1999a) suggest that the RR may decrease more slowly in former smokers for oral cancer than for pharyngeal cancer. Even the largest studies have few cases and wide CIs within each stratum.

The combination of cigarette smoking and alcohol consumption substantially and synergistically increases the risk of oropharyngeal cancer compared with the risk of either alone. For example, in the population-based case-control study by Blot and colleagues (1988) (Table 2.8), men who smoked two or more packs of cigarettes daily for 20 or more years but drank less than one alcoholic beverage per week experienced a risk approximately seven times higher than nonsmokers who were light drinkers. The combination of prolonged smoking of at least two packs daily and drinking 30 or more alcoholic drinks per week is associated with a RR of almost 38 in men and nearly 108 in women.

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[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Evidence Synthesis

Numerous epidemiologic studies provide consistent evidence that cigarette smokers experience a higher incidence of or mortality from cancers of the oral cavity and pharynx than do lifetime nonsmokers. The average risk among persons who currently smoke and have smoked only cigarettes is approximately 10-fold higher in men and 5-fold greater in women compared with lifetime nonsmokers. Incidence and mortality rates increase with the number of cigarettes smoked per day and decrease with years since smoking cessation. All forms of tobacco use (cigarettes, pipes, cigars, snuff, chewing tobacco, betel, and other smoked and smokeless products) increase the occurrence of premalignant lesions and malignant transformations of cells of the tissues of the oral cavity and pharynx, which have the most direct contact with the tobacco, the smoke, or their dissolved constituents. Eliminating the exposure causes most premalignant lesions to regress and reduces the incidence and recurrence of and mortality from invasive cancers of the oral cavity and pharynx. Extensive series of studies have documented genetic changes in the epithelium of smokers, even before the development of malignancy. There are increasing genetic alterations in the sequence from premalignant lesions to malignancy.

Experimental studies in animals cannot precisely replicate human exposures to cigarette smoke, yet the topical application or local injection of tobacco carcinogens induces premalignant leukoplakia in rabbits and oral cavity cancers in hamsters.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and cancers of the oral cavity and pharynx.

Implications

Cigarette smoking, like other forms of tobacco use, is a major cause of cancers of the oral cavity and pharynx in the United States and worldwide. Together, smoking and alcohol account for most cases in the United States and elsewhere. Reductions in smoking (cigarettes, pipes, cigars, and other tobacco products) and in the use of smokeless tobacco could prevent most of the approximately 30,200 new cases and 7,800 deaths from these cancers that occur annually in the United States and the much larger burden of these cancers worldwide.

Table 2.3   Case-control studies on the association between tobacco use and the risk of laryngeal cancer

Study	Population	Tobacco exposure
Sankaranarayanan et al. 1990	191 male laryngeal cancer cases 549 male hospital controls Kerala, Southern India 1983–1984	• Pan tobacco chewing (pan tobacco is a mixture of betel leaf, sliced fresh/dry arecanut, and aqueous lime plus native-cured tobacco leaves/stems) • Bidi smoking (bidi is a local cigarette made by rolling coarse tobacco in a dried temburni leaf) • Cigarette smoking • Bidi and cigarette smoking • Snuff inhalation (snuff is a fine home-ground tobacco powder)

*CI = Confidence interval.
†OR = Odds ratio.

Findings	Risk estimates (95% CI)*	Comments

• There was a significant positive association with bidi smoking and a positive association with cigarette smoking and snuff inhalation	**Pan chewing**
	Never smoked
	  OR[†] = 1.0 (referent)
	<5 times/day
	  OR = 0.69 (0.38–1.24)
	5–9 times/day
	  OR = 0.67 (0.39–1.15)
	 10 times/day
	  OR = 0.73 (0.36–1.46)
	
	Bidi smoking
	Never smoked
	  OR = 1.0 (referent)
	 10/day
	  OR = 1.79 (1.09–2.92)
	11–20/day
	  OR = 2.13 (1.29–3.51)
	 21/day
	  OR = 5.09 (2.69–9.63)
	
	Cigarette smoking
	No
	  OR = 1.0 (referent)
	Yes
	  OR = 1.37 (0.77–2.42)
	
	Bidi and cigarette smoking
	Never smoked
	  OR = 1.0 (referent)
	 10/day
	  OR = 0.33 (0.09–1.10)
	11–20/day
	  OR = 2.94 (1.54–5.58)
	 21/day
	  OR = 4.29 (2.50–7.34)
	
	Snuff inhalation
	No
	  OR = 1.0 (referent)
	Yes
	  OR = 1.24 (0.31–4.88)
		ORs were calculated using unconditional logistic regression; risk estimates were adjusted for age and religion

Table 2.3   Continued

Study	Population	Tobacco exposure
Ahrens et al. 1991	Hospital-based 100 prevalent male laryngeal cancer cases 100 male hospital controls Germany 1986–1987	• Years since smoking cessation
Zatonski et al. 1991	Population-based 249 male incident cases of laryngeal cancer 965 male controls chosen from electoral rolls Poland 1986–1987	• Cigarettes/day • Age at smoking initiation • Years since cessation
Maier et al. 1992	Hospital-based 164 male cases of laryngeal cancer 656 male outpatient clinic controls Germany 1988–1989	• According to tobacco-years (1 tobacco-year = 20 cigarettes/day, 4 cigars/day, or 5 pipes/day for 1 year)

[‡]RR = Relative risk.

Findings	Risk estimates (95% CI)	Comments

• Risk decreased with years of cessation, p <0.01 for linear trend	Never smoked
	  OR = 1.0 (referent)
	Current smoking
	  OR = 3.8 (0.96–14.66)
	1–5 years of cessation
	  OR = 2.4 (0.45–12.90)
	6–15 years of cessation
	  OR = 1.4 (0.28–7.43)
	  16 years of cessation
	  OR = 0.9 (0.17–4.25)
		ORs were calculated using unconditional logistic regression, and were adjusted for age

• Dose-response relationship, but no p value for trend was provided	Cigarettes/day
	0–5 cigarettes/day
	  RR = 1.0 (referent)
	6–10 cigarettes/day
	  RR = 8.4 (1.5–46.0)
	11–15 cigarettes/day
	  RR = 18.1 (3.9–83.2)
	16–20 cigarettes/day
	  RR = 29.9 (7.0–128)
	21–30 cigarettes/day
	  RR = 33.7 (7.6–150)
	>30 cigarettes/day
	  RR = 59.7 (13.0–274)
	
	Age at smoking initiation
	<16 years
	  RR = 1.28 (0.74–2.23)
	16–22 years
	  RR = 1.0 (referent)
	>22 years
	  RR = 0.60 (0.30–1.19)
	
	  Years since cessation
	Current smokers
	  RR = 1.0 (referent)
	5–10 years
	  RR = 0.76 (0.32–1.80)
	>10 years
	  RR = 0.60 (0.30–1.19)
		RRs were calculated using unconditional logistic regression, and were adjusted for age, residence, and educational level

• Dose-response relationship with a 9-fold increase in risk in heavy smokers, but no p value for trend was provided	<5 tobacco-years
	  RR = 1.0 (referent)
	5–50 tobacco-years
	  RR = 2.6 (1.63–3.99)
	>50 tobacco-years
	  RR = 9.0 (5.21–15.53)
		RRs were calculated using logistic regression models

Table 2.3   Continued

Study	Population	Tobacco exposure
Zheng et al. 1992	Population-based 201 incident laryngeal cancer cases 414 population controls Shanghai, China 1988–1990	• Duration of smoking • Average number of cigarettes/day • Pack-years[§]
Tavani et al. 1994	Hospital-based 367 incident cases of laryngeal cancer (350 men) 1,931 hospital controls (1,373 men) Northern Italy 1986–1992	• Never smoked • Moderate smokers (currently smoking <15 cigarettes/day; pipe, cigar, and former smokers) • Heavy smokers (currently smoking 15 cigarettes/day)

[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings	Risk estimates (95% CI)	Comments

• Significant dose-response relationship for duration of smoking (p <0.01), cigarettes/day (p <0.01), and pack-years (p <0.01)	**Duration of smoking**
	<20 years
	  OR = 1.4 (0.4–4.6)
	20–29 years
	  OR = 4.1 (1.6–11.1)
	30–39 years
	  OR = 12.0 (4.8–30.1)
	  40 years
	OR = 13.2 (5.6–31.2)
	
	Cigarettes/day
	<10 cigarettes/day
	  OR = 1.6 (0.5–4.9)
	10–19 cigarettes/day
	  OR = 7.1 (3.1–16.6)
	20 cigarettes/day
	  OR = 12.4 (4.6–33.2)
	>20 cigarettes/day
	  OR = 25.1 (9.9–63.2)
	
	Pack-years
	<10 pack-years
	  OR = 1.4 (0.4–4.5)
	10–19 pack-years
	  OR = 2.9 (1.1–7.9)
	20–29 pack-years
	  OR = 3.1 (1.1–8.6)
	30–39 pack-years
	  OR = 15.4 (6.0–39.6)
	  40 pack-years
	OR = 25.1 (10.3–61.2)
		ORs were calculated using unconditional logistic regression, and were adjusted for age and education

• Significant dose-response relationship (p <0.0001)	**Men**
	Never smoked
	  RR = 1.0 (referent)
	Moderate smokers
	  RR = 3.5 (2.1–6.0)
	Heavy smokers
	  RR = 10.4 (6.2–17.5)
		RRs were calculated using multivariate unconditional logistic regression, and were adjusted for center, age, and education

Table 2.3   Continued

Study	Population	Tobacco exposure
Dosemeci et al. 1997	Hospital-based 832 male laryngeal cancer cases 829 male controls with selected other cancers Turkey 1979–1984	• Cigarettes/day • Duration of smoking • Pack-years
Maier and Tisch 1997	Hospital-based 164 male cases of laryngeal cancer 656 male outpatient clinic controls Germany 1988–1989	• 1 tobacco-year = 20 cigarettes/day, 4 cigars/day, or 5 pipes/day for 1 year

Findings	Risk estimates (95% CI)	Comments

• Significant dose-response relationship for cigarettes/day (p <0.001), duration of smoking (p <0.001), and pack-years (p <0.001)	Cigarettes/day
	1–10 cigarettes/day
	  RR = 1.1 (0.6–1.9)
	11–20 cigarettes/day
	  RR = 4.8 (3.1–7.4)
	 21 cigarettes/day
	  RR = 4.1 (2.8–6.0)
	
	Duration of smoking
	1–10 years
	  RR = 1.1 (0.6–1.9)
	11–20 years
	  RR = 4.8 (3.1–7.4)
	 21 years
	  RR = 4.1 (2.8–6.0)
	
	Pack-years
	1–10 pack-years
	  RR = 1.9 (1.3–3.0)
	11–20 pack-years
	  RR = 4.4 (2.9–6.7)
	 21 pack-years
	  RR = 6.0 (3.8–9.5)
		ORs were calculated using Gart's Method, and were adjusted for age and alcohol use

• Dose-response relationship, but no p value for trend was provided
• 9.5-fold increase in risk in heavy smokers (more than 100 tobacco-years)
	<5 tobacco-years
	  RR = 1.0 (referent)
	5–19 tobacco-years
	  RR = 4.0 (1.7–9.2)
	50–74 tobacco-years
	  RR = 6.3 (3.0–13.3)
	75–99 tobacco-years
	  RR = 7.8 (3.6–16.7)
	 100 tobacco-years
	  RR = 9.5 (4.6–19.6)
		RRs were calculated using logistic regression, and were adjusted for alcohol consumption; risk estimates were not provided for 20–49 tobacco-years

Table 2.3   Continued

Study	Population	Tobacco exposure
Schlecht et al. 1999a	Hospital-based 784 incident cases of upper ADT cancers (386 laryngeal cancer cases) 1,578 hospital controls matched for gender, age, and quarter of admission Brazil 1986–1989	• Years since smoking cessation • Type of tobacco smoked, in pack-years: 1 pack = 20 manufactured cigarettes = 4 hand rolled, black tobacco cigarettes = 4 cigars = 5 pipefuls with regular pipe tobacco

ADT = Aerodigestive tract.

Findings	Risk estimates (95% CI)	Comments

• After 15 years of cessation, RRs for former smokers decreased to near baseline levels	<u>Years since smoking cessation (all tobacco types)</u>
	Never smoked
	  RR = 1.0 (referent)
	Current smokers
	  RR = 11.7 (4.4–31.5)
	  1 year
	  RR = 10.5 (3.0–36.6)
	2–5 years
	  RR = 7.7 (2.4–25.2)
	6–10 years
	  RR = 2.7 (0.8–9.6)
	11–15 years
	  RR = 5.9 (1.4–24.2)
	16–20 years
	  RR = 1.5 (0.3–8.6)
	>20 years
	  RR = 3.1 (1.0–9.4)
	
	  <u>Type of tobacco</u>
	Never smoked
	  RR = 1.0 (referent)
	Filter-tipped cigarettes
	  RR = 8.4 (3.1–22.8)
	Unfiltered cigarettes
	  RR = 12.2 (4.1–35.9)
	
	<u>Commercial cigarettes</u>
	1–20 pack-years
	  RR = 8.2 (3.0–22.6)
	21–40 pack-years
	  RR = 9.4 (3.0–22.6)
	>40 pack-years
	  RR = 16.3 (5.3–49.87)
	
	  <u>Black tobacco</u>
	1–20 pack-years
	  RR = 7.3 (2.4–22.4)
	21–40 pack-years
	  RR = 8.9 (2.9–27.2)
	>40 pack-years
	  RR = 8.5 (3.0–23.9)
	
	  <u>Pipes</u>
	1–20 pack-years
	  RR = 7.7 (1.4–42.8)
	>20 pack-years
	  RR = 2.4 (0.4–13.1)
		RRs were calculated using conditional logistic regression (matching variables: age, gender, location, and admission period); RRs associated with smoking cessation were adjusted for alcohol and tobacco use; RRs associated with tobacco habits were adjusted for cumulative alcohol and tobacco use, race, beverage temperature, religion, wood stove use, and consumption of spicy foods

Table 2.3   Continued

Study	Population	Tobacco exposure
Schlecht et al. 1999b	Hospital-based 784 incident cases of upper ADT cancers (386 laryngeal cancer cases) 1,578 hospital controls matched for gender, age, and quarter of admission Brazil 1986–1989	• In pack-years (1 pack = 20 manufactured cigarettes = 4 hand rolled, black tobacco cigarettes = 4 cigars = 5 pipefuls with regular pipe tobacco) Alcohol exposure • Lifetime consumption of ethanol in kg • Beer = 5% ethanol • Wine = 10% ethanol • Hard liquor = 50% ethanol

ADT = Aerodigestive tract.

Findings	Risk estimates (95% CI)	Comments

• No statistical evidence of effect modification (p = 0.945)
• Effect of alcohol was most marked only at the highest consumption level among light smokers
• Significant dose-response relationships for both tobacco (p <0.0001) and alcohol (p = 0.0004)
	0–10 kg ethanol
	0–5 pack-years
	  OR = 1.0 (referent)
	6–42 pack-years
	  OR = 13.5 (2.7–66.8)
	>42 pack-years
	  OR = 11.4 (2.1–62.0)
	
	11–530 kg ethanol
	0–5 pack-years
	  OR = 1.2 (0.1–14.4)
	6–42 pack-years
	  OR = 16.1 (3.4–76.2)
	>42 pack-years
	  OR = 22.0 (4.5–107)
	
	>530 kg ethanol
	0–5 pack-years
	  OR = 5.5 (0.4–71.5)
	6–42 pack-years
	  OR = 36.9 (0.7–1,800)
	>42 pack-years
	  OR = 43.1 (9.1–206)
		ORs were calculated using multivariate conditional logistic regression, and were adjusted for race, beverage temperature, religion, wood stove use, and consumption of spicy foods; interaction assessments were based on a multiplicative model; risk estimates only were provided as stratified

Table 2.4   Case-control studies showing interactions between tobacco use, alcohol use, and the risk of laryngeal cancer

Study	Population	Alcohol exposure	Tobacco exposure
Wynder et al. 1976	258 male and 56 female cases with histologic evidence of laryngeal cancer 516 male and 168 female hospital controls matched for gender, year of inter-view, hospital status, and age at diagnosis New York City, Houston, Los Angeles, Birmingham, Miami, New Orleans 1970–1973	• Nondrinkers/occasional drinkers • 1–6 units/day • 7 units/day 1 unit = 1 ounce (oz.) hard liquor = 4 oz. wine = 6 oz. beer	Cigarette equivalents: 0/day 1–15/day 16–34/day 35/day 1 cigar = 5 cigarettes 1 pipe = 2.5 cigarettes

Burch et al. 1981	204 incident cases
	204 community controls matched for neighborhood, gender, and age
	Ontario, Canada
	1977–1979
		Lifetime consumption (oz.) of ethanol (in thousands):
		 0
		 <10
		 10–25
		  26
			Lifetime cigarette habit (in thousands):
			 0
			 <150
			 150–299
			  300

*CI = Confidence interval.
†RR = Relative risk.
‡SE = Standard error.

Findings/risk estimates (95% CI)*		Comments
Men Nondrinkers	RR[†]	RRs are from a stratified analysis; there was no formal test for interactions
0 cigarettes/day	1.0	
1–15 cigarettes/day	3.0 (1.0–9.1)	
16–34 cigarettes/day	6.0 (2.2–16.1)	
35 cigarettes/day	7.0 (2.5–19.4)	
1–6 alcohol units/day		
0 cigarettes/day		
1–15 cigarettes/day	4.0 (1.0–15.6)	
16–34 cigarettes/day	6.7 (2.3–19.7)	
35 cigarettes/day	10.3 (3.6–29.8)	
7 alcohol units/day		
0 cigarettes/day		
1–15 cigarettes/day	3.3 (0.9–12.8)	
16–34 cigarettes/day	13.8 (5.1–37.7)	
35 cigarettes/day	22.1 (7.8–62.1)	
Alcohol use	RR	RRs are from a logistic regression model; CIs were not provided; the coefficient for the interaction term (-0.10) was not significant (SE[‡] = 0.11, p = 0.177)
0 oz. ethanol		
0 cigarettes	1.0	
<150,000 cigarettes	2.0	
150,000–299,000 cigarettes	3.9	
300,000 cigarettes	7.6	
<10,000 oz. ethanol		
0 cigarettes	2.0	
<150,000 cigarettes	3.5	
150,000–299,000 cigarettes	6.3	
300,000 cigarettes	11.1	
10,000–25,000 oz. ethanol		
0 cigarettes	3.9	
<150,000 cigarettes	6.3	
150,000–299,000 cigarettes	10.1	
300,000 cigarettes	16.3	
26,000 oz. ethanol		
0 cigarettes	7.7	
<150,000 cigarettes	11.2	
150,000–299,000 cigarettes	16.3	
300,000 cigarettes	23.7	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Flanders and Rothman 1982	87 male cases with laryngeal cancer 956 male controls with cancers of other sites (excluding oral cavity, pharynx, esophagus, stomach, lung, small intestine, colon, pancreatic, bronchus, pleura, bladder, and kidney cancers) 7 cities and 2 states (not named) 1969–1971	Alcohol units (1.5 oz. liquor, 6 oz. wine, or 12 oz. beer)	Tobacco units (1 cigarette = 0.2 cigars = 0.4 pipefuls)

Findings/risk estimates (95% CI)	Comments
Lifetime alcohol and tobacco use	Risk estimates are indices of interactions
0–49 alcohol units	(a value of 1.0 indicates no synergy)
0–49 tobacco units	
50–549 tobacco units	
550–899 tobacco units	
900 tobacco units	
50–349 alcohol units	
0–49 tobacco units	
50–549 tobacco units · 0.1	
550–899 tobacco units · 1.8	
900 tobacco units · 1.1	
360–699 alcohol units	
0–49 tobacco units	
50–549 tobacco units · 6.1	
550–899 tobacco units · 0.7	
900 tobacco units · 1.6	
700 alcohol units	
0–49 tobacco units	
50–549 tobacco units · 3.0	
550–899 tobacco units · 0.7	
900 tobacco units · 1.3	
Daily alcohol and tobacco use	
0 alcohol units	
0 tobacco units	
1–14 tobacco units	
15–34 tobacco units	
35 tobacco units	
1–9 alcohol units	
0 tobacco units	
1–14 tobacco units · 2.3	
15–34 tobacco units · 1.2	
35 tobacco units · 1.7	
>9 alcohol units	
0 tobacco units	
1–14 tobacco units · 1.8	
15–34 tobacco units · 3.0	
35 tobacco units · 3.9	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Herity et al. 1982	59 male cases 152 male hospital controls Dublin, Ireland	• Nondrinkers and light drinkers • Heavy drinkers	• Nonsmokers and light smokers • Heavy smokers

Walter and Iwane 1983	87 male cases with laryngeal cancer
	956 male controls with cancers of other sites (excluding oral cavity, pharynx, esophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder, and kidney cancers)
	7 cities and 2 states (not named)
	1969–1971
		Lifetime alcohol consumption:
		  0–49 units
		  50–349 units
		  350–699 units
		   700 units
		
		1 unit = 1.5 oz. liquor = 6 oz. wine = 12 oz. beer
			Lifetime tobacco habit:
			  1–49 units
			  50–549 units
			  550–899 units
			   900 units

§OR = Odds ratio.
 LL = Log-linear model.
¶FL = Flanders and Rothman model.

Findings/risk estimates (95% CI)		Comments
<u>Nondrinkers and light drinkers</u>	<u>RR</u>	RRs are from a stratified analysis; the authors
Nonsmokers and light smokers	1.0	found a synergistic effect between alcohol and
Heavy smokers	3.3 (1.2–9.1)	tobacco (index of interaction = 2.5)
<u>Heavy drinkers</u>	<u>RR</u>	
Nonsmokers and light smokers	4.0 (1.6–9.9)	
Heavy smokers	14.0 (6.3–31.0)	
<u>0–49 alcohol units</u>	<u>OR[§]</u>	This study was a reanalysis of the data from
0–49 tobacco units	LL[§] = 1.0	Flanders and Rothman 1982; ORs are from
	FL =1.0	both the log-linear model (with an interaction
50–549 tobacco units	LL = 1.7	term) and the stratified model of Flanders and
	FL = 1.5	Rothman; risk estimates were adjusted for age;
550–899 tobacco units	LL = 2.6	CIs were not provided
	FL = 3.5	
900 tobacco units	LL = 5.4	
	FL = 7.9	
<u>50–349 alcohol units</u>	<u>OR</u>	
0–49 tobacco units	LL = 1.5	
	FL = 1.1	
50–549 tobacco units	LL = 2.5	
	FL = 1.9	
550–899 tobacco units	LL = 3.8	
	FL = 4.7	
900 tobacco units	LL = 7.9	
	FL = 11.1	
<u>350–699 alcohol units</u>	<u>OR</u>	
0–49 tobacco units	LL = 2.0	
	FL = 2.5	
50–549 tobacco units	LL = 3.3	
	FL = 4.0	
550–899 tobacco units	LL = 5.1	
	FL = 6.8	
900 tobacco units	LL = 10.5	
	FL = 13.3	
<u>>700 alcohol units</u>	<u>OR</u>	
0–49 tobacco units	LL = 3.0	
	FL = 6.1	
50–549 tobacco units	LL = 5.0	
	FL = 9.3	
550–899 tobacco units	LL = 7.9	
	FL = 12.1	
900 tobacco units	LL = 16.2	
	FL = 18.5	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Brownson and Chang 1987	63 white male cases 200 white male controls with colon cancer St. Louis, Missouri 1972–1984	• 0 drinks/day • <2 drinks/day • 2–6 drinks/day • >6 drinks/day	• 0 packs/day • <1 pack/day • 1–2 packs/day • >2 packs/day
De Stefani et al. 1987	107 male cases aged 30–89 years 290 male hospital controls Uruguay 1985–1986	• 0–64 mL/day • 65 mL/day	• 0–15 cigarettes/day • 16 cigarettes/day

Findings/risk estimates (95% CI)		Comments
Drinking	**OR**	ORs are from a logistic regression model; risk estimates were adjusted for age; the numbers of cases and controls were stratified by each drinking and smoking stratum, but only marginal ORs were provided; for joint effects, CIs were not provided; the synergy index used to measure interactions between smoking and alcohol = 1.77 (77% greater than predicted additivity)
0 drinks/day	1.00	
<2 drinks/day	1.72 (0.70–4.24)	
2–6 drinks/day	1.64 (1.08–2.48)	
>6 drinks/day	4.85 (2.82–8.39)	
Smoking	**OR**	
0 packs/day	1.00	
<1 pack/day	2.57 (1.07–6.14)	
1–2 packs/day	3.70 (1.49–9.19)	
>2 packs/day	7.04 (1.31–37.86)	
Joint effects	**OR**	
No smoking or alcohol	1.00	
No smoking with alcohol use	2.37	
Smoking with no alcohol use	3.44	
Smoking and alcohol use	7.73	
0–64 mL alcohol/day	**RR**	RRs are from a stratified analysis; CIs were not provided; there was no formal test for interactions
0–15 cigarettes/day	1.0	
16 cigarettes/day	20.6	
65 mL alcohol/day	**RR**	
0–15 cigarettes/day	16.7	
16 cigarettes/day	123.4	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Guenel et al. 1988	197 glottic and 214 supra-glottic male cancer cases aged >25 years 4,135 male community controls aged 25 years Curie Institute, Paris 1975–1985	• 0–39 g/day • 40–99 g/day • 100–159 g/day • 160 g/day	• 0–9 g tobacco/day • 10–19 g tobacco/day • 20–29 g tobacco/day • 30 g tobacco/day

**df = Degrees of freedom.

Findings/risk estimates (95% CI)		Comments
Cancer of the glottis	RR	RRs are from a stratified analysis; risk esti-mates were adjusted for age; to test deviation from the multiplicative model, a logistic model with cross-product variables of alcohol and tobacco was compared with the simple multi-plicative model (glottis: χ^2 for trend = 10.2, p = 0.33 [9 df**]; supraglottis: χ^2 for trend = 4.78, p = 0.85 [9 df]); these data indicate that the multiplicative model fits well
0–39 g alcohol/day		
0–9 g tobacco/day	1.0	
10–19 g tobacco/day	0.4 (0.2–4.5)	
20–29 g tobacco/day	9.3 (4.9–36.4)	
30 g tobacco/day	19.2 (7.7–58.4)	
40–99 g alcohol/day		
0–9 g tobacco/day	1.6 (0.6–4.1)	
10–19 g tobacco/day	2.9 (1.1–8.0)	
20–29 g tobacco/day	12.3 (4.3–27.5)	
30 g tobacco/day	27.4 (8.4–64.4)	
100–159 g alcohol/day		
0–9 g tobacco/day	2.8 (1.2–15.2)	
10–19 g tobacco/day	15.1 (5.2–43.4)	
20–29 g tobacco/day	26.4 (7.8–62.3)	
30 g tobacco/day	48.9 (16.9–132.8)	
160 g alcohol/day		
0–9 g tobacco/day	5.1 (2.3–53.8)	
10–19 g tobacco/day	40.9 (10.3–191.5)	
20–29 g tobacco/day	125.3 (34.1–367.4)	
30 g tobacco/day	289.4 (83.0–705.8)	
Cancer of the supraglottis	RR	
0–39 g alcohol/day		
0–9 g tobacco/day	1.0	
10–19 g tobacco/day	3.4 (0.6–20.9)	
20–29 g tobacco/day	32.3 (4.4–82.1)	
30 g tobacco/day	46.8 (6.7–152.6)	
40–99 g alcohol/day		
0–9 g tobacco/day	2.6 (0.3–10.4)	
10–19 g tobacco/day	27.5 (2.1–49.8)	
20–29 g tobacco/day	48.5 (6.7–101.0)	
30 g tobacco/day	132.3 (16.6–283.8)	
100–159 g alcohol/day		
0–9 g tobacco/day	7.3 (1.6–57.3)	
10–19 g tobacco/day	75.4 (8.4–187.0)	
20–29 g tobacco/day	180.7 (27.3–415.2)	
30 g tobacco/day	530.6 (77.7–1,175.7)	
160 g alcohol/day		
0–9 g tobacco/day	50.6 (8.4–280.2)	
10–19 g tobacco/day	115.5 (22.8–671.0)	
20–29 g tobacco/day	647.7 (106.4–1,749.1)	
30 g tobacco/day	1,094.2 (185.8–2,970.7)	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Tuyns et al. 1988	1,147 male cases 3,057 male population controls, individually matched for area (frequency matched for age) Turin and Varese, Italy; Zaragoza and Navarra, Spain; Geneva, Switzerland; and Calvados, France	• 0–40 g/day • 41–80 g/day • 81–120 g/day • 121 g/day	• 0–7 cigarettes/day • 8–15 cigarettes/day • 16–25 cigarettes/day • 26 cigarettes/day

**df = Degrees of freedom.

Findings/risk estimates (95% CI)		Comments
Cancer of the endolarynx	RR	RRs are from a logistic regression model; CIs were not provided; for the multiplicative model, χ^2 for trend = 5.8 (9 df**)
0–40 g alcohol/day		
0–7 cigarettes/day	1.0	
8–15 cigarettes/day	6.68	
16–25 cigarettes/day	12.72	
26 cigarettes/day	11.47	
41–80 g alcohol/day		
0–7 cigarettes/day	1.65	
8–15 cigarettes/day	5.94	
16–25 cigarettes/day	12.23	
26 cigarettes/day	18.51	
81–120 g alcohol/day		
0–7 cigarettes/day	2.31	
8–15 cigarettes/day	10.70	
16–25 cigarettes/day	21.01	
26 cigarettes/day	23.55	
121 g alcohol/day		
0–7 cigarettes/day	3.78	
8–15 cigarettes/day	12.20	
16–25 cigarettes/day	31.55	
26 cigarettes/day	43.21	
Cancer of the hypopharynx/epilarynx	RR	For the multiplicative model, χ^2 for trend = 14.5 (9 df)
0–40 g alcohol/day		
0–7 cigarettes/day	1.0	
8–15 cigarettes/day	4.65	
16–25 cigarettes/day	13.91	
26 cigarettes/day	4.90	
41–80 g alcohol/day		
0–7 cigarettes/day	2.99	
8–15 cigarettes/day	14.58	
16–25 cigarettes/day	19.54	
26 cigarettes/day	18.43	
81–120 g alcohol/day		
0–7 cigarettes/day	5.52	
8–15 cigarettes/day	27.47	
16–25 cigarettes/day	48.25	
26 cigarettes/day	37.62	
121 g alcohol/day		
0–7 cigarettes/day	14.67	
8–15 cigarettes/day	71.59	
16–25 cigarettes/day	67.81	
26 cigarettes/day	135.46	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Falk et al. 1989	151 living white male cases aged 30–79 years 235 living white male community controls Texas Gulf Coast region 1975–1980	• <4 drinks/week • 4 drinks/week	• Nonsmokers • 1–10 cigarettes/day • 11–20 cigarettes/day • 21–39 cigarettes/day • 40 cigarettes/day
Franceschi et al. 1990	162 male cases aged <75 years Male controls were <75 years of age, admitted to the same hospitals for acute illnesses Northern Italy 1986–1989	Drinks/week: <35 35–59 60 1 drink = 150 mL wine, 330 mL beer, 30 mL hard liquor	• Nonsmokers • Light smokers (former smokers who quit 10 years ago or smokers of 1–14 cigarettes/day for <30 years) • Intermediate smokers (30–39 years' duration regardless of amount, 15–24 cigarettes/day regardless of duration, 1–24 cigarettes/day for 40 years, or 15 cigarettes/day for <30 years) • Heavy smokers (25 cigarettes/day for >40 years)

Findings/risk estimates (95% CI)		Comments
<4 drinks/week	**OR**	ORs are from a logistic regression model; risk estimates were adjusted for age; goodness-of-fit for the additive model: ^{2} for trend = 4.44, p = 0.73; goodness-of-fit for the multiplicative model: ^{2} for trend = 4.09, p = 0.77
Nonsmokers	1.00	
1–10 cigarettes/day	2.94 (2.24–3.85)	
11–20 cigarettes/day	5.15 (2.48–10.69)	
21–39 cigarettes/day	8.00 (5.81–11.03)	
40 cigarettes/day	10.23 (8.57–12.20)	
4 drinks/week	**OR**	
Nonsmokers	1.75 (1.45–2.11)	
1–10 cigarettes/day	4.55 (3.09–6.68)	
11–20 cigarettes/day	6.48 (3.50–11.99)	
21–39 cigarettes/day	10.50 (7.79–14.15)	
40 cigarettes/day	15.39 (10.85–21.84)	
<35 drinks/week	**OR**	CIs were not provided; there was no formal test for interactions; ORs are from a regression model; risk estimates were adjusted for age, area of residence, and years of education
Nonsmokers	1.0	
Light smokers	0.9	
Intermediate smokers	4.5	
Heavy smokers	6.1	
35–59 drinks/week	**OR**	
Nonsmokers	1.6	
Light smokers	5.0	
Intermediate smokers	7.1	
Heavy smokers	10.4	
60 drinks/week	**OR**	
Nonsmokers		
Light smokers	5.4	
Intermediate smokers	9.5	
Heavy smokers	11.7	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Choi and Kahyo 1991	94 male and 6 female cases 282 male and 18 female hospital controls matched for age, gender, and admission date Seoul, South Korea 1986–1989	None Light (<8,100 mL/day) Medium (8,100–16,200 mL/day) Heavy (>16,200 mL/day)	• None • 1 pack/day • >1 pack/day
Freudenheim et al. 1992	250 incident white cases 250 white neighborhood controls matched for age and neighborhood New York state 1975–1985	Drink-years (drinks/ month multiplied by the number of years at that level of intake)	Pack-years[††]
Zheng et al. 1992	201 incident cases 414 community controls, frequency matched for gender and age Shanghai 1988–1990	Lifetime ethanol intake: 0 kg <300 kg 300–899 kg 900 kg	Pack-years

[††]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings/risk estimates (95% CI)		Comments
Nondrinkers	<u>OR</u>	Extrapolated ORs are from Choi and Kahyo
Nonsmokers	1.0	1991, Figure 1; ORs were calculated using a
1 pack/day	2.0	stratified analysis; there was no formal test for
>1 pack/day	4.0	interactions; all alcohol consumption was
		reported in amounts equivalent to units of
Light drinkers	<u>OR</u>	soju, a commercially distilled spirit made from
Nonsmokers	0.5	barley and potatoes (this is the most com-
1 pack/day	0.8	monly consumed type of alcohol)
>1 pack/day	1.0	
Medium drinkers	<u>OR</u>	
Nonsmokers	1.5	
1 pack/day	3.0	
>1 pack/day	2.5	
Heavy drinkers	<u>OR</u>	
Nonsmokers	0.5	
1 pack/day	4.0	
>1 pack/day	20.71	
1,243 drink-years	<u>OR</u>	ORs are from a logistic regression model; risk
24 pack-years	1.00	estimates were adjusted for education; the
>24 pack-years	2.66 (1.35–5.24)	authors found interactions between tobacco
		and alcohol, but there was no formal test for
>1,243 drink-years	<u>OR</u>	interactions
24 pack-years	0.98 (0.46–2.09)	
>24 pack-years	5.80 (3.25–10.37)	
<u>Men</u>		ORs were calculated using a stratified
0 kg alcohol	<u>OR</u>	analysis; risk estimates were adjusted for age
0–9 pack-years	1.0	and education; there was no formal test for
10–29 pack-years	3.1 (1.1–8.7)	interactions
30 pack-years	35.7 (13.6–93.9)	
<300 kg alcohol	<u>OR</u>	
0–9 pack-years	1.0 (0.2–5.5)	
10–29 pack-years	3.8 (1.1–12.1)	
30 pack-years	12.1 (3.8–38.6)	
300–899 kg alcohol	<u>OR</u>	
0–9 pack-years	7.5 (1.4–38.8)	
10–29 pack-years	3.7 (1.1–12.0)	
30 pack-years	23.2 (8.3–65.0)	
900 kg alcohol	<u>OR</u>	
0–9 pack-years	2.5 (0.2–27.0)	
10–29 pack-years	7.4 (1.0–55.0)	
30 pack-years	25.1 (9.6–70.0)	

Table 2.4   Continued

Study	Population	Alcohol exposure	Tobacco exposure
Baron et al. 1993	224 male cases 1,754 male hospital controls matched for age and residence Italy 1989–1991	• Moderate (<35 drinks/ week) • Heavy (35–59 drinks/ week) • Very heavy (60 drinks/week)	• Nonsmokers • Light (former smokers who quit 10 years ago or smokers of 1–14 cigarettes/ day for <30 years) • Moderate (15–24 cigarettes/ day regardless of duration, 30–39 years of duration regardless of amount, or 15 cigarettes/day for <30 years) • Heavy (25 cigarettes/day for 40 years)
Dosemeci et al. 1997	832 male cases 829 male hospital controls with selected cancers Turkey 1979–1984	• Never drank • 1–20 years of drinking • 21 years of drinking	• Never smoked • 1–20 cigarettes/day • 21 cigarettes/day
Schlecht et al. 1999b	194 incident cases 388 hospital controls matched for hospital, admission quarter, age, and gender Brazil 1986–1989	Lifetime kg: 0–10 11–530 >530	• 0–5 pack-years • 6–42 pack-years • >42 pack-years

Findings/risk estimates (95% CI)		Comments
Moderate drinkers	OR	CIs were not provided; risk estimates are from a regression model; risk estimates were adjusted for area of residence, age, education, and profession; there was no formal test for interactions
Nonsmokers	1.0	
Light smokers	1.3	
Moderate smokers	5.2	
Heavy smokers	11.2	
Heavy drinkers	OR	
Nonsmokers	1.3	
Light smokers	1.7	
Moderate smokers	6.8	
Heavy smokers	14.6	
Very heavy drinkers	OR	
Nonsmokers	1.9	
Light smokers	2.5	
Moderate smokers	9.9	
Heavy smokers	21.3	
Any cell type of cancer	OR	ORs are from a stratified analysis; there was no formal test for interactions; separate risk estimates were also provided for glottis, supraglottis, and other sites
Never drank		
Never smoked	1.0	
1–20 cigarettes/day	3.0 (2.2–4.1)	
21 cigarettes/day	6.2 (3.9–9.9)	
1–20 years of drinking		
Never smoked		
1–20 cigarettes/day	5.6 (3.2–9.8)	
21 cigarettes/day	6.0 (2.5–14.3)	
21 years of drinking		
Never smoked		
1–20 cigarettes/day	5.2 (1.9–15.1)	
21 cigarettes/day	12.2 (3.1–57.6)	
0–10 kg alcohol	OR	ORs are from a logistic regression model that included an interaction term; risk estimates were adjusted for race, beverage temperature, religion, wood stove use, and consumption of spicy foods; there is no statistical evidence for effect modification ($p = 0.945$)
0–5 pack-years	1.0	
6–42 pack-years	13.5 (2.7–66.8)	
>42 pack-years	11.4 (2.1–62.0)	
11–530 kg alcohol	OR	
0–5 pack-years	1.2 (0.1–14.4)	
6–42 pack-years	16.1 (3.4–76.2)	
>42 pack-years	22.0 (4.5–107.0)	
>530 kg alcohol	OR	
0–5 pack-years	5.5 (0.4–71.5)	
6–42 pack-years	36.9 (0.7–180.0)	
>42 pack-years	43.1 (9.1–208.0)	

Table 2.5 Cohort and case-control studies on the association between smoking status and the risk of cancers of the oral cavity and pharynx

Cohort studies		
Study **Location/population**	**Cancer site**	**Smoking status** **(number of deaths)**
McLaughlin 1995a United States, 26-year follow-up of 248,046 U.S. veterans Outcome = total cancer mortality	Oral	Never smoked (see comments) Ever smoked Former smokers Current smokers
	Pharynx	Never smoked (see comments) Ever smoked Former smokers Current smokers

American Cancer Society,
unpublished data
 	
United States, 1982–1996, Cancer
Prevention Study II (352,363 men
and 553,593 women)
Outcome = mortality
	Oropharynx	Men
		  Never smoked (34)
		  Current smokers (196)
		  Former smokers (67)
		
		Women
		  Never smoked (73)
		  Current smokers (84)
		  Former smokers (21)

Case-control studies		
Study **Location/population**	**Cancer site**	**Smoking status** **(cases/controls)**
Franceschi et al. 1992 Italy, 1986–1990 Hospital-based study (men aged <75 years)	Tongue	Never smoked (3/153) Current smokers (83/306) Former smokers (15/260)
	Mouth	Never smoked (3/153) Current smokers (78/306) Former smokers (18/260)

Muscat et al. 1996
 	
United States, 1981–1990,
hospital-based study (cases
matched to controls for gender,
age, race, and date of admission)
	Oropharynx	Men
		  Never smoked (70/138)
		  Current smokers (459/219)
		  Former smokers (158/262)
		
		Women
		  Never smoked (77/167)
		  Current smokers (196/65)
		  Former smokers (49/72)

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.
§NR = Data were not reported.

RR*	95% CI†	Comments
1.0		Total number of deaths = 189
2.6	1.8–3.9	
1.5	0.9–2.4	
4.1	3.0–5.6	
1.0		Total number of deaths = 143
9.5	4.6–19.4	
2.6	1.1–6.2	
14.1	6.9–28.9	
		Adjusted for age; excluded cigar/pipe smokers and persons with
1.00		prevalent cancers
9.30	6.42–13.48	
1.79	1.18–2.71	
		Adjusted for age; excluded persons with prevalent cancers
1.00		
4.91	3.53–6.83	
1.13	0.69–1.85	

OR‡	95% CI	Comments
1.0		Did not include cancers of the lip, salivary gland, and
10.5	3.2–34.1	oropharynx; cigarette smoking only; adjusted for age, area of
2.1	0.6–7.7	residence (Pordonone Province and greater Milan in Italy),
		occupation, and alcohol intake
1.0		
11.8	3.6–38.4	
3.6	1.0–12.6	
		Crude OR by smoking status was computed from Muscat et al.
1.0		1996, Table 1; excluded pipe/cigar smokers
4.1	NR§	
1.2	NR	
1.0		
6.5	NR	
1.5	NR	

Table 2.5   Continued

Case-control studies		
Study Location/population	**Cancer site**	**Smoking status (cases/controls)**
Levi et al. 1998 Swiss hospital-based controls, 1992–1997, matched for age and residence	Oropharynx	Never smoked (11/109) Current smokers (125/103) Former smokers (20/72)
La Vecchia et al. 1999 Italian and Swiss hospital-based study, 1984–1997 (men and women aged <75 years)	Oral	Never smoked (70/1,556) Current smokers (441/1,456) Former smokers (NR)
	Pharynx	Never smoked (32/1,556) Current smokers (459/1,456) Former smokers (NR)

OR	95% CI	Comments
1.0		Excluded pipe/cigar smokers; adjusted for age, education, and
7.1	NR	alcohol and total energy (caloric) intake
1.6	NR	
1.00		Cigarette smoking only; adjusted for age, gender, study center,
6.18	4.62–8.26	education, and alcohol intake
NR	NR	
1.00		
13.45	9.13–19.81	
NR	NR	

Table 2.6 Cohort and case-control studies on the association between current smoking, the number of cigarettes smoked per day, and the risk of oropharyngeal cancer

	Cohort studies	
Study **Location/population**	**Cancer site**	**Cigarettes per day** **(number of deaths)**

Kahn 1966
 	
United States, veterans, followed for 8.5 years (293,658 men aged 35–84 years)
Outcome = mortality
	Buccal cavity	Never or occasional smokers only (11)
		Current smokers
		  1–9 cigarettes/day (1)
		  10–20 cigarettes/day (13)
		  21–39 cigarettes/day (20)
		    40 cigarettes/day (3)

	Pharynx	Never or occasional smokers (4)
		Current smokers
		  1–9 cigarettes/day (3)
		  10–20 cigarettes/day (19)
		  21–39 cigarettes/day (12)
		    40 cigarettes/day (3)

American Cancer Society (ACS), unpublished data
 	
United States, 1982–1996, Cancer Prevention Study II (352,363 men and 553,593 women)
Outcome = mortality
	Oropharynx	Men
		  Never smoked (34)
		  Current smokers
		    <20 cigarettes/day (23)
		    20 cigarettes/day (58)
		    21–39 cigarettes/day (61)
		      40 cigarettes/day (54)
		
		Women
		  Never smoked (73)
		  Current smokers
		    <20 cigarettes/day (16)
		    20 cigarettes/day (34)
		    21–39 cigarettes/day (16)
		      40 cigarettes/day (18)

*RR = Relative risk.
†CI = Confidence interval.
‡NR = Data were not reported.

RR*	95% CI[†]	Comments
1.00		Adjusted for age; cigarette smoking only
0.86	NR[‡]	
2.93	NR	
7.34	NR	
5.73	NR	
1.00		
7.11	NR	
12.81	NR	
14.59	NR	
19.34	NR	
1.00		Adjusted for age; excluded pipe/cigar smokers and persons with prevalent cancers
4.23	2.49–7.19	
9.21	6.00–14.15	
13.57	8.82–20.88	
12.90	8.29–20.07	
1.00		Adjusted for age; women were not asked about pipe/cigar smoking
2.20	1.27–3.80	
6.00	3.94–9.16	
7.07	4.04–12.39	
12.34	7.22–21.11	

Table 2.6   Continued

	Case-control studies	
Study Location/population	**Cancer site**	**Cigarettes per day (number of deaths)**
Franceschi et al. 1992 Italy, 1986–1990, hospital-based study (men aged <75 years)	Tongue	Never smoked (3/153) Current/former smokers <15 cigarettes/day (15/206) 15–24 cigarettes/day (52/229) 25 cigarettes/day (29/125) χ^2 *for trend*
	Mouth	Never smoked (3/153) Current/former smokers <15 cigarettes/day (18/206) 15–24 cigarettes/day (51/229) 25 cigarettes/day (26/125) χ^2 *for trend*
Muscat et al. 1996 United States, 1981–1990, hospital-based study (cases matched to controls for gender, age, race, and date of admission)	Oropharynx	Men Never smoked (70/138) Current smokers 1–20 cigarettes/day (183/114) 21–39 cigarettes/day (88/46) 40 cigarettes/day (188/59) Women Never smoked (77/167) Current smokers 1–20 cigarettes/day (104/45) 21–39 cigarettes/day (41/11) 40 cigarettes/day (51/9)
La Vecchia et al. 1999 Italian and Swiss hospital-based study, 1984–1997	Oropharynx	Never smoked (12/76) Current smokers <20 cigarettes/day (5/26) 20 cigarettes/day (20/22)

§OR = Odds ratio.

OR[§]	95% CI	Comments
1.0		Did not include cancers of the lip, salivary gland, and oropharynx; cigarette smoking only; adjusted for age, area of residence, occupation, and alcohol intake
2.9	0.8–10.20	
9.0	2.7–29.8	
9.8	2.8–33.6	
p <0.01		
1.0		
4.5	1.3–15.8	
11.0	3.3–36.4	
9.6	2.8–33.1	
p <0.01		
		Crude ORs computed from Muscat et al. 1996, Table 1
1.0		
3.2	NR	
3.8	NR	
6.3	NR	
		Crude ORs computed from Muscat et al. 1996, Table 1
1.0		
5.0	NR	
8.1	NR	
12.3	NR	
1.00		Adjusted for age, gender, study center, education, and alcohol intake
1.3	0.4–4.2	
7.5	2.7–20.4	

Table 2.7   Cohort and case-control studies on the association between former smoking, the number of years since quitting, and the risk of oropharyngeal cancer

	Cohort study	
Study Location/population	**Cancer site**	**Smoking status (number of deaths or cases/controls)**

American Cancer Society, unpublished data
 	
United States, 1982–1996, Cancer Prevention Study II (352,363 men and 553,593 women)
Outcome = mortality
	Oropharynx	Men
		  Current smokers (196)
		  Former smokers
		   <11 years since cessation (37)
		   11–19 years since cessation (10)
		    20 years since cessation (20)
		  Never smoked (34)
		
		Women
		  Current smokers (84)
		  Former smokers
		   <11 years since cessation (9)
		   11–19 years since cessation (7)
		    20 years since cessation (5)
		  Never smoked (73)

	Case-control studies	

Blot et al. 1988
 	
United States, 1984–1985, population cancer registry-based study (Atlanta, Los Angeles, Santa Clara and San Mateo counties south of San Francisco-Oakland, and New Jersey); men and women aged 18–79 years; population-based controls identified by random-digit telephone dialing/ Health Care Financing Administration
	Oropharynx	Men
		  Current smokers (485/239)
		  Former smokers
		   1–9 years since cessation (64/98)
		   10–19 years since cessation (56/114)
		    20 years since cessation (43/141)
		  Never smoked (50/185)
		
		Women
		  Current smokers (258/129)
		  Former smokers
		   1–9 years since cessation (24/39)
		   10–19 years since cessation (10/35)
		    20 years since cessation (4/26)
		  Never smoked (54/202)

*RR = Relative risk.
†CI = Confidence interval.

RR*	95% CI†	Comments
		Adjusted for age; excluded pipe/cigar smokers and persons with prevalent cancers
9.30	6.41–13.48	
3.25	2.03–5.20	
0.92	0.45–1.86	
1.34	0.77–2.32	
1.00		
		Adjusted for age; excluded persons with prevalent cancers
4.91	3.53–6.84	
1.47	0.73–2.96	
1.33	0.61–2.90	
0.70	0.28–1.74	
1.00		
		Excluded pipe/cigar smokers; adjusted for age, race, study
3.4	2.3–5.1	location, alcohol intake, and respondent status (self vs. next of kin); controls were matched for gender and selected by age and
1.1	0.7–1.9	race groups; included interviews conducted with next of kin (22%
1.1	0.7–1.9	of cases, 2% of controls)
0.7	0.4–1.2	
1.0		
4.7	3.0–7.3	
1.8	0.9–3.6	
0.8	0.4–1.9	
0.4	0.1–1.4	
1.0		

Table 2.7   Continued

Case-control studies		
Study **Location/population**	**Cancer site**	**Smoking status (number of** **deaths or cases/controls)**
Franceschi et al. 1992 Italy, 1986–1990, hospital-based study (male cases aged <75 years)	Tongue	Current smokers (83/306) Former smokers <10 years since cessation (12/122) 10 years since cessation (3/138) Never smoked (3/153) χ^2 *for trend*
	Mouth	Current smokers (78/306) Former smokers <10 years since cessation (13/122) 10 years since cessation (3/138) Never smoked (3/153) χ^2 *for trend*

La Vecchia et al. 1999
 	
Italian and Swiss hospital-based
study, 1984–1997 (men and women
aged <75 years)
	Oral	Current smokers (441/1,456)
		Former smokers
		  1–2 years since cessation (28/127)
		  3–5 years since cessation (38/195)
		  6–9 years since cessation (31/183)
		  10–14 years since cessation (12/238)
		   15 years since cessation (18/424)
		Never smoked (70/1,556)

	Pharynx	Current smokers (459/1,456)
		Former smokers
		  1–2 years since cessation (31/127)
		  3–5 years since cessation (28/195)
		  6–9 years since cessation (27/183)
		  10–14 years since cessation (26/238)
		   15 years since cessation (39/424)
		Never smoked (32/1,556)

Schlecht et al. 1999a
 	
Brazil, 1986–1989, hospital-based
study in metropolitan areas (cases
of oropharyngeal cancer; controls
matched for gender, 5-year age
groups, quarter of admission, and
hospital)
	Mouth	Current smokers (214/256)
		Former smokers
		  <5 years since cessation (19/54)
		  6–10 years since cessation (8/37)
		  11–15 years since cessation (2/21)
		  >15 years since cessation (6/47)
		Never smoked (21/180)

	Pharynx	Current smokers (138/184)
		Former smokers
		  <5 years since cessation (12/41)
		  6–10 years since cessation (2/19)
		  11–15 years since cessation (2/12)
		  >15 years since cessation (2/23)
		Never smoked (5/82)

RR	95% CI	Comments
10.5	3.1–34.1	Did not include cancers of the lip, salivary gland, and oropharynx; cigarette smoking only; adjusted for age, area of residence, occupation, and alcohol intake
3.8	1.0–14.5	
0.7	0.8–3.8	
1.0		
p <0.01		
11.8	3.6–38.4	
3.8	1.0–14.4	
0.7	0.1–3.9	
1.0		
p <0.01		
6.18	4.62–8.26	Cigarette smoking only; adjusted for age, gender, study center, education, and alcohol intake
4.64	2.77–7.76	
3.93	2.49–6.21	
2.89	1.78–4.67	
0.82	0.42–1.60	
0.71	0.41–1.24	
1.00		
13.45	9.13–19.81	
9.88	5.59–17.47	
6.27	3.58–10.98	
4.78	2.72–8.40	
3.23	1.83–5.71	
2.87	1.73–4.75	
1.00		
8.0	4.3–14.9	Adjusted for alcohol intake; smokers of commercial cigarettes only
3.1	1.3–7.0	
2.1	0.8–5.7	
0.7	0.1–3.7	
1.0	0.3–2.9	
1.0		
5.9	2.2–15.3	
2.6	0.8–8.5	
1.2	0.2–7.0	
1.4	0.2–9.8	
0.9	0.1–5.5	
1.0		

Table 2.8   Case-control studies on the association between smoking, alcohol use, and the risk of oropharyngeal cancer

Study Location/population	Cancer site	Alcohol use
Blot et al. 1988		
United States, 1984–1985, population cancer registry-based study (Atlanta, Los Angeles, Santa Clara and San Mateo counties south of San Francisco-Oakland, and New Jersey; men and women aged 18–79 years); population-based controls identified by random-digit telephone dialing/Health Care Financing Administration (adjusted for race, age, study location, and respondent status)	Oropharynx	<1 drink/week
		1–4 drinks/week
		5–14 drinks/week
		15–29 drinks/week
		30 drinks/week

*OR = Odds ratio.
†Those who had quit smoking for 10 years or had smoked for <20 years.
‡NR = Data were not reported.

Smoking status	OR*	
	Men (cases/controls)	Women (cases/controls)
Nonsmokers	1.0 (12/66)	1.0 (36/112)
Short duration or former smokers[†]	0.7 (8/42)	1.0 (7/27)
Current smokers		
1–19 cigarettes/day for 20 years	1.7 (2/6)	0.9 (4/13)
20–39 cigarettes/day for 20 years	1.9 (8/17)	2.2 (12/19)
40 cigarettes/day for 20 years	7.4 (9/4)	NR[‡] (4/0)
Nonsmokers	1.3 (12/52)	0.7 (11/62)
Short duration or former smokers	2.2 (24/61)	1.6 (8/21)
Current smokers		
1–19 cigarettes/day for 20 years	1.5 (7/21)	5.1 (22/15)
20–39 cigarettes/day for 20 years	2.4 (17/34)	2.7 (20/25)
40 cigarettes/day for 20 years	0.7 (6/14)	9.3 (14/6)
Nonsmokers	1.6 (15/39)	1.3 (7/23)
Short duration or former smokers	1.4 (21/90)	0.4 (4/30)
Current smokers		
1–19 cigarettes/day for 20 years	2.7 (8/18)	2.8 (11/15)
20–39 cigarettes/day for 20 years	4.4 (28/40)	6.9 (35/18)
40 cigarettes/day for 20 years	4.4 (19/19)	7.8 (15/7)
Nonsmokers	1.4 (5/21)	0.0 (0/3)
Short duration or former smokers	3.2 (25/49)	1.1 (3/10)
Current smokers		
1–19 cigarettes/day for 20 years	5.4 (16/18)	4.6 (3/3)
20–39 cigarettes/day for 20 years	7.2 (52/42)	12.4 (31/9)
40 cigarettes/day for 20 years	20.2 (43/11)	18.0 (18/4)
Nonsmokers	5.8 (6/7)	0.0 (0/2)
Short duration or former smokers	6.4 (43/37)	NR (3/0)
Current smokers		
1–19 cigarettes/day for 20 years	7.9 (22/14)	11.0 (9/3)
20–39 cigarettes/day for 20 years	23.8 (145/33)	46.0 (38/3)
40 cigarettes/day for 20 years	37.7 (148/21)	107.9 (37/1)

Table 2.8   Continued

Study Location/population	Cancer site	Alcohol use
La Vecchia et al. 1999		
Italian and Swiss hospital-based study, 1992–1997 (cases of oropharyngeal cancer among men and women included smokers of cigarettes, pipes, and cigars). Statistical models included area of residence, inter-viewer, age, education, vegetable and fruit intake, and total energy intake	Oral cavity	0–20 drinks/week
		21–48 drinks/week
		49–76 drinks/week
		77 drinks/week
	Pharynx	0–20 drinks/week
		21–48 drinks/week

§CI = Confidence interval.

Smoking status (cases/controls)	OR
	Men and women (95% CI§)
Never smoked (3/193)	1.0
Current smokers	
1–14 cigarettes/day (2/62)	2.2 (0.4–13.5)
15–24 cigarettes/day (4/78)	3.0 (0.6–13.8)
25 cigarettes/day (4/41)	5.6 (1.2–26.3)
Former smokers (12/187)	3.9 (1.1–14.1)
Never smoked (5/119)	2.7 (0.6–11.6)
Current smokers	
1–14 cigarettes/day (6/49)	5.9 (1.4–25.1)
15–24 cigarettes/day (28/65)	22.9 (6.6–79.4)
25 cigarettes/day (12/27)	22.7 (5.9–86.9)
Former smokers (20/212)	6.0 (1.7–21.0)
Never smoked (3/34)	4.5 (0.8–24.2)
Current smokers	
1–14 cigarettes/day (11/16)	30.6 (7.3–128.2)
15–24 cigarettes/day (35/28)	62.5 (17.4–224.2)
25 cigarettes/day (25/11)	103.1 (26.4–402.7)
Former smokers (17/71)	10.5 (2.9–38.6)
Never smoked (3/34)	4.5 (0.8–24.2)
Current smokers	
1–14 cigarettes/day (8/6)	52.4 (10.4–264.2)
15–24 cigarettes/day (31/15)	110.3 (29.1–418.1)
25 cigarettes/day (31/7)	227.8 (54.6–950.7)
Former smokers (17/33)	25.4 (6.7–96.0)
Never smoked (6/193)	1.0
Current smokers	
1–14 cigarettes/day (4/62)	2.3 (0.6–8.4)
15–24 cigarettes/day (12/78)	4.4 (1.6–12.5)
25 cigarettes/day (7/41)	5.5 (1.7–17.8)
Former smokers (11/187)	1.7 (0.6–4.9)
Never smoked (2/119)	0.4 (0.1–2.3)
Current smokers	
1–14 cigarettes/day (11/49)	4.5 (1.5–13.4)
15–24 cigarettes/day (32/65)	11.7 (4.6–30.2)
25 cigarettes/day (22/27)	18.6 (6.8–51.3)
Former smokers (22/212)	2.7 (1.0–7.1)

Table 2.8   Continued

Study Location/population	Cancer site	Alcohol use
La Vecchia (continued)		
		49–76 drinks/week
		77 drinks/week
Schlecht et al. 1999a Hospital-based study in 3 metropolitan areas of Brazil (cases of oropharyngeal cancer were matched to controls for gender, 5-year age group, quarter of admission, and hospital). Data from statistical models assumed independence between alcohol and tobacco use (including cigarettes, pipes, and cigars). Models included race, beverage temperature, religion, wood stove use, and consumption of spicy foods	Mouth	0–10 kg/lifetime alcohol use
		11–530 kg/lifetime alcohol use
		>530 kg/lifetime alcohol use
	Pharynx	0–10 kg/lifetime alcohol use
		11–530 kg/lifetime alcohol use
		>530 kg/lifetime alcohol use

Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Smoking status (cases/controls)	OR
	Men and women (95% CI)
Never smoked (1/34)	0.5 (0.1–4.3)
Current smokers	
1–14 cigarettes/day (17/16)	16.3 (5.3–50.5)
15–24 cigarettes/day (40/28)	26.9 (10.0–72.3)
25 cigarettes/day (18/11)	32.2 (10.3–100.4)
Former smokers (31/71)	6.8 (2.6–17.8)
Never smoked (1/34)	0.5 (0.1–4.3)
Current smokers	
1–14 cigarettes/day (13/6)	27.5 (7.2–105.1)
15–24 cigarettes/day (48/15)	58.3 (20.3–167.3)
25 cigarettes/day (36/7)	100.4 (30.8–327.7)
Former smokers (31/33)	14.8 (5.4–40.9)
	Men and women (95% CI)
0–5 pack-years (18/139)	1.0
6–42 pack-years (23/54)	4.8 (2.7–8.7)
>42 pack-years (15/28)	6.7 (3.6–12.5)
0–5 pack-years (8/70)	1.6 (0.9–2.8)
6–42 pack-years (38/44)	7.5 (3.5–15.8)
>42 pack-years (44/86)	10.3 (4.8–22.2)
0–5 pack-years (4/30)	3.6 (2.0–6.5)
6–42 pack-years (84/84)	17.5 (8.2–37.0)
>42 pack-years (139/134)	24.1 (11.4–51.1)
0–5 pack-years (3/43)	1.0
6–42 pack-years (2/65)	3.6 (1.6–8.0)
>42 pack-years (9/12)	5.4 (2.4–12.2)
0–5 pack-years (4/38)	2.0 (0.9–4.6)
6–42 pack-years (21/71)	7.4 (2.5–21.7)
>42 pack-years (26/55)	11.0 (3.7–32.4)
0–5 pack-years (4/20)	4.6 (2.0–10.5)
6–42 pack-years (59/71)	16.6 (5.7–48.5)
>42 pack-years (88/94)	24.9 (8.6–72.1)

Esophageal Cancer

An estimated 13,900 new cases and 13,000 deaths from cancer of the esophagus were expected to occur in the United States in 2003 (ACS 2003). Esophageal cancer ranks 19th in terms of incident cancers in the United States and 6th in developing countries (IARC 2003). Age-adjusted incidence rates per 100,000 for 1996–2000 in areas of the SEER Program were highest among black men (11.4), intermediate among white men (7.5), and lowest among black (4.2) and white (2.1) women (Ries et al. 2003). The disease is rapidly fatal in most cases. Relative five-year survival has increased in the United States from 4.9 percent for patients diagnosed in 1975 (Ries et al. 1999) to 14 percent for patients diagnosed in 1992, yet median survival remains less than one year after diagnosis (Ries et al. 2003).

Internationally, death rates from esophageal cancer vary more than 100-fold across countries (IARC 2003). Mortality rates in north-central China and in certain parts of Iran exceed 100 per 100,000. Pockets of elevated mortality are reported in South Africa and parts of France, whereas mortality rates are below 10 per 100,000 in most countries (Muñoz and Day 1996).

The predominant histologic type and location of cancers within the esophagus have changed since the 1970s in the United States (Blot and McLaughlin 1999) and in many European countries (Botterweck et al. 2000), although a similar change has not yet been reported in high-incidence regions of Asia or Africa. Historically, the most common esophageal cancer in developed and developing countries was squamous cell carcinoma, occurring largely in the proximal two-thirds of the esophagus (Blot 1994). Since the 1970s in the United States, the incidence of adenocarcinoma of the distal esophagus has increased more than fivefold among white and African American men, while the incidence of squamous cell carcinoma has decreased moderately (Blot and McLaughlin 1999). Rates of adenocarcinoma are also rising in women but are much lower than in men. Adenocarcinoma now comprises more than half of all esophageal cancers in white males, whereas squamous cell carcinoma remains the predominant histologic type among African American patients and in high-incidence populations worldwide (Blot and McLaughlin 1999).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports on smoking and health have presented growing evidence of an association between smoking and esophageal cancer without distinguishing between squamous cell carcinoma and adenocarcinoma. The 1982 report concluded that smoking is a major cause of esophageal cancer (USDHHS 1982). Key conclusions from the reports are chronologically summarized below:

> The evidence. . .supports the belief that an association exists. However, the data are not adequate to decide whether the relationship is causal (USDHEW 1964, p. 218).

> Additional epidemiological evidence confirms a significant association between the combined use of cigarettes and alcohol, and cancer of the esophagus (USDHEW 1972, p. 75).

> Cigarette smoking is a significant causal factor in the development of cancer of the esophagus. The risk. . .increases with the amount smoked (USDHEW 1979, p. 5-44).

> Cigarette smoking is a major cause of esophageal cancer in the United States. Cigar and pipe smokers experience a risk of esophageal cancer similar to that of cigarette smokers. The risk of esophageal cancer increases with increased smoke exposure, as measured by the number of cigarettes smoked per day, and is diminished by discontinuing the habit. The use of alcohol in combination with smoking acts synergistically to greatly increase the risk for esophageal cancer mortality (USDHHS 1982, p. 101).

> The proportion of esophageal cancer deaths attributable to tobacco use in the United States is estimated to be 78 percent for men and 75 percent for women (USDHHS 1989, p. 156).

Smoking cessation halves the risk for cancers of the oral cavity and esophagus. . .as soon as 5 years after cessation, with further reduction over a longer period of abstinence (USDHHS 1990, p. 178).

Biologic Basis

Squamous cell carcinoma and adenocarcinoma of the esophagus typically develop from premalignant lesions (Montesano et al. 1997). Neoplastic progression has been studied in longitudinal clinical studies of high-incidence communities in northern China. Sequential endoscopy (Dawsey et al. 1994) and cytologic evaluations (Shen et al. 1993; Dawsey et al. 1997) confirm that dysplastic histologic and cytologic changes predict the clinical risk of developing squamous cell carcinoma. More than 80 percent of biopsies of esophageal tissue with moderate or severe dysplasia are taken from visually abnormal sites characterized by friability or by the presence of erosion, plaques, or nodules (Dawsey et al. 1993). The severity of dysplasia correlates closely with epithelial proliferation, as measured by tritiated thymidine labeling (Liu et al. 1993).

Autopsy studies conducted in the United States in the 1950s and 1960s documented that smoking is associated with more severe preneoplastic lesions and a higher risk of squamous cell carcinomas than found in nonsmokers. Auerbach and colleagues (1965) systematically examined sections of esophageal tissue from autopsies of 1,268 male veterans at the East Orange Veterans Administration Hospital. Investigators completed detailed histopathologic characterizations of these men without any knowledge of their smoking histories, which were obtained separately from next of kin. Current cigarette, pipe, and cigar smokers had more frequent and more severe nuclear atypia in basal epithelial cells and hyperplastic thickening of the basal cell layer compared with nonsmokers. Former smokers had fewer cells with atypical nuclei than did current smokers.

Adenocarcinoma of the esophagus develops from Barrett's esophagus, a premalignant condition in which normal squamous epithelium of the distal esophagus is replaced by metaplastic columnar epithelium (Phillips and Wong 1991). The main cause of Barrett's esophagus is thought to be chronic gastroesophageal reflux (Winters et al. 1987; Lagergren et al. 1999). One small study suggests that tobacco smoking is strongly associated with the malignant transformation of Barrett's columnar epithelium, rather than predisposing to the emergence of columnar epithelium in the distal esophagus (Gray et al. 1993). Clinical markers that detect neoplastic transformations and predict which patients are likely to develop adenocarcinoma are still being developed (Galipeau et al. 1999).

Using the tools of molecular and genetic biology, research is now addressing the molecular changes of esophageal cancer. Losses of chromosome 9p21 are common in esophageal cancer and often precede the onset of aneuploidy in Barrett's esophagus (Wong et al. 1997). *p16INK4a*, a critical regulator of cell cycle progression, appears to be an important target in this region. *p14^{ARF}*, which stabilizes the *p53* gene by binding MDM2, is also deleted in some of these tumors. Somatic mutations of the *p53* tumor suppressor gene and the *p53* protein accumulation occur at an early stage in the development of squamous cell esophageal cancer (Gao et al. 1994; Wang et al. 1996; Shi et al. 1999). Mutated *p53* genes are seen in most invasive carcinomas and in many cases of dysplasia or carcinoma in situ, but in fewer than half of the patients with basal cell hyperplasia (Wang et al. 1996). Point mutations of the *p53* gene produce protein with an altered conformation and increased stability, leading to the accumulation of abnormal *p53* genes (Wang et al. 1993). The specific inactivating mutations that disrupt the *p53* gene's control of the cell cycle and apoptosis in esophageal cancers resemble *p53* gene mutations in other cancers associated with tobacco and alcohol use (Robert et al. 2000). Other somatic changes associated with squamous cell carcinoma of the esophagus include a disruption of cell cycle control in *G1* by several mechanisms (inactivation of the *p16INK4a*, amplification of *Cyclin D1*, and alterations of the retinoblastoma gene), the activation of oncogenes such as *EGFR*, and the inactivation of several tumor suppressor genes (Hu et al. 2000; Lu 2000; Mandard et al. 2000; Mori et al. 2000b).

Loss of the *p53* gene function (Prevo et al. 1999) and *p53* protein accumulation also frequently occurs in the development of adenocarcinoma of the esophagus (Mueller et al. 2000). The malignant progression is associated with an overexpression of growth factors (such as the epidermal growth factor [EGF], c-erbB2, and the transforming growth factor [TGF-]), and with an underexpression of the normal cell adhesion molecule E-cadherin with a loss of *APC* gene activity (Dolan et al. 1999; Tselepis et al. 2000). These changes progressively disrupt cell cycling and intercellular adhesion as the esophageal epithelium progresses from metaplasia to dysplasia to carcinoma (Tselepis et al. 2000).

Several animal models demonstrate the carcinogenicity of tobacco smoke on the esophagus. The 1979 Surgeon General's report (USDHEW 1979) noted that benzo[*a*]pyrene is able to penetrate the cell membranes of the esophageal epithelium, producing papillomas and squamous cell carcinoma (Horie et al. 1965; Kuratsune et al. 1965). Tobacco smoke condensate and specific chemicals found in tobacco smoke are known to cause cancers of the rodent esophagus and forestomach when administered orally or by gavage (USDHHS 2000). The chemical n-nitrosodiethylamine in cigarette smoke causes esophageal cancer when administered through diet or gavage to mice, or by subcutaneous injection into Chinese hamsters. N-nitrosodiethylamine also induces esophageal cancer in the offspring of pregnant mice after intrauterine exposure through diet or gavage. Other constituents of tobacco smoke that cause forestomach tumors in rodents and are classified as "reasonably anticipated to be a human carcinogen" by the National Toxicology Program include dibenz(*a,h*)anthracene (mouse: diet), 7H-dibenzo(*c,g*)-carbazole (mouse: gavage), and n-nitrosodi-n-butylamine (mouse and hamster: diet, drinking water, and gavage) (USDHHS 2000).

Epidemiologic Evidence

This section considers all published studies (in English) that provide data on lifetime nonsmokers and current and former smokers of cigarettes only. Where multiple follow-ups have been reported on the same cohort, only the longest follow-up is considered unless otherwise stated. Studies were identified by searching the MEDLINE database for resources from January 1966 to July 2000 under the headings "tobacco," "smoking," and "esophageal neoplasms," and from the reference lists of published original and review articles.

Cohort studies conducted in the United States, Western Europe, and Asia consistently find higher death rates from esophageal cancer among current cigarette smokers than among lifetime nonsmokers, and intermediate death rates among persons who have quit smoking (Hammond 1966; Weir and Dunn 1970; Williams and Horm 1977; Cartensen et al. 1987; Kono et al. 1987; Hirayama 1990; Yu et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Burns et al. 1997; Schildt et al. 1998; ACS, unpublished data). The data in Table 2.9 represent the five cohort studies with the longest follow-up periods (Cartensen et al. 1987; Doll et al. 1994; McLaughlin et al. 1995a; Burns et al. 1997; ACS CPS-II, unpublished data). In these studies, the death rate from esophageal cancer is from 3.7 times (Cartensen et al. 1987; Burns et al. 1997) to 7.5 times higher (Doll et al. 1994) among male current smokers than among male lifetime nonsmokers. The increase is smaller among men who have stopped smoking, ranging from 1.3 (Cartensen et al. 1987) to 4.8 times higher (Doll et al. 1994) than the rate among lifetime nonsmokers. Women smokers in CPS-II have an increase in esophageal cancer mortality rates similar to male smokers. CPS-II is the only large Western cohort study to report an association between cigarette smoking and cancer of the esophagus in women (ACS, unpublished data).

The magnitude of the association between current cigarette smoking and esophageal cancer may be underestimated in cohort studies that only consider smoking status at the time of enrollment, and do not account for cessation of smoking during follow-up. For example, the RR for esophageal cancer in the veterans study decreases from 6.3 (95 percent CI, 3.9–10.1) during the first 16 years of follow-up to 2.6 (95 percent CI, 1.7–4.0) during the second 10 years (McLaughlin et al. 1995a). A similar decline in the RR estimate is observed with a longer follow-up in CPS-II (ACS, unpublished data). Of the studies included in Table 2.9, only the analysis of British doctors (Doll et al. 1994) periodically updated smoking status during the follow-up. In comparison with other studies, less misclassification of smoking may contribute to the higher RR estimate observed among currently smoking male British doctors compared with the estimates for current smokers in other cohorts.

Case-control studies also consistently report a higher risk of cancer of the esophagus among current smokers compared with lifetime nonsmokers, and an intermediate risk among former smokers (Table 2.11). Cigarette smoking is associated with both squamous cell carcinoma and adenocarcinoma of the esophagus in all case-control studies that have considered the histologic type of cancer. The association of smoking with risk is less strong for adenocarcinomas than for squamous cell carcinomas in recent case-control studies (Kabat et al. 1993; Gammon et al. 1997; Lagergren et al. 2000), although this pattern of association was not observed in a case-control study in China (Gao et al. 1994). The association between squamous cell carcinoma and cigarette smoking also appears to be weaker in China (Gao et al. 1994) than in the Americas (Kabat et al. 1993; Gammon et al. 1997; Castellsagué et al. 1999) and northern Europe (Lagergren et al. 2000).

The risk of esophageal cancer increases with the number of cigarettes smoked per day or with pack-years of smoking in current smokers (Tables 2.10 and

2.12), and decreases in former smokers with a younger age at cessation or with an increase in the number of years since successfully quitting (Tables 2.13 and 2.14). Two case-control studies listed in Table 2.14 suggest that the risk of squamous cell carcinoma may decrease more rapidly after cessation than does the risk of adenocarcinoma (Gammon et al. 1997; Lagergren et al. 2000), but this pattern is not apparent in all studies (Kabat et al. 1993). This pattern suggests the hypothesis that smoking might act differently in the two cancer types, acting in the earlier stages of adenocarcinoma and in the later stages of squamous cell carcinoma.

The combination of cigarette smoking and alcohol intake, particularly heavy alcohol consumption, is much more strongly associated with esophageal cancer than either smoking or alcohol consumption alone, although both independently increase esophageal cancer risks (Table 2.15). The joint effects of smoking and drinking on esophageal cancer have been reported in high-incidence populations in China (Gao et al. 1994) as well as in the Americas (Castellsagué et al. 1999) and Europe (Zambon et al. 2000). Because of the synergism between smoking and alcohol, persons who drink heavily are at a particularly high risk for esophageal cancer if they smoke, and the number of smoking attributable cases of esophageal cancer also depends on the extent of drinking.

Evidence Synthesis

Smoking has long been identified as a cause of esophageal cancer; a strong association is well documented in many studies, as is dose-response and a decline in risk following cessation. Numerous case-control and cohort studies provide consistent evidence that cigarette smokers experience a higher incidence of and/or mortality from esophageal cancer than do lifetime nonsmokers. The risk among persons who currently smoke and have smoked only cigarettes is up to seven or eight times higher than the risk for lifetime nonsmokers. Incidence and mortality rates increase with the number of cigarettes smoked per day and decrease with years since cessation. The reduction in risks among former compared with continuing smokers occurs rapidly after cessation, beginning within the first 10 years. Cigarette smoking is consistently associated with both squamous cell carcinoma and adenocarcinoma in case-control studies that classify esophageal cancer by histologic type. The combination of cigarette smoking with heavy alcohol consumption synergistically increases the risk of esophageal cancer.

Adenocarcinoma of the esophagus now comprises more than half of all esophageal cancers among white men in the United States (Blot et al. 1991). Some epidemiologic studies suggest that cigarette smoking may be more strongly associated with squamous cell carcinoma than with adenocarcinoma. Smoking is also more strongly associated with squamous cell carcinoma in the United States and Europe than in high-incidence populations in China. Nonetheless, smoking has been consistently associated with adenocarcinoma of the esophagus. Risks are highest for current smokers and lower for former smokers, in comparison with lifetime nonsmokers. Several case-control studies showed an increase in risk with the number of cigarettes smoked and a decrease in risk with the number of years since quitting. These findings cannot be plausibly explained by confounding nor by the modifying effect of alcohol consumption. The well-documented association of smoking with squamous cell carcinoma and the exposure of the esophageal epithelium to tobacco smoke carcinogens further support a causal relationship of smoking with adenocarcinoma of the esophagus.

Experimental studies in animals show that multiple carcinogens in tobacco smoke and smoke condensate induce premalignant papillomas and carcinomas of the esophagus and forestomach in multiple species (USDHHS 2000).

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and cancers of the esophagus.

2. The evidence is sufficient to infer a causal relationship between smoking and both squamous cell carcinoma and adenocarcinoma of the esophagus.

Implications

Cigarette smoking is a major cause of esophageal cancer in the United States and worldwide, and smoking and alcohol consumption together cause most cases in the United States. Reductions in smoking (cigarettes, pipes, cigars, and other tobacco products) and reductions in the use of smokeless tobacco could prevent most of the approximately 12,300 new cases and 12,100 deaths from esophageal cancer that occur annually in the United States, and could reduce the much larger burden of these cancers worldwide.

Table 2.9 **Cohort studies on the association between smoking status and the risk of esophageal cancer***

Study Location/population	Smoking status (number of deaths)	RR[†]	95% CI[‡]	Comments
Men				
Carstensen et al. 1987 1963–1979, Sweden, 16-year follow-up (25,129 men; 18 deaths)	Never or occasional smokers (5) Current smokers (9) Former smokers (4)	1.0 3.7 1.3	 NR[§] NR	Adjusted for age and residence
Doll et al. 1994 British physicians, 1951–1991, 40-year follow-up (34,440 men; 172 deaths)	Never or occasional smokers Current smokers Former smokers	1.0 7.5 4.75	 NR NR	Adjusted for age and calendar period
McLaughlin et al. 1995a U.S. veterans, 1954–1980, 26-year follow-up (177,903 men aged 31–84 years; 318 deaths)	Never smoked Current smokers Former smokers	1.0 4.1 1.5	 3.0–5.6 1.0–2.2	Adjusted for age and calendar period
Burns et al. 1997 Cancer Prevention Study I, 1959–1972, 12-year follow-up (456,491 men; 190 deaths)	Never smoked (30) Current smokers (160)	1.0 3.7	 NR	Adjusted for age
American Cancer Society, unpublished data Cancer Prevention Study II United States, 1982–1996, 14-year follow-up (352,363 men; 649 deaths)	Never smoked (92) Current smokers (292) Former smokers (265)	1.0 4.73 2.57	 3.75–6.00 2.02–3.25	Adjusted for age
Women				
American Cancer Society, unpublished data Cancer Prevention Study II United States, 1982–1996, 14-year follow-up (553,593 women; 181 deaths)	Never smoked (60) Current smokers (86) Former smokers (35)	1.0 6.71 2.51	 4.73–9.52 1.63–3.85	Adjusted for age

*Includes only the 5 cohort studies with the longest follow-up periods and with reported data on persons who exclusively smoked cigarettes.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]NR = Data were not reported.
 Number of deaths by smoking category was not reported.

Table 2.10 Cohort studies on the association between current smoking, the number of cigarettes smoked per day, and the risk of esophageal cancer

Study Location/population	Smoking status (number of deaths)	RR*	95% CI†	Comments
Men				
Doll et al. 1994 British physicians 1951–1991, 40-year follow-up (34,440 men; 172 deaths)	Never smoked regularly‡ Current smokers 1–14 cigarettes/day‡ 15–24 cigarettes/day‡ 25 cigarettes/day‡	1.0 4.25 8.25 11.25	 NR§ NR NR	Adjusted for age and calendar period; p <0.001
McLaughlin et al. 1995a U.S. veterans, 1954–1980, 26-year follow-up (177,903 men aged 31–84 years; 318 deaths)	Never smoked‡ Current smokers 1–9 cigarettes/day‡ 10–20 cigarettes/day‡ 21–39 cigarettes/day‡ 40 cigarettes/day‡	1.0 1.4 3.3 6.7 6.1	 0.7–2.7 2.4–4.7 4.7–9.4 3.5–10.7	Adjusted for age and calendar period; p for trend >0.01
Burns et al. 1997 Cancer Prevention Study I, 1959–1972, 12-year follow-up (456,491 men; 190 deaths)	Never smoked (30) Current smokers 1–19 cigarettes/day‡ 20 cigarettes/day‡ 21 cigarettes/day‡	1.0 2.4 3.9 5.4	 NR NR NR	None
American Cancer Society, unpublished data Cancer Prevention Study II United States, 1982–1996, 14-year follow-up (352,363 men; 649 deaths)	Never smoked (92) Current smokers <20 cigarettes/day (52) 20 cigarettes/day (74) 21–39 cigarettes/day (84) 40 cigarettes/day (82)	1.00 3.35 4.01 6.03 6.30	 2.39–4.71 2.95–5.46 4.46–8.14 4.64–8.54	Adjusted for age
Women				
American Cancer Society, unpublished data Cancer Prevention Study II United States, 1982–1996, 14-year follow-up (553,593 women; 181 deaths)	Never smoked (60) Current smokers <20 cigarettes/day (27) 20 cigarettes/day (36) 21–39 cigarettes/day (10) 40 cigarettes/day (13)	1.00 4.80 8.41 6.07 12.15	 3.02–7.64 5.46–12.95 3.05–12.10 6.52–22.64	Adjusted for age

*RR = Relative risk.
†CI = Confidence interval.
‡Number of deaths by smoking category was not reported.
§NR = Data were not reported.

Table 2.11 Case-control studies on the association between smoking status and the risk of esophageal cancer stratified by histologic type

Study Location/population	Smoking status	Squamous cell carcinoma		
		Number of cases/controls	RR*	95% CI[†]
Men				
Kabat et al. 1993	Never smoked	NR[‡]	1.0	
	Current smokers	NR	4.5	2.5–8.1
United States, 1981–1990	Former smokers	NR	1.3	0.7–2.4
Hospital controls matched for age, gender, race, and hospital				
Castellsagué et al. 1999	Never smoked	655/1,408	1.0	
	Current smokers	415/581	5.1	3.4–7.6
South America, 1986–1992	Former smokers	208/494	2.8	1.8–4.3
Pooled analysis Hospital controls matched for age, gender, and hospital				
Women				
Kabat et al. 1993	Never smoked	NR	1.0	
	Current smokers	NR	6.8	3.7–12.1
United States, 1981–1990	Former smokers	NR	2.2	1.1–4.3
Hospital controls matched for age, gender, race, and hospital				
Castellsagué et al. 1999	Never smoked	112/297	1.0	
	Current smokers	43/41	3.1	1.8–5.3
South America, 1986–1992	Former smokers	20/33	1.6	0.8–3.1
Pooled analysis Hospital controls matched for age, gender, and hospital				

*RR = Relative risk.
[†]CI = Confidence interval.
[‡]NR = Data were not reported.

Adenocarcinoma			
Number of cases/controls	**RR**	**95% CI**	**Comments**
NR	1.0		Adjusted for age, education, alcohol intake, hospital, and calendar period
NR	2.3	1.4–3.9	
NR	1.9	1.2–3.0	
NR	NR	NR	Adjusted for age, hospital, education, and alcohol intake
NR	NR	NR	
NR	NR	NR	
NR	1.0		Adjusted for age, education, alcohol intake, hospital, and calendar period
NR	4.8	1.7–14.0	
NR	1.4	0.4–4.4	
NR	NR	NR	Adjusted for age, hospital, education, and alcohol intake
NR	NR	NR	
NR	NR	NR	

Table 2.11   Continued

Study Location/population	Smoking status	Squamous cell carcinoma		
		Number of cases/controls	RR	95% CI
Men and women				
Gao et al. 1994	Never smoked	195/882	1.0[§]	
	Current smokers	303/493	1.9	1.5–2.3
Shanghai, China, 1990–1993	Former smokers	57/114	1.6	1.1–2.3
Population controls matched for age and gender				
Gammon et al. 1997	Never smoked	22/244	1.0	
	Current smokers	108/155	5.1	2.8–9.2
United States, 1993–1995	Former smokers	91/296	2.8	1.5–4.9
Population controls matched for age and gender				
Lagergren et al. 2000	Never smoked	22/325	1.0	
	Current smokers	101/181	9.3	5.1–17.0
Sweden, 1995–1997	Former smokers	44/314	2.5	1.4–4.7
Population controls matched for age and gender				

[§]Approximate confidence intervals were calculated from cell counts.

Adenocarcinoma			
Number of cases/controls	**RR**	**95% CI**	**Comments**
15/882	1.0[§]		Adjusted for age, gender, education, alcohol and tea
25/493	2.1	1.1–4.0	consumption, other dietary factors, and birthplace
5/114	1.8	0.7–4.5	
63/244	1.0		Adjusted for age, gender, race, alcohol intake, body
86/155	2.2	1.4–3.3	mass index (BMI), income, and study site
144/296	2.0	1.4–2.9	
57/325	1.0		Adjusted for age, gender, education, alcohol intake,
43/181	1.6	0.9–2.7	BMI, reflux symptoms, fruit and vegetable intake,
89/314	1.9	1.2–2.9	energy intake (total calories), and physical activity

Table 2.12 Case-control studies on the association between current smoking, the number of cigarettes smoked per day, and the risk of esophageal cancer stratified by histologic type

Study Location/population	Cigarettes/day	Squamous cell carcinoma		
		Number of cases/controls	RR*	95% CI[†]
Men				
Zambon et al. 2000	Never smoked	19/139	1.0	
	Current smokers			
Northern Italy, 1992–1997	1–14	32/72	3.18	1.59–6.37
Hospital controls	15–24	79/84	5.35	2.82–10.12
	25[§]	40/28	6.97	3.22–15.06
			p <0.001	
Men and women				
Gao et al. 1994	Never smoked	195/882	1.0	
	Current smokers			
Shanghai, China, 1990–1993	1–9	30/114	1.1	0.7–1.7
Population controls matched	10–19	72/157	1.7	1.2–2.3
for age and gender	20–29	148/200	2.5	1.9–3.3
	30	53/22	4.8	2.9–8.1
			p <0.001	
Vaughan et al. 1995	Never smoked	10/240	1.0	
	Current smokers			
Washington, United States,	1–39 pack-years[¶]	14/69	5.2	1.7–16.2
1983–1990	40–79 pack-years	36/83	7.9	2.8–22.1
Population controls matched	80 pack-years	16/17	16.9	4.1–69.1
for age and gender			p <0.001	

*RR = Relative risk.
[†]CI = Confidence interval.
[‡]NR = Data were not reported.
[§]Category   25 cigarettes/day includes 12 cases and 30 controls who smoked pipes or cigars.
  Approximate confidence intervals were calculated from cell counts.
[¶]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Adenocarcinoma			
Number of cases/controls	RR	95% CI	Comments
NR‡	NR		Adjusted for age, education, alcohol intake, and geographic area
NR	NR	NR	
NR	NR	NR	
NR	NR	NR	
15/882	1.0		Adjusted for gender, education, alcohol and tea consumption, other dietary factors, and birthplace
5/114	2.0	0.8–5.0	
4/157	1.1	0.4–3.0	
13/200	2.0	1.1–3.6	
3/22	3.5	1.0–11.8	
	p >0.05		
56/240	1.0		Adjusted for age, gender, race, education, alcohol intake, and body mass index
21/69	1.4	0.7–2.7	
54/83	2.4	1.4–4.1	
21/17	3.4	1.4–8.0	
	p = 0.03		

Table 2.13   Cohort study on the association between smoking and the risk of esophageal cancer stratified by age at smoking cessation

Study Location/population	Age at cessation (deaths)	RR*	95% CI†	Comments
Men				
American Cancer Society, unpublished data	Current smokers (292)	4.73	3.73–6.00	Adjusted for age
	Age at cessation (years)			
	>60 (31)	3.60	2.35–5.52	
Cancer Prevention Study II	51–60 (76)	3.30	2.43–4.50	
United States, 1982–1996,	41–50 (85)	2.79	2.07–3.75	
14-year follow-up (352,363	31–40 (48)	1.84	1.30–2.62	
men; 649 deaths)	<31 (25)	1.68	1.07–2.62	
	Never smoked (92)	1.00		
Women				
American Cancer Society, unpublished data	Current smokers (86)	6.71	4.73–9.52	Adjusted for age
	Age at cessation (years)			
	>60 (6)	2.64	1.13–6.18	
Cancer Prevention Study II	51–60 (9)	2.77	1.36–5.63	
United States, 1982–1996,	41–50 (11)	3.16	1.64–6.10	
14-year follow-up (553,593	31–40 (4)	1.42	0.51–3.96	
women; 181 deaths)	<31 (5)	2.26	0.89–5.76	
	Never smoked (60)	1.00		

*RR = Relative risk.
†CI = Confidence interval.

Table 2.14 follows on page 130.

Table 2.14 Case-control studies on the association between smoking and the risk of esophageal cancer stratified by histologic type and years since smoking cessation

Study Location/population	Years since quitting	Squamous cell carcinoma		
		Number of cases/controls	RR*	95% CI[†]
Men				
Kabat et al. 1993	Current smokers	NR[‡]	1.0	
	1–5	NR	0.5	0.3–1.0
United States, 1981–1990	6–10	NR	0.4	0.2–0.8
Hospital controls matched for age,	11–20	NR	0.3	0.2–0.6
gender, race, and hospital	21	NR	0.2	0.1–0.3
Brown et al. 1994	Current smokers	NR	NR	NR
	1–9	NR	NR	NR
United States, 1986–1989	10–19	NR	NR	NR
Population controls matched for age	20–29	NR	NR	NR
	30	NR	NR	NR
	Never smoked	NR	NR	NR
Castellsagué et al. 1999	Current smokers	415/581	1.0	
	1–4	68/123	0.7	0.5–1.0
South America, 1986–1992	5–9	39/93	0.5	0.3–0.8
Pooled analysis of hospital controls matched for age, gender, and hospital	10	101/278	0.5	0.4–0.7
Zambon et al. 2000	<5	27/28	7.70	3.21–18.49
	5–9	27/44	4.10	1.84–9.10
Northern Italy, 1992–1997	10	51/198	1.54	0.79–3.02
Hospital controls	Never smoked	19/139	1.00 p <0.001	

*RR = Relative risk.
[†]CI = Confidence interval.
[‡]NR = Data were not reported.

Adenocarcinoma			
Number of cases/controls	**RR**	**95% CI**	**Comments**
NR	1.0		Adjusted for age, hospital, education, and alcohol intake
NR	0.5	0.2–1.1	
NR	1.1	0.6–1.9	
NR	1.2	0.8–1.9	
NR	0.5	0.3–0.9	
47/186	1.7	0.9–3.2	Adjusted for age, geographic area, alcohol intake, and income
26/97	2.0	1.0–4.1	
28/92	2.4	1.2–4.9	
21/78	2.2	1.0–4.7	
23/64	3.1	1.5–6.6	
16/160	1.0		
NR	NR	NR	Adjusted for age, hospital, education, and alcohol intake
NR	NR	NR	
NR	NR	NR	
NR	NR	NR	
NR	NR	NR	Adjusted for age, education, alcohol intake, and geographic area
NR	NR	NR	
NR	NR	NR	
NR	NR	NR	

Table 2.14 Continued

Study Location/population	Years since quitting	Squamous cell carcinoma		
		Number of cases/controls	RR	95% CI
	Women			
Kabat et al. 1993	Current smokers	NR	1.0	
	1–10	NR	0.4	0.2–0.9
United States, 1981–1990	11	NR	0.3	0.1–0.5
Hospital controls matched for age, gender, race, and hospital				
Castellsagué et al. 1999	Current smokers	43/41	1.0	
	1–9	11/12	1.0	0.3–3.1
South America, 1986–1992	10	9/21	0.4	0.1–1.2
Pooled analysis of hospital controls matched for age, gender, and hospital				
	Men and women			
Gammon et al. 1997	Current smokers	108/155	5.1	
	<11	47/74	5.6	2.8–9.2
United States, 1993–1995	11–20	24/77	2.3	2.9–10.8
Population controls matched for	21–30	8/78	1.0	1.1–4.8
age and gender	>30	12/67	1.8	0.4–2.7
	Never smoked	22/244	1.0	0.8–4.2
Lagergren et al. 2000	Current smokers	101/181	9.3	
	<3	93/152	10.3	5.1–17.0
Sweden, 1995–1997	3–10	18/62	5.2	5.6–19.1
Population controls matched for	11–25	15/112	2.1	2.4–11.3
age and gender	26	13/126	1.9	1.0–4.7
	Never smoked	22/325	1.0	0.8–4.0

| Number of cases/controls | Adenocarcinoma | | Comments |
	RR	95% CI	
	Women		
NR	1.0		Adjusted for age, hospital, education, and alcohol
NR	0.3	0.1–1.1	intake
NR	0.3	0.1–1.7	
NR	NR	NR	Adjusted for age, hospital, education, and alcohol
NR	NR	NR	intake
NR	NR	NR	
	Men and women		
86/155	2.2	1.4–3.3	Adjusted for age, gender, race, alcohol intake, body
44/74	2.7	1.6–4.4	mass index (BMI), income, and geographic area
43/77	2.3	1.4–3.8	
31/78	1.9	1.1–3.2	
26/67	1.2	0.7–2.2	
63/244	1.0		
43/181	1.6	0.9–2.7	Adjusted for age, gender, education, alcohol intake,
40/126	1.7	1.0–3.0	BMI, reflux symptoms, fruit and vegetable intake,
20/112	2.4	1.2–4.8	energy intake (total calories), and physical activity
29/62	1.6	0.9–2.5	
30/152	1.6	0.9–2.8	
57/325	1.0		

Table 2.15   Case-control studies on the association between smoking, alcohol use, and the risk of esophageal cancer

Study Location/population	Smoking status

Kabat et al. 1993
 	
United States, 1981–1990
Hospital controls matched for age, gender, race, and hospital
	Squamous cell carcinoma
	  Never smoked
	  Ever smoked
	Adenocarcinoma
	  Never smoked
	  Ever smoked

Brown et al. 1994 United States, 1986–1989 Population controls matched for age	Adenocarcinoma <1 pack/day (ever) 1 pack/day (ever)

Gao et al. 1994
 	
Shanghai, China, 1990–1993
Population controls matched for age and gender
	None
	Current smokers
	  <10 cigarettes/day
	  10–19 cigarettes/day
	  20 cigarettes/day

Castellsagué et al. 1999
 	
South America, 1986–1992
Pooled analysis of hospital controls matched for age, gender, and hospital
	Men
	  Never smoked
	  Ever smoked
	Women
	  Never smoked
	  Ever smoked

Zambon et al. 2000
 	
Northern Italy, 1992–1997
Hospital controls
	Never smoked
	Current smokers
	  1–14 cigarettes/day
	  15–24 cigarettes/day
	  25 cigarettes/day

*RR = Relative risk.
†CI = Confidence interval.
‡NR = Data were not reported.

			Alcohol use				
RR*	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI
Nondrinker		**≥1 drink/day**					
1.0		4.3	1.4–12.5	–	–	–	–
1.5	0.5–4.2	7.6	3.1–18.6	–	–	–	–
1.0		1.5	0.7–3.5	–	–	–	–
2.0	1.1–3.7	2.4	1.3–4.2	–	–	–	–
<8 drinks/week		**≥8 drinks/week**					
1.0		2.4	1.1–5.1	–	–	–	–
2.4	1.5–3.8	3.8	2.2–6.4	–	–	–	–
None		**<250 g/week**		**250–749 g/week**		**≥750 g/week**	
1.0		0.7	0.3–1.6	0.8	0.3–1.9	1.1	0.3–3.8
1.3	0.7–2.7	1.5	0.6–3.8	0.9	0.4–2.4	3.6	0.7–18.4
1.5	0.8–2.5	2.2	1.0–4.7	0.8	0.4–1.8	8.5	3.2–22.5
1.9	1.2–3.1	3.2	1.6–6.4	2.4	1.4–3.9	12.0	6.6–22.1
None		**Ever**					
1.00		4.03	1.76–9.21	–	–	–	–
4.45	2.09–9.47	17.00	8.36–34.78	–	–	–	–
1.00		1.42	0.82–2.48	–	–	–	–
1.57	0.89–2.75	7.26	3.68–14.33	–	–	–	–
0–20 drinks/week		**21–34 drinks/week**		**35–59 drinks/week**		**≥60 drinks/week**	
1.00		2.05	0.18–23.45	8.90	1.02–77.76	56.08	6.19–507.95
NR‡	NR	18.92	2.21–161.78	36.46	4.35–305.73	40.26	4.56–355.42
3.33	0.36–31.07	35.25	4.30–288.87	57.21	7.16–456.89	117.62	14.99–923.11
NR	NR	44.08	5.51–352.92	66.76	7.78–573.26	130.32	15.20–980.10

Pancreatic Cancer

In 2003, an estimated 30,700 new cases were diagnosed and 30,000 deaths attributable to pancreatic cancer were expected to occur (ACS 2003). Since 1980, incidence rates of pancreatic cancer have declined for men but remain stable for women. In parallel, mortality has decreased by 0.9 percent per year during the past 20 years among men, but has increased slightly among women. One proposed explanation for this trend is a lagged relationship between the prevalence of cigarette smoking and mortality from pancreatic cancer (Weiss and Bernarde 1983). The epidemiologic study of pancreatic cancer is hampered by poor survival rates, which reflect diagnoses at a late or advanced stage of the disease and the difficulty of surgical treatment. The median time from diagnosis to death is about three months, so persons diagnosed with pancreatic cancer may not be alive to participate in case-control studies.

Conclusions of Previous Surgeon General's Reports

The 1972 Surgeon General's report (USDHEW 1972) noted that epidemiologic evidence demonstrates a significant association between cigarette smoking and cancer of the pancreas. In 1979, the Surgeon General's report (USDHEW 1979) indicated that a dose-response relationship between cigarette smoking and pancreatic cancer had been demonstrated. Cigarette smoking was regarded as a contributing factor to pancreatic cancer in both the 1982 (USDHHS 1982) and 1989 (USDHHS 1989) reports. The 1982 report concluded, "Cigarette smoking is a contributory factor in the development of pancreatic cancer. . . .The term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site" (p. 7). The 1989 report estimated that 29 percent of pancreatic cancer deaths in men and 34 percent in women could be attributed to smoking. The 1990 report stated that "there is a weak, but consistently observed, association between smoking and pancreatic cancer and that former smokers experience a lower risk of pancreatic cancer than current smokers" (USDHHS 1990, p. 155).

Biologic Basis

Most pancreatic cancers arise in exocrine cells lining the pancreatic ductules. Animal models show that exposures to nitrosamines cause ductlike adenocarcinomas. Similar invasive tumors are produced by feeding the tobacco-specific N-nitrosamine, NNK, to rats (Rivenson et al. 1988). *K-ras* mutations occur in some experimental models of pancreatic cancer. For humans, there is now a large body of evidence that mutations in cellular proto-oncogenes and tumor suppressor genes are important events in pancreatic carcinogenesis. The highest frequency of *ras* mutations has been found in case series of adenocarcinoma of the pancreas. Numerous lines of evidence suggest that *K-ras* mutations are an early and key event in the pathogenesis of pancreatic cancer (Anderson et al. 1996). Investigations of *K-ras* mutations in pancreatic cancer show that the odds of mutation were significantly higher among smokers compared with nonsmokers in several but not all studies (Nagata et al. 1990; Hruban et al. 1993; Malats et al. 1997). Because *ras* mutations appear to be strongly related to cigarette smoking in other malignancies, this association adds support to a causal relationship between smoking and pancreatic cancer. Other potential mechanisms are supported by animal studies, which show that nitrosamines administered parenterally (any way except by mouth) or in drinking water experimentally induce pancreatic cancer (Rivenson et al. 1988). Tobacco-specific carcinogens

may reach the pancreas through the blood or through refluxed bile that is in contact with the pancreatic duct.

In addition to the nitrosamines that are present in high levels in cigarette smoke, aromatic amines also may play a role in pancreatic carcinogenesis. These agents require metabolic activation, probably in the liver or pancreas, to bind to DNA and cause mutations.

Epidemiologic Evidence

Since the association between smoking and pancreatic cancer was last considered in the Surgeon General's reports, substantial new evidence has been reported from both cohort (Table 2.16) and case-control studies (Table 2.17). The findings of these two types of studies are consistent in showing that smoking is associated with increased risk and that the risk increases with the number of cigarettes smoked. The cohort design has the advantage of prospective ascertainment of smoking, before the diagnosis of pancreatic cancer, but only the largest cohorts have substantial numbers of cases. Some of the case-control studies include large numbers of cases, but this approach is weakened by the need to use surrogate respondents for ill or deceased index cases. Alcohol, the principal potential confounding factor, was considered in many of the studies.

Studies conducted around the world provide consistent evidence for increased risk in smokers compared with lifetime nonsmokers. The RR estimates increase with pack-years or number of cigarettes smoked daily. At the highest levels of smoking, the RRs range from three up to five. Risks tend to be lower for former smokers than for current smokers.

Evidence Synthesis

There is now substantial observational evidence on smoking and cancer of the pancreas. Studies of case-control and cohort designs conducted around the world consistently show an increased risk for pancreatic cancer in smokers compared with lifetime nonsmokers. There is evidence for a dose-response relationship of risk with the amount smoked, and evidence that risk declines after quitting. New observations in *ras* mutations in pancreatic cancer further support a causal role for smoking, and pancreatic malignancy can be produced in rats with the tobacco-specific N-nitrosamine, NNK.

In 1986, IARC concluded that smoking causes cancer of the pancreas (IARC 1986). Since that report was published, many more studies support these causal links. In 2002, IARC again concluded that smoking causes cancer of the pancreas and that the risk for pancreatic cancer increases with the duration of smoking and the number of cigarettes smoked daily; the risk remains high after allowing for potential confounding factors such as alcohol consumption; and the risk decreases with increasing time since quitting smoking (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer.

Implications

Unfortunately, little can be done therapeutically once pancreatic cancer is diagnosed. Smoking prevention and cessation are the only potentially effective strategies for reducing the occurrence of pancreatic cancer.

Table 2.16   Cohort studies on the association between tobacco use and the risk of pancreatic cancer

Study	Population	Outcome	Tobacco exposure

Heuch et al. 1983	16,713 persons Norway 1964–1978	Diagnosis of pancreatic cancer	• Level of cigarette smoking
			    Never smoked
			    Former smokers
			    Current smokers
			        1–9 cigarettes/day
			        10 cigarettes/day
			• Tobacco chewing level
			    Never
			    Former or occasional
			        current use
			    Regular use

Zheng et al. 1993	26,030 white male policy-holders of the Lutheran Brotherhood Insurance Society Followed for 20 years (286,731 person-years) United States (nationwide) 1967–1986	Mortality from pancreatic cancer	• Never/former/current smokers • Tobacco use other than cigarettes
Doll et al. 1994	34,439 British male doctors United Kingdom 1951–1991 (40-year follow-up)	Mortality from pancreatic cancer	• Never/former/current smokers • Cigarettes/day
Shibata et al. 1994	13,979 residents of a retirement community outside of Los Angeles Began in 1981 9-year follow-up	Incident pancreatic cancer	• Cigarettes • Never smoked • Quit smoking 20 years ago • Recent quitters (<20 years) or current smokers

*CI = Confidence interval.
†RR = Relative risk.

Findings	Risk estimates (95% CI*)		Comments

• Some increased mortality was associated with tobacco use	*Men only*
	 Observed/expected number of cases
	 Level of cigarette smoking
	   Never smoked
	   Former smokers and 1–9
	    cigarettes/day
	   Current smokers of 10
	   cigarettes/day
	
	 Level of tobacco chewing
	   Never used
	   Former or occasional current use
	   Regular current use
	
	 Odds ratio
	 10 cigarettes/day vs. never
	 smokers
	 Regular chew users vs. never used
		
		 16/18.1
		 16/13.6
		
		 6/6.3
		
		 32/36.2
		 12/8.2
		 12/11.6
		
		 1.13
		
		 1.34
			Risk estimates were adjusted for region, urban/ rural place of residence, age, and gender; p values and 95% CIs were not provided

• 57 outcome events • Significant dose-response relation-ship	RR[†] Never used tobacco Used tobacco other than cigarettes Former cigarette smokers Current cigarette smokers <25 cigarettes/day 25 cigarettes/day p value for trend <0.01	 1.0 (referent) 0.8 (0.3–2.5) 1.0 (0.4–2.2) 1.4 (0.6–3.2) 3.9 (1.5–10.3)	RRs were adjusted for age and alcohol index

• ". . .clearly related to smoking." (p. 903)	Annual mortality per 100,000 men
	 Nonsmokers
	 Former smokers
	 Current smokers
	   1–14 cigarettes/day
	   15–24 cigarettes/day
	   25 cigarettes/day
		
		 16
		 23
		 35
		 30
		 29
		 49
			Mortality rates were standardized for age and calendar period; p value was not provided

• 65 outcome events	RR Never smoked Quit 20 years ago Quit <20 years ago and current smokers	 1.00 (referent) 1.38 (0.73–2.62) 1.20 (0.65–2.20)	RRs were adjusted for gender and age

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure
Engeland et al. 1996	26,000 men and women 230,000 person-years from men 310,000 person-years from women Norway 1966–1993	Diagnosis of pancreatic cancer	• Never/former smokers • Cigarettes/day
Fuchs et al. 1996	2 cohorts Nurses Health Study 118,339 female nurses Aged 30–55 years Began in 1976 Health Professionals Follow-Up Study 49,428 men Aged 40–75 years Began in 1986 2,116,229 person-years of follow-up were used for this analysis	NR[‡]	• Never/former/current smokers • Pack-years[§]

[‡]NR = Data were not reported.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
 BMI = Body mass index.

Findings	Risk estimates (95% CI)		Comments
• Significant risk for women smoking 5 cigarettes/day		RR	Risk estimates were adjusted for urban/rural place of residence
	Male cigarette behavior		
	Never smoked	1.0 (referent)	
	Former smokers	0.9 (0.6–1.5)	
	1–4 cigarettes/day	0.9 (0.5–1.8)	
	5–9 cigarettes/day	1.0 (0.5–2.1)	
	10–14 cigarettes/day	1.3 (0.7–2.4)	
	15 cigarettes/day	1.6 (0.8–3.2)	
	Female cigarette behavior		
	Never smoked	1.0 (referent)	
	Former smokers	0.6 (0.2–1.5)	
	1–4 cigarettes/day	0.9 (0.4–1.8)	
	5 cigarettes/day	1.8 (1.1–3.0)	
• Significant dose-response relationship for men and women with pack-years	Men	RR	RRs were adjusted for age, gender, BMI , and history of diabetes mellitus
	Never smoked	1.0 (referent)	
	Former smokers	1.3 (0.7–2.3)	
	Current smokers	3.0 (1.5–6.3)	
	Pack-years		
	Never smoked	1.0 (referent)	
	1–10 years	0.9 (0.3–2.6)	
	11–25 years	1.3 (0.7–2.7)	
	26–50 years	1.5 (0.7–3.1)	
	>50 years	2.8 (1.3–5.7)	
	p value for trend = 0.004		
	Women	RR	
	Never smoked	1.0 (referent)	
	Former smokers	1.1 (0.7–1.7)	
	Current smokers	2.4 (1.6–3.6)	
	Pack-years		
	Never smoked	1.0 (referent)	
	1–10 years	1.1 (0.6–1.9)	
	11–25 years	1.6 (1.0–2.7)	
	26–50 years	2.1 (1.4–3.3)	
	>50 years	1.3 (0.7–2.7)	
	p value for trend = 0.01		

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure
Burns et al. 1997	CPS-I[¶] ±68,000 ACS** volunteers Questionnaires were administered in 1959–1960, 1961, 1963, 1965, 1972 United States (nationwide)	Mortality from pancreatic cancer	• Cigarettes/day, stratified by age
Harnack et al. 1997	33,976 women Aged 55–69 years Iowa 1986–1994	Diagnosis of pancreatic cancer	• Never/former/current smokers • Pack-years

[¶]CPS-I = Cancer Prevention Study I.
**ACS = American Cancer Society.

Findings	Risk estimates (95% CI)		Comments
NR	Mortality risk ratios		Age distributions were standardized using the 1980 distribution of the U.S. population; p values and 95% CIs were not provided
	Men		
	1–19 cigarettes/day		
	Aged 35–49 years	1.4	
	Aged 50–64 years	1.8	
	Aged 65–79 years	1.8	
	Aged 80 years	1.1	
	20 cigarettes/day		
	Aged 35–49 years	1.2	
	Aged 50–64 years	2.4	
	Aged 65–79 years	2.3	
	Aged 80 years	1.3	
	>20 cigarettes/day		
	Aged 35–49 years	1.5	
	Aged 50–64 years	2.5	
	Aged 65–79 years	2.6	
	Aged 80 years	2.2	
	Women		
	1–19 cigarettes/day		
	Aged 35–49 years	2.4	
	Aged 50–64 years	1.5	
	Aged 65–79 years	1.4	
	Aged 80 years	1.3	
	20 cigarettes/day		
	Aged 35–49 years	4.7	
	Aged 50–64 years	1.4	
	Aged 65–79 years	1.1	
	Aged 80 years	2.5	
	>20 cigarettes/day		
	Aged 35–49 years	2.5	
	Aged 50–64 years	2.2	
	Aged 65–79 years	2.2	
	Aged 80 years	NR	
• 83 outcome events • Significant dose-response relationship with pack-years	RR		RRs were adjusted for age
	Never smoked	1.00 (referent)	
	Former smokers	1.08 (0.55–2.11)	
	Current smokers	2.35 (1.32–4.17)	
	Pack-years		
	Never smoked	1.00 (referent)	
	<20 pack-years	1.14 (0.53–2.45)	
	20 pack-years	1.92 (1.12–3.30)	
	p value for trend = 0.02		

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure
Hrubec and McLaughlin 1997	U.S. Veterans Study (update) 293,658 persons Aged 31–84 years (mainly white male World War I veterans who held active U.S. government life insurance policies in December 1953) Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 26 years of follow-up United States (nationwide)	Mortality from pancreatic cancer	• Never smoked • Former cigarette smokers • Current cigarette smokers • Cigarettes/day • Cigars only • Pipes only
Coughlin et al. 2000	CPS-II[††] ±77,000 ACS[**] volunteers Initial questionnaire administered in 1982 United States (nationwide and Puerto Rico) 1982–1996	NR	• Years since smoking cessation • Cigarettes/day (current smokers) • Duration of smoking (years; current smokers)

[**]ACS = American Cancer Society.
[††]CPS-II = Cancer Prevention Study II.

Findings	Risk estimates (95% CI)		Comments
• Risk estimate was not significant	Former smokers RR = 1.1 (0.9–1.3)		RRs were adjusted for age

• Significant risk for both male and female current smokers
• Significant dose-response relationship for cigarettes/day (men and women)
• Significant dose-response relationship for duration of smoking in men only
	RR
	Men
	  Years since cessation
	    <10 years
	    10–19 years
	    20 years
	
	  Current smokers
	    <10 cigarettes/day
	    10–19 cigarettes/day
	    20 cigarettes/day
	    >20 cigarettes/day
	  p value for trend = 0.03
	
	  Duration of smoking
	    25 years
	    >25–35 years
	    >35–45 years
	    >45 years
	  p value for trend = 0.02
	
	Women
	  Years since cessation
	    <10 years
	    10–19 years
	    20 years
	
	  Current smokers
	    <10 cigarettes/day
	    10–19 cigarettes/day
	    20 cigarettes/day
	    >20 cigarettes/day
	  p value for trend = 0.001
		1.6 (1.2–2.0)
		1.3 (1.0–1.5)
		1.0 (0.9–1.2)
		
		2.1 (1.9–2.4)
		1.8 (1.4–2.5)
		1.7 (1.3–2.2)
		2.1 (1.8–2.6)
		2.4 (2.0–2.8)
		
		1.6 (1.1–2.3)
		2.4 (2.0–3.0)
		2.1 (1.7–2.5)
		2.0 (1.7–2.5)
		
		1.3 (1.0–1.8)
		1.7 (1.4–2.0)
		0.9 (0.8–1.1)
		
		2.0 (1.8–2.3)
		1.2 (0.9–1.6)
		1.9 (1.6–2.4)
		2.3 (1.9–2.7)
		2.3 (1.9–2.8)
			Death rates were standardized to the CPS-II population; RRs were adjusted for age; race; years of education; family history of pancreatic cancer in first-degree relative; history of gallstones; history of diabetes; BMI; and consumption of alcohol, total red meat, citrus fruits and juices, and vegetables

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure
Coughlin et al. 2000 (risk estimates continued)			
Nilsen and Vatten 2000	31,000 men 32,374 women Norway 1984–1996 (12-year follow-up)	Incident cases of pancreatic cancer	• Never/former/current smokers • Pack-years for ever and current smokers • Cigarettes/day • Time since cessation

Findings	Risk estimates (95% CI)		Comments
	Duration of smoking		
	25 years	2.0 (1.6–2.6)	
	>25–35 years	2.1 (1.7–2.6)	
	>35–45 years	1.7 (1.4–2.1)	
	>45 years	2.3 (1.9–2.9)	
	p value for trend = 0.42		
• 166 outcome events	Men	RR	RRs were adjusted for age
• Significant risk was associated with current smoking in men and women	Never smoked	1.0 (referent)	
	Former smokers	1.3 (0.8–2.4)	
	Current smokers	2.1 (1.2–3.6)	
	p value for trend = 0.007		
• For women, all trends were significant	Pack-years among ever smokers		
	1–14 pack-years	1.4 (0.7–2.8)	
	>14 pack-years	1.5 (0.8–2.9)	
	p value for trend = 0.17		
	Pack-years among current smokers		
	1–14 pack-years	1.1 (0.4–3.3)	
	>14 pack-years	2.3 (1.2–4.3)	
	p value for trend = 0.02		
	Cigarettes/day		
	1–10 cigarettes/day	1.5 (0.7–3.1)	
	>10 cigarettes/day	2.5 (1.2–5.4)	
	p value for trend = 0.02		
	Time since cessation		
	Current smokers	1.0 (referent)	
	5 years	1.0 (0.5–2.2)	
	>5 years	0.6 (0.3–1.0)	
	Never smoked	0.5 (0.3–0.8)	
	p value for trend = 0.004		
	Women	RR	
	Never smoked	1.0 (referent)	
	Former smokers	1.8 (0.8–4.2)	
	Current smokers	2.1 (1.1–4.2)	
	p value for trend = 0.03		
	Pack-years among ever smokers		
	1–8.5 pack-years	0.9 (0.3–3.1)	
	>8.5 pack-years	2.5 (1.2–5.2)	
	p value for trend = 0.03		

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure
Nilsen and Vatten 2000 (risk estimates continued)			
Shapiro et al. 2000	CPS-II[††] ±77,000 ACS** volunteers Initial questionnaire administered in 1982 12-year follow-up United States (nationwide and Puerto Rico) 1982–1996	Mortality from pancreatic cancer	• Never smoked • Cigars/day • Duration of cigar smoking
Lowenfels et al. 2001	497 patients with hereditary pancreatitis	Diagnosis of pancreatic cancer	• Ever/never smoked

**ACS = American Cancer Society.
[††]CPS-II = Cancer Prevention Study II.

Findings	Risk estimates (95% CI)	Comments
	Pack-years among current smokers	
	1–8.5 pack-years 0.2 (0.3–5.4)	
	>8.5 pack-years 2.8 (1.3–6.2)	
	p value for trend = 0.01	
	Cigarettes/day	
	1–9 cigarettes/day 1.6 (0.6–4.6)	
	>9 cigarettes/day 2.7 (1.2–6.1)	
	p value for trend = 0.02	
	Time since cessation	
	Current smokers 1.0 (referent)	
	5 years 1.3 (0.4–4.6)	
	>5 years 0.5 (0.2–1.9)	
	Never smoked 0.5 (0.2–1.0)	
	p value for trend = 0.03	

• 327 outcome events
• No significant
  associations
	<u>Mortality rate ratios</u>
	Never smoked 1.0 (referent)
	1–2 cigars/day 0.6 (0.3–1.4)
	  3 cigars/day 1.6 (1.0–2.5)
	
	Years of cigar smoking
	  <25 years 1.5 (0.7–3.3)
	  25 years 1.1 (0.7–1.8)
		RRs were adjusted for age, alcohol consumption, and smokeless tobacco use

NR	<u>Median age at diagnosis of pancreatic cancer</u> Never smoked 50 years old Ever smoked 70 years old p = 0.02	

Table 2.16   Continued

Study	Population	Outcome	Tobacco exposure

Michaud et al. 2001	2 cohorts
	  Nurses Health Study
	    118,339 female nurses
	    Aged 30–55 years
	    Began in 1976
	  Health Professionals Follow-Up Study
	    49,428 men
	    Aged 40–75 years
	    Began in 1986
	  1,907,222 total person-years of follow-up
		Incident cases of pancreatic cancer	• Never/former/current smokers, stratified by coffee and alcohol intake

Findings	Risk estimates (95% CI)		Comments
• 288 outcome events • Positive risk association with current smokers who drink alcohol	<u>RR by coffee intake</u>		RRs were adjusted for age, history of diabetes mellitus, history of cholecystectomy, energy intake, period, and pack-years of smoking; p values and 95% CIs were not provided
	Never smoked		
	No coffee	1.0 (referent)	
	<1/day	1.25	
	1/day	0.72	
	2–3/day	1.01	
	>3/day	NR	
	Former smokers		
	No coffee	1.0 (referent)	
	<1/day	0.95	
	1/day	0.46	
	2–3/day	0.75	
	>3/day	0.43	
	Current smokers		
	No coffee	1.0 (referent)	
	<1/day	0.35	
	1/day	0.56	
	2–3/day	0.74	
	>3/day	0.43	
	<u>RR by alcohol intake</u>		
	Never smoked		
	No alcohol	1.0 (referent)	
	0.1–4.9 g/day	0.95	
	5.0–14.9 g/day	0.77	
	15 g/day	0.96	
	Former smokers		
	No alcohol	1.0 (referent)	
	0.1–4.9 g/day	0.82	
	5.0–14.9 g/day	0.74	
	15 g/day	0.72	
	Current smokers		
	No alcohol	1.0 (referent)	
	0.1–4.9 g/day	1.28	
	5.0–14.9 g/day	1.25	
	15 g/day	1.65	

Table 2.16 Continued

Study	Population	Outcome	Tobacco exposure
Stolzenberg-Solomon et al. 2001	Alpha-tocopherol, beta-carotene Cancer Prevention Survey 27,101 healthy male smokers Finland 1985–1997 (13-year follow-up)	Diagnosis of pancreatic cancer	• Cigarettes/day • Duration of smoking • Pack-years • Age at smoking initiation
Isaksson et al. 2002	Swedish Twin Registry 12,204 women 9,680 men Sweden 1969–1997	Diagnosis of pancreatic cancer	• Nonsmokers • Former cigarette smokers • Current cigarette smokers • Light smokers (1–10 cigarettes/day) • Regular smokers (11 cigarettes/day) • Cigars or pipes

Findings	Risk estimates (95% CI)		Comments
• 157 outcome events • Significant positive dose-response relationship with cigarettes/day and pack-years	Multivariate hazards ratios		Risk estimates were adjusted for age and intervention
	<14 cigarettes/day	1.00 (referent)	
	14–19 cigarettes/day	1.42 (0.85–2.40)	
	20 cigarettes/day	1.14 (0.70–1.86)	
	21–25 cigarettes/day	1.32 (0.75–2.32)	
	>25 cigarettes/day	1.82 (1.10–3.03)	
	p value for trend = 0.05		
	Duration of smoking		
	<30 years	1.00 (referent)	
	30–34 years	1.13 (0.61–2.10)	
	35–39 years	1.20 (0.72–2.02)	
	40–42 years	1.49 (0.89–2.50)	
	>42 years	1.39 (0.75–2.56)	
	p value for trend = 0.22		
	Pack-years		
	<22 pack-years	1.00 (referent)	
	22–31 pack-years	1.18 (0.69–2.03)	
	32–39 pack-years	1.23 (0.71–2.12)	
	40–49 pack-years	1.26 (0.75–2.13)	
	>49 pack-years	1.66 (1.02–2.72)	
	p value for trend = 0.04		
	Age at smoking initiation		
	<17 years old	1.00 (referent)	
	17–18 years old	0.88 (0.56–1.41)	
	19 years old	0.99 (0.52–1.87)	
	20–21 years old	0.87 (0.55–1.38)	
	>21 years old	1.02 (0.64–1.64)	
	p value for trend = 0.85		
• No significant associations	RR		RRs were adjusted for gender and age
	Nonsmokers	1.00 (referent)	
	Former smokers	0.75 (0.42–1.43)	
	Current smokers	1.39 (0.96–1.99)	
	Light smokers	1.37 (0.94–2.00)	
	Regular smokers	1.25 (0.75–2.08)	
	Cigars or pipes	0.58 (0.28–1.19)	

Table 2.17   Case-control studies on the association between smoking and the risk of pancreatic cancer

Study	Population	Tobacco exposure	Findings
Mack et al. 1986	490 cases of pancreatic cancer diagnosed after 1976 490 controls individually matched for age, gender, race, and neighborhood Los Angeles	• Cigarette smoking • Years since cessation • Number of packs/day	• Significant risk was associated with smoking cigarettes
Falk et al. 1988	363 incident cases of pancreatic cancer 1,234 hospital controls Louisiana 1979–1983	• Cigarettes/day • Duration of smoking (years)	• Significant risk was associated with smoking >15 cigarettes/day
Farrow and Davis 1990	148 cases of married men with cancer of the pancreas Aged 20–74 years 188 population controls, frequency matched for age Washington state 1982–1986	• Ever/never smoked cigarettes • Duration of smoking (years) • Cigarettes/day • Pack-years[§]	• Significant dose-response relationship with duration of smoking (years), cigarettes/day, and pack-years

*CI = Confidence interval.
†RR = Relative risk.
‡OR = Odds ratio.
§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Risk estimates (95% CI*)		Comments
RR[†]		No adjustments
Never smoked	1.0 (referent)	
Years since cessation (former smokers)		
0–4 years	3.3 (1.6–6.9)	
5–9 years	2.3 (1.2–4.3)	
10 years		
1 pack/day	1.1 (0.7–1.8)	
>1 pack/day	0.9 (0.5–1.7)	
Current smokers		
1 pack/day	2.4 (1.7–3.6)	
>1 pack/day	2.1 (1.4–3.2)	
OR[‡]		95% CIs were not provided; ORs were adjusted for age; respondent type; residence; gender; history of diabetes mellitus; and coffee, alcohol, and fruit consumption
Never smoked	1.0 (referent)	
Cigarettes/day		
1–15	1.50	
16–25	1.90 (p <0.05)	
26	2.03 (p <0.05)	
p value for trend = <0.05		
Duration of smoking		
1–26 years	2.00	
27–39 years	2.11 (p <0.05)	
40–47 years	1.49	
48 years	1.74	
p value for trend not significant		
OR		ORs were adjusted for age, race, and education
Never smoked	1.0 (referent)	
Ever smoked	1.8 (1.1–2.9)	
Duration of smoking		
<1 year	1.0 (referent)	
1–26 years	1.1 (0.6–2.4)	
27–40 years	1.3 (0.6–2.7)	
>40 years	2.4 (1.3–4.7)	
p value for trend = 0.003		
Cigarettes/day		
0 cigarettes/day	1.0 (referent)	
<20 cigarettes/day	1.6 (0.8–3.0)	
20–29 cigarettes/day	1.7 (1.0–3.2)	
30 cigarettes/day	2.4 (1.3–4.7)	
p value for trend = 0.017		

Table 2.17 Continued

Study	Population	Tobacco exposure	Findings
Farrow and Davis 1990 (continued)			
Ghadirian et al. 1991	179 cases of pancreatic cancer Aged 35–79 years 239 population controls matched for age, gender, and place of residence Quebec 1984–1988	• Lifetime cigarette use • Duration of cigarette smoking	• Significant risks for former smokers for any number of years of smoking
Howe et al. 1991	249 cases of pancreatic cancer 505 population controls matched for gender and age Toronto 1983–1986	• Pack-years	• Significant risk in women who smoked more than 17.9 pack-years

Risk estimates (95% CI)		Comments
Pack-years		
<1 pack-year	1.0 (referent)	
1–20 pack-years	1.0 (0.5–2.0)	
21–50 pack-years	1.7 (0.9–3.1)	
>50 pack-years	2.3 (1.3–4.2)	
p value for trend = 0.003		
<u>OR</u>		ORs were adjusted for age, gender, and response status; controls were matched to cases for age and gender; risk brackets were not the same for current smokers and former smokers
Never smoked	1.0 (referent)	
<u>Lifetime cigarette habit</u>		
Current smokers		
1–146,000 cigarettes	3.61 (1.31–9.95)	
146,000–301,125 cigarettes	1.86 (0.65–5.35)	
301,125–459,900	2.36 (0.89–6.23)	
>459,900 cigarettes	5.15 (1.65–16.1)	
χ^2 for trend = 8.30		
Former smokers		
1–104,025 cigarettes	0.97 (0.34–2.78)	
104,025–219,000 cigarettes	3.40 (1.23–9.43)	
219,000–405,150 cigarettes	5.44 (1.77–16.7)	
>405,150 cigarettes	3.99 (1.31–12.2)	
χ^2 for trend = 11.70		
<u>Duration of smoking</u>		
Current smokers		
1–28 years	2.13 (0.63–7.24)	
29–40 years	2.89 (1.01–8.30)	
41–48 years	3.61 (1.28–10.2)	
>48 years	3.23 (1.14–9.17)	
χ^2 for trend = 9.03		
Former smokers		
1–20 years	1.19 (0.42–3.41)	
21–32 years	2.87 (1.01–8.13)	
33–39 years	3.03 (1.05–8.71)	
>39 years	6.17 (1.95–19.5)	
χ^2 for trend = 11.97		
<u>Men</u>	<u>RR</u>	Risk estimates were adjusted for calories and fiber intake; 95% CIs were not provided for RRs for years since smoking cessation
0 pack-years	1.00 (referent)	
>0–17 pack-years	0.87 (0.40–1.86)	
18–37 pack-years	1.57 (0.81–3.07)	
38 pack-years	1.63 (0.84–3.16)	
<u>Women</u>	<u>RR</u>	
0 pack-years	1.00 (referent)	
>0–17 pack-years	1.40 (0.71–2.77)	
18–37 pack-years	3.38 (1.53–7.50)	
38 pack-years	4.73 (1.96–11.4)	

Table 2.17   Continued

Study	Population	Tobacco exposure	Findings
Kalapothaki et al. 1993	181 cases that were operated on for cancer of the exocrine pancreas 181 hospital patient controls and 181 hospital visitor controls matched individually for hospital, gender, and age Athens, Greece 1991–1992	• Cigarettes/day	• "Tobacco smoking was related positively to risk of pancreas cancer, although the association was more evident in the comparison with visitor controls. . . ." (p. 378)
Zatonski et al. 1993	110 cases of pancreatic cancer 195 controls, frequency matched for age, gender, and residence Opole, Poland 1985–1988	• Never/ever smoked • Lifetime cigarette use (grouped by quartiles)	• No significant associations
Silverman et al. 1994	526 cases of pancreatic cancer Aged 30–79 years 2,153 population controls, frequency matched for area, age, race, and gender Atlanta, Detroit, and New Jersey 1986–1989	• Never/former/current smokers • Cigarettes/day • Duration of smoking (years) • Pack-years	• Significant dose-response relationship with all exposure categories

Risk estimates (95% CI)		Comments
Hospital controls	Rate ratios	RRs were adjusted for age, gender, and hospital
Nonsmokers	1.00 (referent)	
1–10 cigarettes/day	1.25 (0.54–2.88)	
11–20 cigarettes/day	1.52 (0.85–2.74)	
21 cigarettes/day	1.36 (0.76–2.44)	
Visitor controls	Rate ratios	
Nonsmokers	1.00 (referent)	
1–10 cigarettes/day	1.01 (0.45–2.28)	
11–20 cigarettes/day	1.89 (1.02–3.50)	
21 cigarettes/day	1.84 (0.93–3.63)	
<u>OR</u>		ORs were adjusted for age, gender, and years of schooling
Never smoked	1.00 (referent)	
Ever smoked	1.49 (0.79–2.80)	
Second quartile	0.81 (0.36–1.83)	
Third quartile	2.93 (1.31–6.58)	
Fourth quartile	1.54 (0.68–3.49)	
p value for trend = 0.061		
<u>OR</u>		ORs were adjusted for age, race, gender, area, income, alcohol consumption, and gallbladder disease
Never smoked	1.0 (referent)	
Ever smoked	1.7 (1.3–2.2)	
Former smokers	1.4 (1.1–1.9)	
Current smokers	2.0 (1.5–2.6)	
<20 cigarettes/day	1.3 (0.9–1.7)	
20–39 cigarettes/day	2.2 (1.7–3.0)	
40 cigarettes/day	1.8 (1.2–2.8)	
p value for trend = <0.0001		
Duration of smoking		
<20 years	1.1 (0.7–1.6)	
20–39 years	1.8 (1.3–2.4)	
40 years	1.8 (1.2–2.8)	
p value for trend = <0.0001		
Pack-years		
<20 pack-years	1.3 (0.9–1.7)	
20–44 pack-years	1.9 (1.4–2.6)	
45 pack-years	2.2 (1.6–3.1)	
p value for trend = <0.0001		

Table 2.17   Continued

Study	Population	Tobacco exposure	Findings
Ji et al. 1995	451 incident cases of pancreatic cancer in patients aged 30–74 years 1,552 population controls, frequency matched for gender and age Shanghai 1987–1989	• Nonsmokers • Former smokers • Current smokers • Cigarettes/day • Duration of smoking • Pack-years • Age at smoking initiation	• Significant dose-response relationship with cigarettes/day, duration of smoking, pack-years, and age at smoking initiation among men

Risk estimates (95% CI)		Comments
<u>Men</u>	<u>OR</u>	ORs were adjusted for age, income, education (women only), and green tea consumption (women only)
Nonsmokers	1.0 (referent)	
Former smokers	1.2 (0.8–2.0)	
Current smokers	1.6 (1.1–2.2)	
1–9 cigarettes/day	0.9 (0.5–1.6)	
10–19 cigarettes/day	1.3 (0.8–2.0)	
20–29 cigarettes/day	1.7 (1.1–2.4)	
30 cigarettes/day	5.0 (2.7–9.3)	
p value for trend = <0.0001		
Duration of smoking		
0.5–19 years	0.8 (0.4–1.5)	
20–29 years	1.4 (0.8–2.3)	
30–39 years	1.7 (1.0–2.7)	
40 years	2.3 (1.5–3.5)	
p value for trend = <0.001		
Pack-years		
<15 pack-years	0.8 (0.5–1.4)	
15–34 pack-years	1.5 (1.0–2.2)	
35 pack-years	2.4 (1.6–3.6)	
p value for trend = <0.0001		
Age at smoking initiation		
<20 years	1.7 (1.0–2.6)	
20–29 years	1.6 (1.1–2.3)	
30 years	1.5 (1.0–2.3)	
p value for trend = 0.01		
<u>Women</u>	<u>OR</u>	
Nonsmokers	1.0 (referent)	
Former smokers	1.6 (0.6–4.0)	
Current smokers	1.4 (0.9–2.4)	
1–9 cigarettes/day	1.1 (0.5–2.3)	
10–19 cigarettes/day	1.3 (0.5–3.2)	
20 cigarettes/day	2.8 (1.1–7.0)	
p value for trend = 0.05		
Duration of smoking		
0.5–19 years	0.6 (0.2–2.2)	
20–29 years	1.4 (0.5–4.0)	
30–39 years	1.7 (0.9–4.4)	
40 years	2.0 (0.9–4.4)	
p value for trend = 0.06		
Pack-years		
<10 pack-years	1.0 (0.5–2.0)	
10 pack-years	2.0 (1.0–3.8)	
p value for trend = 0.07		

Table 2.17   Continued

Study	Population	Tobacco exposure	Findings
Ji et al. 1995 (risk estimates continued)			
Partanen et al. 1997	662 decedent pancreatic cancer cases 1,770 cancer controls Finland 1984–1987	• Cigarettes/day • Pipes/cigars only	• All smoking (except cigarettes occasionally) was a significant positive risk factor
Villeneuve et al. 2000	583 cases of pancreatic cancer 4,813 population controls, frequency matched for age and gender Canada (nationwide) 1994–1997	• Duration of smoking • Cigarettes/day • Pack-years	Data were not reported

Risk estimates (95% CI)		Comments
Age at smoking initiation		
<25 years	2.4 (1.0–5.6)	
25 years	1.2 (0.6–2.1)	
p value for trend = 0.07		
	OR	ORs were adjusted for age and gender
Never smoked	1.00 (referent)	
Cigarettes occasionally	1.68 (0.98–2.87)	
1–9 cigarettes/day	1.61 (1.16–2.23)	
10–20 cigarettes/day	1.91 (1.47–2.49)	
>20 cigarettes/day	2.29 (1.65–3.19)	
Pipes/cigars only	2.34 (1.26–4.35)	
All smokers	1.96 (1.58–2.43)	
Men	OR	For men, ORs were adjusted for age, province, alcohol and coffee consumption, energy intake, and dietary fat; for women, ORs were adjusted for age, province, number of live births, alcohol and coffee consumption, energy intake, and dietary fat
Never smoked	1.00 (referent)	
Duration of smoking		
<20 years	0.76 (0.50–1.16)	
20–39 years	1.31 (0.92–1.86)	
40 years	1.14 (0.76–1.71)	
1–9 cigarettes/day	0.81 (0.48–1.36)	
10–24 cigarettes/day	1.07 (0.76–1.50)	
25 cigarettes/day	1.22 (0.82–1.82)	
1–14 pack-years	0.70 (0.46–1.07)	
15–29 pack-years	1.18 (0.81–1.72)	
30 pack-years	1.46 (1.00–2.14)	
Women	OR	
Never smoked	1.00 (referent)	
Duration of smoking		
<20 years	1.06 (0.68–1.65)	
20–39 years	1.44 (1.00–2.07)	
40 years	1.78 (1.12–2.81)	
1–9 cigarettes/day	1.07 (0.68–1.69)	
10–24 cigarettes/day	1.51 (1.07–2.13)	
25 cigarettes/day	1.53 (0.89–2.62)	
1–14 pack-years	0.86 (0.53–1.39)	
15–29 pack-years	1.44 (0.96–2.16)	
30 pack-years	1.84 (1.25–2.69)	

Table 2.17 Continued

Study	Population	Tobacco exposure	Findings
Chiu et al. 2001	376 pancreatic cancer cases 2,434 population controls, frequency matched for gender and age Iowa 1986–1989	• Never/ever smoked • Former smokers • Current smokers • Cigarettes/day • Duration of smoking • Pack-years	• Dose-response relationship with cigarettes/day was significant for women but not for men (p values for trend were not provided)

Risk estimates (95% CI)		Comments
<u>Men</u>	<u>OR</u>	Risk estimates were adjusted for age, total
Never smoked	1.0 (referent)	energy intake, education, meat and coffee
Ever smoked	1.8 (1.2–2.8)	consumption, pancreatitis, jaundice, and
Former smokers	1.5 (1.0–2.4)	number of first-degree relatives with
Current smokers	2.5 (1.2–4.1)	pancreatic cancer
10 cigarettes/day	2.2 (1.2–3.9)	
11–20 cigarettes/day	1.3 (0.7–2.1)	
21–40 cigarettes/day	2.3 (1.4–3.8)	
>40 cigarettes/day	1.4 (0.6–3.1)	
Duration of smoking		
20 years	1.5 (0.8–2.8)	
21–40 years	1.3 (1.0–1.6)	
>40 years	1.2 (1.0–1.5)	
Pack-years		
20 pack-years	2.0 (1.2–3.4)	
21–40 pack-years	1.5 (0.9–2.6)	
>40 pack-years	1.9 (1.2–3.0)	
<u>Women</u>	<u>OR</u>	
Never smoked	1.0 (referent)	
Ever smoked	2.1 (1.4–3.1)	
Former smokers	1.7 (1.0–2.9)	
Current smokers	2.4 (1.5–3.9)	
10 cigarettes/day	1.8 (1.0–3.1)	
11–20 cigarettes/day	1.8 (1.1–3.2)	
21–40 cigarettes/day	2.2 (1.1–4.2)	
>40 cigarettes/day	8.9 (1.8–43.5)	
Duration of smoking		
20 years	1.5 (0.6–3.9)	
21–40 years	1.5 (1.2–2.0)	
>40 years	1.2 (1.0–1.5)	
Pack-years		
20 pack-years	2.4 (1.4–4.0)	
21–40 pack-years	1.1 (0.5–2.3)	
>40 pack-years	2.5 (1.5–4.3)	

Bladder and Kidney Cancers

Incidence and mortality rates from bladder cancer vary by gender, race, ethnicity, and age. Bladder cancer incidence rates declined significantly during the 1990s. In 2003, an estimated 57,400 new cases were diagnosed, and an estimated 12,500 deaths were expected to occur (ACS 2003). Overall, bladder cancer incidence is about four times higher in men than in women, and two times higher in whites than in blacks (Ries et al. 2003). Since the 1970s, the mortality rates for bladder cancer have decreased significantly in both whites and blacks.

Cancer can arise in the kidney as renal cell carcinoma or adenocarcinoma, or as a transitional cell carcinoma in the renal pelvis. Transitional cell carcinomas can also occur in the ureters that carry urine to the bladder. The incidence of kidney cancer (including the renal pelvis) is lower than that of bladder cancer, and is higher in men than in women, but the gender difference is less marked than for bladder cancer (Ries et al. 2003). In 2003, an estimated 31,900 new cases were diagnosed and 11,900 deaths were expected to occur (ACS 2003).

Conclusions of Previous Surgeon General's Reports

A relationship between smoking and bladder cancer was noted in the 1964 Surgeon General's report (USDHEW 1964). The 1972 report (USDHEW 1972) concluded that epidemiologic studies demonstrate a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. Further, the report noted that the risk of developing bladder cancer increases with the number of cigarettes smoked. The 1979 report (USDHEW 1979) concluded that cigarette smoking acts independently of and synergistically with other factors to increase the risk of bladder cancer. The 1980 report (USDHHS 1980) noted a dose-response relationship between cigarette smoking and the risk of bladder cancer, and the 1990 report (USDHHS 1990) concluded that smoking causes bladder cancer. Cigarette smoking may account for 30 to 40 percent of bladder cancer cases (USDHHS 1982), and successfully quitting smoking before 50 years of age reduces the risk by about 50 percent after 15 years,

in comparison with continued smoking (USDHHS 1990).

Previous Surgeon General's reports summarized evidence regarding kidney cancer in 1982 and 1989. The 1982 report concluded that cigarette smoking is a contributory factor in the development of kidney cancer (USDHHS 1982). The 1989 report indicated a positive association between smoking and kidney cancer, with a RR ranging from 1.0 to more than 5.0 (USDHHS 1989). The risk increased with the number of cigarettes smoked and with the duration of smoking in both men and women.

Biologic Basis

Many products of metabolized components of tobacco smoke are cleared from the body through the kidneys and urine, thus exposing the kidney and bladder to these carcinogenic agents and their metabolites. N-nitrosodimethylamine, a substance found in cigarette smoke, causes kidney tumors in a number of animal models (Shiao et al. 1998). In humans, the urine of smokers has increased mutagenic activity, implying a potential to change the DNA of epithelial cells (Yamasaki and Ames 1977). An analysis of tissue samples from 89 renal cell carcinomas indicated that *p53* mutations identified in these malignancies were similar to those identified in bladder cancers (Bringuier et al. 1998). This observation points to smoking as a shared etiologic factor for cancers of both sites.

Epidemiologic Evidence

Increased risks for cancers of the bladder, kidney, renal pelvis, and ureter have been documented for both male and female smokers. Cigarette smoking is well established as a cause of bladder cancer, with results from approximately 30 case-control studies and 10 prospective cohort studies supporting this relationship (Silverman et al. 1996). The risk increases with the number of cigarettes smoked and the duration of smoking, and declines after smoking cessation. For kidney cancer, a number of studies have shown a dose-response relationship with the number of cigarettes smoked in men and women. Further, the risk

associated with cigarette smoking declines significantly with years of cessation (McLaughlin et al. 1996). Results for renal pelvis and ureter cancer are somewhat stronger, and cigarette smoking accounts for most of these cancers in the United States (70 to 82 percent in men and 37 to 61 percent in women) (McLaughlin et al. 1996).

Recent epidemiologic studies confirm these earlier findings. The 40-year follow-up study of the British physicians cohort shows increasing risks of bladder cancer with an increase in the number of cigarettes smoked per day, and lower risks among former smokers compared with current smokers (Doll et al. 1994). Likewise, the 26-year follow-up of the U.S. veterans cohort shows increasing risks of bladder and kidney cancers with higher numbers of cigarettes smoked. Men smoking more than 40 cigarettes per day had a twofold increase in the risk of bladder and kidney cancers (McLaughlin et al. 1995a). The risks for renal-cell cancer are present in both men and women, although of a lesser magnitude than that observed for transitional-cell tumors of the renal pelvis, where risks resemble those observed for bladder cancer.

The international renal-cell cancer study conducted in Australia, Denmark, Germany, Sweden, and the United States also showed an increase in cancer risks with increasing intensity and duration of smoking (McLaughlin et al. 1995b). This case-control study included 1,050 men and 682 women with renal cell cancer. Long-term quitters experienced a reduction in risk of about 25 percent compared with current smokers.

Evidence Synthesis

The urinary tract is exposed to tobacco carcinogens as they are cleared from the body through the kidneys. In fact, urine of smokers is more mutagenic than that of nonsmokers. Accumulated evidence shows a consistent relationship between cigarette smoking and bladder and kidney cancer risks, a dose-response relationship with the number of cigarettes smoked, and a reduction in risk after successful cessation. In the general population, there are no specific potential confounding factors that need to be considered. Both cohort and case-control studies have found a relationship between smoking and these types of cancer. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the kidney (renal cell carcinoma) (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and renal cell, renal pelvis, and bladder cancers.

Implication

Smoking is an established cause of bladder cancer and kidney cancer, and a substantial number of cases could be prevented with smoking prevention and cessation.

Cervical Cancer

Cancer of the cervix is one of the leading causes of morbidity and mortality in women throughout the world. In the United States, rates have declined substantially during the past 50 years, reflecting in part a success of screening. In 2003, an estimated 12,200 new cases of cervical cancer were diagnosed, and an estimated 4,100 women were expected to die from this cancer (ACS 2003). From 1996–2000, the incidence in black women (7.0 per 100,000) was higher than in white women (4.7 per 100,000) (Ries et al. 2003). As cervical cancer screening with Papanicolaou smears has become more widespread, the diagnosis of carcinoma in situ has become far more common, and fortunately, invasive carcinoma of the cervix less common.

Cervical cancer is closely linked to sexual behaviors and sexually transmitted infections with human papilloma virus (HPV) (Bosch et al. 2002). In fact, HPV is now considered to be a necessary cause of cervical cancer. Women who begin having sex at a younger age, who have had many sexual partners, or whose

partners have had many partners are at a higher risk of developing this disease, likely through increased risk for HPV infection. Against this background, the principal epidemiologic challenges have been to separate the effects of cigarette smoking from the risk factor profile associated with low socioeconomic status, which currently is strongly associated with smoking, and to explore possible causal pathways by which smoking may act with HPV in causing cervical cancer.

Conclusions of Previous Surgeon General's Reports

The topic of smoking and cancer of the uterine cervix was first reviewed in the 1982 Surgeon General's report (USDHHS 1982), which concluded that further research was necessary to define whether there was an association between cigarette smoking and cervical cancer. Subsequently, the 1989 report (USDHHS 1989) reviewed more than 15 epidemiologic studies consistently showing an increased risk for cervical cancer in cigarette smokers. Supportive biochemical studies that have detected products of cigarette smoke in cervical mucosa provided a plausible biologic basis for the relationship between cigarette smoking and cervical cancer (USDHHS 1989).

The 1990 report (USDHHS 1990) examined changes in cervical cancer risks after smoking cessation. In the studies that were reviewed, the RR of cervical cancer among current smokers compared with persons who had never smoked ranged from 1.0 to 5.0. After the first year of not smoking, former smokers had lower cervical cancer risks than continuing smokers. The report concluded that the observed diminution in risk after cessation lends support to the hypothesis that smoking is a contributing cause of cervical cancer.

The 2001 report on women and smoking (USDHHS 2001) concluded that smoking has consistently been associated with an increased risk of cervical cancer. It reviewed a large number of case-control studies of invasive cervical cancer and cervical intraepithelial neoplasia, finding smoking to be associated with increased risk in most. However, the report also concluded that the extent to which this association is independent of HPV infection is uncertain. The 2001 report also noted substantial advances in understanding the biology of cervical cancer, notably the role of HPV in carcinogenesis.

Biologic Basis

During the two decades that the Surgeon General's reports have considered smoking and cervical cancer, there have been substantial advances in understanding the role of HPV in causing this malignancy. In almost all cases, HPV DNA can be identified in the tissue, implying that HPV is necessary to cause cervical cancer (Bosch et al. 1995; Walboomers et al. 1999). In the current pathogenetic model for cervical cancer, smoking might act to increase the rate at which malignancy develops in women with persistent infection or possibly to increase the risk for persistent infection.

A range of evidence supports a possible causal association between cigarette smoking and cervical cancer. Cervical mucous in smokers is mutagenic (Holly et al. 1986) and contains nicotine (McCann et al. 1992) and the carcinogen NNK (Prokopcyzk et al. 1997). DNA adducts reflecting damage to DNA by tobacco products were significantly higher in cervical biopsies of smokers compared with nonsmokers (Phillips and Shé 1994). The adducts detected were consistent with tobacco smoking based on comparisons with tobacco-related adducts found in other tissues. Similar results were reported by the same investigators in a second sample of women undergoing a colposcopy or hysterectomy (Simons et al. 1994). Further studies of DNA adduct formation in normal and HPV-16 immortalized human epithelial cervical cells in cultures show that HPV-16 immortalized cells had significantly greater levels of adducts than did normal cells (Melikian et al. 1999). In vitro model systems also have been used to show that smoking may have an effect on the progression of HPV-initiated carcinogenesis of cervical cancer (Nakao et al. 1996).

Epidemiologic Evidence

As an understanding of the role of HPV in causing cervical cancer has advanced, the approach taken in epidemiologic investigations of smoking has also evolved. In the earliest studies, which antedated any consideration of HPV, smoking was treated as a potential independent risk factor, and possible confounding by indicators of sexual behavior was considered (Winkelstein 1977). As the role of HPV was recognized, investigators attempted to control for HPV by introducing indicators for HPV positivity into risk models

or stratifying by HPV status. In these studies, the HPV-negative women with cervical cancer probably included many HPV-positive women incorrectly classified by the early, insensitive-HPV tests. We now have evidence from prospective cohort studies that appropriately reflect the recurring presence of HPV in causing cervical cancer: studies that follow HPV-positive women and compare incidence of cervical cancer precursors in smokers and nonsmokers (Moscicki et al. 2001; Castle et al. 2002).

The Surgeon General's report on women and smoking (USDHHS 2001) summarized studies of smoking and cervical cancer as well as studies of smoking and intraepithelial neoplasia. An excess risk of cervical cancer among cigarette smokers has been observed in a number of case-control studies, particularly those that controlled for HPV status. However, the extent to which the relationship between smoking and cervical cancer reflects a causal association that is independent of HPV infection was considered uncertain. Studies that did not adjust for HPV status show a RR of approximately 2.0 for current smokers compared with women who never smoked. The risk of cervical cancer increases with the duration of smoking. In two studies of women with a history of smoking for more than 20 years, one found a RR of 4.0 (Peters et al. 1986) and the other a RR of 2.8 (Daling et al. 1996) when compared with women who had never smoked. As summarized in the report on women and smoking (USDHHS 2001), the association between smoking and cervical cancer is seen for both invasive cervical cancer and for precursor conditions, including carcinoma in situ and cervical dysplasia (also known as squamous intraepithelial neoplasia). For premalignant lesions, former smokers have a consistently lower RR than current smokers.

The evidence on cervical cancer has only recently included studies that took into account HPV status by stratifying on infection status. Early studies in Latin America did not find an independent effect for smoking after controlling for HPV. Several studies that considered HPV status reported that smoking was not associated with a risk of cervical cancer among HPV-positive women (Bosch et al. 1992; Muñoz et al. 1993; Eluf-Neto et al. 1994). In Latin American countries,

women generally smoke small numbers of cigarettes daily, however, and findings are different in other countries.

Among women who tested positive for HPV, two studies found smoking to be a risk factor in both HPV-positive and HPV-negative women. In a population-based, case-control study of invasive cervical cancer in western Washington state, Daling and colleagues (1996) found women with cervical cancer were more likely to be current smokers at diagnosis than population controls (RR = 2.5 [95 percent CI, 1.8–3.4]). The risk associated with smoking was present to a similar extent among women who tested positive and negative for HPV. In a case-control study nested in a population-based cohort consisting of women participating in cytological screening in Sweden, Ylitalo and colleagues (1999) found that after multivariate adjustment, a twofold higher risk was observed among current smokers compared with lifetime nonsmokers (odds ratio [OR] = 1.94 [95 percent CI, 1.32–2.85]), an association apparently confined to women younger than 45 years. Other studies reported since the 2001 report of the Surgeon General also show an association of smoking with cervical neoplasia. In two prospective cohort studies in the United States, smoking was associated with an increased risk in women who were HPV positive on enrollment. Moscicki and colleagues (2001) followed 496 women who were HPV positive over a median of 26 months. Daily cigarette smoking was associated with an increased risk for incident low-grade squamous intraepithelial lesion development (relative hazard = 1.67 [95 percent CI, 1.12–2.48]). In a 10-year cohort study of 1,812 Oregon women infected with HPV, women who smoked had an increased risk for high-grade cervical intraepithelial neoplasia (Castle et al. 2002). Compared with lifetime nonsmokers, the RRs were 2.9 (95 percent CI, 1.4–6.1) for smokers of less than one pack of cigarettes per day, 4.3 (95 percent CI, 2.0–9.3) for one or more packs per day, and 3.9 (95 percent CI, 1.6–6.7) for former smokers (Castle et al. 2002). Two nested case-control studies, one in Costa Rica (Hildesheim et al. 2001) and the other in the United Kingdom (Deacon et al. 2000), had similar findings in HPV-positive women.

Evidence Synthesis

Strong biologic evidence supports a mechanism for direct action of tobacco smoke components on the epithelial cells of the cervix. DNA adducts isolated from cervical cells reflect tobacco exposures among smokers. A large body of epidemiologic evidence supports a positive relationship between smoking and cervical cancer. Smoking has consistently been associated with higher risks of cervical cancer that increase with the duration of smoking and the number of cigarettes smoked per day (USDHHS 2001). Similar associations have been observed for premalignant lesions. Until recently, few studies appropriately considered HPV exposure and infection. HPV is now recognized as a likely contributor to the etiology of most cases and that the risk of smoking is most appropriately assessed in HPV-positive women. The most recent studies consistently show that smoking is associated with an increased risk among HPV-positive women. The increased risk is of a moderate strength and not likely to be explained by confounding by sexual behavior, as all women were HPV-positive in these analyses. Dose-response relationships were also demonstrated. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the uterine cervix (IARC 2002).

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and cervical cancer.

Implication

Further study to refine epidemiologic and mechanistic understanding of the independent association between smoking and HPV infection will clarify the causal association between smoking and cervical cancer.

Ovarian Cancer

Ovarian cancer is a leading cause of cancer mortality among women. In 2003, an estimated 25,400 new cases and 14,300 deaths attributed to this cancer were expected to occur. It ranks second among gynecologic cancers, and accounts for nearly 4 percent of all cancers among women (ACS 2003). From 1900–1970, ovarian cancer rates increased, perhaps reflecting changes in childbirth toward smaller families. Incidence and mortality have decreased slightly since 1970, probably reflecting the use of oral contraceptives, a known protective factor against ovarian cancer (Hankinson et al. 1992; McKean-Cowdin et al. 2000).

Conclusions of Previous Surgeon General's Reports

Ovarian cancer was first addressed in the 2001 Surgeon General's report on women and smoking (USDHHS 2001), which noted that smoking is probably not related to ovarian cancer.

Biologic Basis

A broad range of possible biologic mechanisms could lead to an effect of smoking on ovarian cancer risks, reflecting the effects of smoking on ovarian tissue and possibly female hormones. Evidence supports the possibility that cigarette smoke products and their metabolites act directly on tissue with estrogen receptors. Smoking may also influence risks by modifying hormone levels (see the section on "Breast Cancer" later in this chapter for a review of the hormonal effects of cigarette smoking). Metabolic products of tobacco smoke can be found in ovarian follicular fluid as can indicators of oxidative stress (Hellberg and Nilsson 1988; USDHHS 1990; Paszkowski et al. 2002). Alkaloids in cigarette smoke have been shown to inhibit corpus lutea progesterone synthesis (Gocze et al. 1996). In a model with primary granulosa cells, the alkaloids and smoke extract decreased DNA production, suggesting a cytotoxic effect. This wide range of potential effects of tobacco smoke could potentially influence the risks of ovarian cancer either directly or indirectly.

Epidemiologic Evidence

The available epidemiologic evidence is not consistent with regard to the strength of an association between smoking and ovarian cancer, or with regard to the temporal changes in risks following smoking cessation. Although some case-control studies have not distinguished current smokers from former smokers (Polychronopoulou et al. 1993; Purdie et al. 1995), others that have separately evaluated current and former smokers observed few differences between these two groups in the risk of ovarian cancer (Franks et al. 1987; Stockwell and Lyman 1987).

A recent study of the relationship between smoking and histologic subtypes of ovarian cancer found a RR of 2.9 (95 percent CI, 1.7–4.9) for mucinous epithelial tumors when comparing current smokers with those who had never smoked (Marchbanks et al. 2000). These data come from a population-based, case-control study that included 447 cases of ovarian cancer and 3,868 controls. This elevated risk was evident regardless of the age at smoking initiation, although the risk increased slightly as the cumulative pack-years of smoking increased. Similar patterns of risk were not observed among serous, endometrioid, or other histologic types. In a population-based, case-control study conducted in Australia, Green and colleagues (2001) observed a similar relationship. In an analysis of 794 cases and 855 controls, the histologic subtype of ovarian cancer most strongly related to cigarette smoking was the mucinous subtype. For current smokers, the RR was 3.1 (95 percent CI, 1.8–5.4) compared with women who had never smoked, and the risk of mucinous ovarian cancer increased with the maximum number of cigarettes smoked per day. For nonmucinous tumors, the RR was 1.5 (95 percent CI, 1.1–2.1) for smokers compared with nonsmokers.

Evidence Synthesis

Data on the relationship between cigarette smoking and ovarian cancer remain inconclusive. Evidence for patterns of risks with the duration of smoking and time since quitting is limited. Histologic subtypes of ovarian cancer appear to have distinct etiologic factors. Consistent findings suggest that a relationship to cigarette smoking for the mucinous subtype of ovarian cancer is plausible (Marchbanks et al. 2000; Green et al. 2001).

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and ovarian cancer.

Implication

Further research is needed to evaluate risks by histologic subtypes, to evaluate duration of smoking and risk, and to determine the time course of risk following smoking cessation.

Endometrial Cancer

Cancer of the endometrium (uterine corpus) is now the most commonly occurring gynecologic malignancy in women. In 2003, an estimated 40,100 new cases and 6,800 deaths were expected to occur from endometrial cancer (ACS 2003). Incidence rates are higher in white women (14.0 per 100,000) than in black women (10.0 per 100,000), but mortality rates are nearly twice as high for black women (Ries et al. 2003).

Endometrial cancer risks are predominantly determined by various hormonal risk factors: exposures to estrogens from estrogen replacement therapy after menopause, the use of tamoxifen, early menarche or late menopause, nulliparity, and a failure to ovulate (except while taking oral contraceptives). Obesity is also associated with increased risk. Pregnancy and the use of combination oral contraceptive pills (which include both estrogen and progesterone) are each protective against endometrial cancer (Grady and Ernster 1996).

Because of the strong dependence of endometrial cancer risk on exposure to estrogens, separating direct and indirect causal pathways for the effect of smoking on ovarian cancer risk has been difficult.

Women who smoke are more likely to be lean and to enter menopause earlier than nonsmokers (Willett et al. 1983). They are thus more likely to take estrogen therapy after menopause and to have more years of estrogen exposure (Pike et al. 1998). Separating causal paths involving smoking from those involving hormonal factors has consequently been complicated.

Conclusions of Previous Surgeon General's Reports

The inverse relationship between cigarette smoking and the risk of endometrial cancer was first noted in the 1989 Surgeon General's report (USDHHS 1989). Endometrial cancer is less frequent in women who smoke cigarettes. The 2001 Surgeon General's report on women and smoking (USDHHS 2001) updated this conclusion by noting that current smoking is associated with a reduced risk of endometrial cancer, although the effect is probably limited to postmenopausal women. The risk of endometrial cancer in former smokers generally appears more similar to that in women who have never smoked.

Biologic Basis

As reviewed in the section on "Breast Cancer" later in this chapter, several lines of evidence support a biologic pathway for cigarette smoking in influencing hormone levels from exogenous estrogen and the risk of hormone-related cancers. Such potential pathways include an altered metabolism as well as a lower production of estrogens because of lower adiposity.

Epidemiologic Evidence

More recent studies continue to show a reduced risk for endometrial cancer in smokers compared with nonsmokers. In a cohort study of participants in the Canadian Mammography Screening Trial, risk was reduced in current smokers compared with lifetime nonsmokers, but only among those smoking 20 or more cigarettes per day (hazard ratio = 0.62 [95 percent CI, 0.42–0.92]) (Terry et al. 2002). Case-control studies in Wisconsin (Newcomer et al. 2001), Washington state (Littman et al. 2001), and Sweden (Weiderpass and Baron 2001) also provide evidence of a reduced risk in smokers compared with nonsmokers (Table 2.18).

Evidence Synthesis

A consistent association between smoking and a lower risk of endometrial cancer has been found. The biologic basis for this association is consistent with the antiestrogenic effect attributed to smoking.

Conclusion

1. The evidence is sufficient to infer that current smoking reduces the risk of endometrial cancer in postmenopausal women.

Implication

Because smoking has numerous adverse health effects as summarized in this report, the modest reduction in the risk of endometrial cancer associated with smoking is far outweighed by the increase in other causes of smoking-related morbidity and mortality.

Table 2.18   Studies on the association between smoking and the risk of endometrial cancer

Study	Design/population	Tobacco exposure	Findings
Littman et al. 2001	Case-control study Women aged 45–74 years 697 incident cases of endometrial cancer diagnosed between 1985 and 1991 944 population controls chosen between 1986 and 1993, frequency matched for age and county Washington state	• Never smoked • Former/current smokers	• Relative to controls, cases tended to be never smokers • There was a monotonic increase in risk among never smokers, relative to the lowest category, for each quintile of percent energy from fat • Among current/former smokers, no consistent pattern was observed • p value for interaction = 0.03
Newcomer et al. 2001	Case-control study Women aged 40–79 years 740 incident cases of endometrial cancer 2,372 population controls Wisconsin 1991–1994	• Never smoked • Former smokers • Current smokers • Pack-years[§] • Age at smoking initiation	Data were not reported

*CI = Confidence interval.
†OR = Odds ratio.
‡BMI = Body mass index.
§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Risk estimates (95% CI*)		Comments
<u>Never smoked</u>	<u>OR</u>†	ORs were calculated using unconditional
1st quintile (% energy from fat)	1.0 (referent)	logistic regression; risk estimates were adjusted
2nd quintile	1.7 (1.0–2.7)	for age, county, BMI‡, and unopposed estrogen
3rd quintile	1.7 (1.1–2.8)	use
4th quintile	2.2 (1.3–3.6)	
5th quintile	2.8 (1.7–4.7)	
<u>Current/former smokers</u>	<u>OR</u>	
1st quintile	1.0 (referent)	
2nd quintile	0.89 (0.54–1.5)	
3rd quintile	1.4 (0.82–2.2)	
4th quintile	1.1 (0.67–1.8)	
5th quintile	1.2 (0.71–1.9)	
<u>Smoking status</u>	<u>OR</u>	ORs were calculated using multivariate logistic
Never smoked	1.0 (referent)	regression; risk estimates were adjusted for
Former smokers	0.8 (0.7–0.9)	age, menopausal status, BMI, hormone replace-
Current smokers	0.8 (0.6–1.0)	ment therapy, diabetes, and parity
<u>Measure of smoking</u>	<u>OR</u>	
20 pack-years	0.9 (0.7–1.2)	
21–40 pack-years	0.7 (0.5–1.0)	
41–60 pack-years	0.5 (0.4–0.8)	
61–80 pack-years	0.8 (0.5–1.3)	
>80 pack-years	0.9 (0.5–1.4)	
p value for trend = 0.38		
<u>Age at smoking initiation</u>	<u>OR</u>	
20 years	0.8 (0.6–1.0)	
21–25 years	0.8 (0.5–1.1)	
26–30 years	0.8 (0.4–1.5)	
>30 years	0.9 (0.5–1.5)	
p value for trend = 0.79		

Table 2.18   Continued

Study	Design/population	Tobacco exposure	Findings
Weiderpass and Baron 2001	Case-control study Women aged 50–74 years 709 incident endometrial cancer cases 3,368 population controls Sweden 1994–1995	• Never smoked • Former smokers • Current smokers • Cigarettes/day • Duration of smoking	• Current smokers had a significantly decreased risk compared with never smokers • Dose-response relationship was observed with the number of cigarettes smoked per day (p value for trend was not provided)
Terry et al. 2002	Cohort study 70,591 women aged 40–59 years who participated in a randomized controlled trial of mammography screening for breast cancer Enrollment: 1980–1985 Average 10.6 years of follow-up Canada (nationwide)	• Cigarettes/day • Pack-years	• 403 outcome events • Endometrial cancer risk was significantly reduced only among women who smoked >20 cigarettes/day

Risk estimates (95% CI)		Comments
Smoking status	OR	ORs were calculated from unconditional logistic regression models; risk estimates were adjusted for age, use of hormone replacement therapy, BMI, parity, age at menopause, age at last birth, use of oral contraceptives, and diabetes mellitus
Never smoked	1.0 (referent)	
Former smokers	0.61 (0.47–0.80)	
Current smokers	0.90 (0.72–1.14)	
Cigarettes/day	OR	
1–10 cigarettes/day	0.86 (0.68–1.08)	
11–20 cigarettes/day	0.67 (0.51–0.88)	
>20 cigarettes/day	0.74 (0.42–1.29)	
Duration of smoking	OR	
1–14 years	0.7 (0.19–2.55)	
15–30 years	0.60 (0.32–1.12)	
31–45 years	0.64 (0.45–0.92)	
>45 years	0.56 (0.34–0.98)	
Rate ratios		Hazard ratios were calculated using Cox proportional hazards regression; risk estimates were adjusted for age, Quetelet's index, education, vigorous physical activity, hormone replacement therapy, menopausal status, parity, and alcohol consumption; outcome = incident endometrial cancer
Never smoked	1.0 (referent)	
1–20 cigarettes/day	1.09 (0.77–1.55)	
>20 cigarettes/day	0.62 (0.42–0.92)	
p value for trend = 0.03		
1–20 pack-years	0.99 (0.68–1.45)	
>20 pack-years	0.73 (0.51–1.05)	
p value for trend = 0.10		

Stomach Cancer

Despite a major decline in the incidence of stomach cancer in industrialized countries across the last century, gastric carcinoma remains the second most common fatal cancer worldwide (Pisani et al. 1999). An estimated 22,400 new cases and 12,100 deaths from cancer of the stomach were expected to occur in the United States in 2003 (ACS 2003).

Incidence and death rates for stomach cancer vary by race, gender, and ethnicity. Incidence is approximately twice as high among men as among women and higher among nonwhites than whites. A substantial variation of incidence is evident among both men and women, respectively, across various racial and ethnic groups: Asian/Pacific Islanders (23.0 and 12.8), blacks (19.9 and 9.9), Hispanics (18.1 and 10.0), American Indians/Alaska Natives (14.4 and 8.3), and white non-Hispanics (10.0 and 4.3). In the United States, the median survival of persons with stomach cancer is less than one year after diagnosis, although the relative five-year survival rate has increased slightly from 15.1 percent for patients diagnosed in 1975 to 22.5 percent for patients diagnosed in 1992 (Ries et al. 2000a, 2003).

Internationally, death rates from stomach cancer vary nearly 100-fold across countries (IARC 2003). Stomach cancer is the most common malignancy in China and in parts of eastern Asia and Latin America (Parkin et al. 1999; Pisani et al. 1999). Mortality rates have been decreasing worldwide but are as high as 50 per 100,000 among men and 26 per 100,000 among women in the highest risk countries (IARC 2003).

Assessments of the independent contribution of cigarette smoking to the development of stomach cancer are complicated by two factors. First, the background occurrence of stomach cancer decreased globally during much of the twentieth century for reasons unrelated to changes in cigarette smoking. This decline is exemplified by the falling mortality rate from stomach cancer in the United States since 1930, when cause-specific national mortality statistics first became available (Figure 2.6) (Greenlee et al. 2000). The age-adjusted mortality rate (per 100,000) decreased 85 percent in men and 90 percent in women between 1930 and 1997. Figure 2.6 also shows the increase in per capita use of manufactured cigarettes that began in the early 1900s and persisted through 1963 (Giovino et al. 1994), coinciding with much of the decrease in stomach cancer mortality. The main factors proposed to account for the decline in stomach cancer are the introduction of refrigeration (with the resultant increased availability of fresh fruits and vegetables and reduced consumption of salted, smoked, and pickled foods), improved sanitation, and the introduction of antibiotic therapy (reducing chronic *Helicobacter pylori* (*H. pylori*) infections) (Nomura 1996). It has been challenging to identify the contribution to stomach cancer risk from cigarette smoking in the context of large temporal changes in other apparently important risk factors.

A second challenge in determining whether cigarette smoking causes stomach cancer is that the gastric cancers at different subsites appear to differ etiologically, yet are combined in most epidemiologic studies. Subsites of stomach cancer usually are not considered in mortality studies, because death certificates seldom record the histology or location of the tumor within the stomach. The predominant type of stomach cancer observed in incidence registries in the United States and Europe has changed over time, particularly among men. The incidence of cancers of the gastric cardia subsite, occurring near the junction of the esophagus with the stomach, increased by 4.3 percent annually among men in United States SEER areas between 1976 and 1987 (Devesa and Fraumeni 1999). A similar increase in gastric cardia cancers has been observed in Europe (Golematis et al. 1990; Craanen et al. 1992; Botterweck et al. 2000), at the same time that the incidence of cancers of the gastric antrum, corpus, or fundus (termed noncardia cancers) has been decreasing worldwide. The decline in noncardia cancers accounts for most of the global decline in stomach cancer. As a consequence of these opposing trends, tumors of the gastric cardia now compose about one-third of all stomach cancers among white men in the United States (Blot et al. 1991).

Conclusions of Previous Surgeon General's Reports

Stomach cancer has not been classified among the diseases definitely caused by tobacco smoking by the Surgeon General (USDHEW 1964, 1974; USDHHS 1982, 1989a) or IARC until the most recent monographs

Figure 2.6   Stomach cancer death rates stratified by gender and per capita number of cigarettes smoked in the United States, 1930–1994
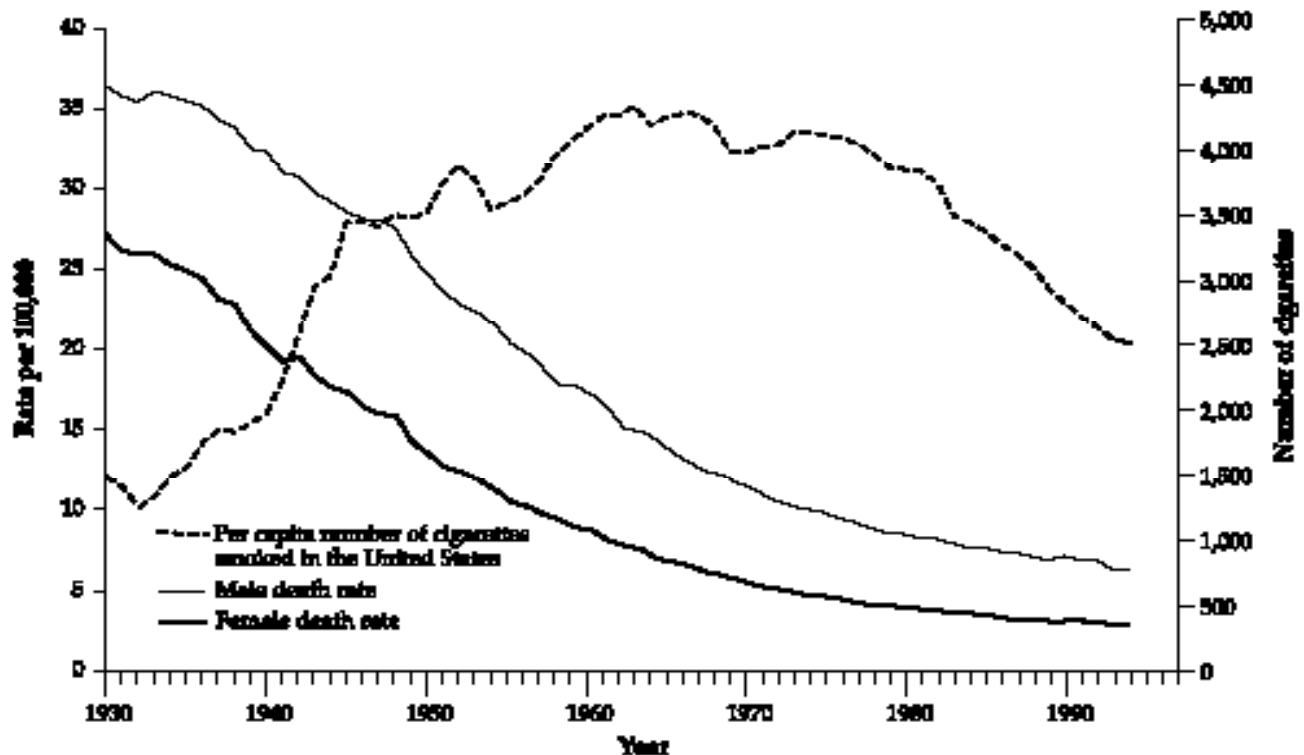
Sources: Centers for Disease Control and Prevention, National Center for Health Statistics, U.S. Mortality Volumes 1930–1959, U.S. Mortality public use data tapes 1960–1994; Tobacco Yearbook 1981; Creek et al. 1994; U.S. Department of Agriculture 1996.

(IARC 2002). However, the evidence supporting a causal relationship has become stronger over time. Key conclusions from previous Surgeon General's reports are presented as follows by year:

> No relationship has been established between tobacco use and stomach cancer (USDHEW 1964, p. 229).

> No firm relationship between stomach cancer and cigarette smoking has been established (USDHEW 1974, p. 55).

> In epidemiological studies, an association between cigarette smoking and stomach cancer has been noted. The association is small in comparison with that noted for smoking and some other cancers (USDHHS 1982, p. 22).

Evidence from prospective and retrospective studies available more recently has shown a small but consistent increase in mortality ratios [for stomach cancer], averaging approximately 1.5 for smokers compared with nonsmokers. Dose-response relationships have been demonstrated for the number of cigarettes smoked per day (USDHHS 1989, p. 57).

Tobacco has been associated with stomach cancer, but whether this association is causal remains unclear (USDHHS 1990, p. 176).

Biologic Basis

More than 90 percent of stomach cancers diagnosed in the United States are adenocarcinomas, the remainder being predominantly non-Hodgkin's lymphomas or leiomyosarcomas (Rotterdam 1989; Fuchs and Mayer 1995). Gastric adenocarcinoma is further subdivided into two histopathologic categories: an intestinal or glandular subtype (in which the cells resemble intestinal columnar epithelium and form gland-like, tubular structures) and a diffuse form (characterized by poorly cohesive tumor cells that infiltrate and thicken the stomach wall without forming a discrete mass) (Fuchs and Mayer 1995; Nomura 1996). The intestinal subtype is the predominant noncardia cancer in regions where the risk for noncardia cancer is high and where the intestinal subtype accounts for most of the excess risk (Correa 1992). Clinical differences between intestinal and diffuse gastric cancers are that the former occur at older ages, more frequently in the distal stomach, and are usually preceded by several decades of chronic gastritis, inflammation, and premalignant abnormalities (Correa 1992; Fuchs and Mayer 1995).

Cigarette smoking was associated with more severe premalignant gastric abnormalities in a population-based study that performed gastroscopic examinations on approximately 3,000 residents of Linqu County, China, in 1989 and 1990 (Kneller et al. 1992). This region has one of the highest rates of gastric cancers in the world (mostly of the intestinal subtype). Smokers were more likely than nonsmokers in the study to have been diagnosed with intestinal metaplasia and/or dysplasia. Nonsmokers were more likely than smokers to have the less severe superficial gastritis and/or chronic atrophic gastritis. The risk for dysplasia increased with the number of cigarettes smoked per day and years of smoking (Kneller et al. 1992). The authors attributed virtually all of the 55 percent higher prevalence of gastric dysplasia in men than in women to the higher smoking prevalence in men (80 percent) versus women (5 percent). A second endoscopic examination of persons in this study in 1994 demonstrated longitudinally that persons with more severe baseline lesions were more likely to experience progression to dysplasia or a gastric cancer (You et al. 2000).

Although certain somatic mutations are frequently observed in genetic studies of gastric adenocarcinomas, there is as yet no well-defined molecular model of tumorigenesis (Powell 1998), and specific genetic changes have not been studied in relation to cigarette smoking. Somatic mutations of the *p53* tumor suppressor gene are detected in 60 percent of gastric adenocarcinomas of both histologic types (Powell 1998). Mutations in *p53* are most often observed in the advanced stages of gastric dysplasia rather than as an early stage in carcinogenesis. Other genetic changes associated with gastric adenocarcinomas include deletions and amplifications of the gene for transforming the growth factor beta type II receptor, the deleted *DCC* gene in colon cancer, and the candidate tumor suppressor genes *DPC4* and *madd* (Tahara 1995; Powell 1998). A subset of gastric tumors also displays microsatellite instability (Gong et al. 1999) similar to that seen in a subset of colon cancers from hereditary nonpolyposis coli families predisposed to various malignancies. Molecular changes that may be unique to the diffuse type of gastric cancers include the reduction or loss of cadherins and catenins and amplification of *K-sam* genes. Unique to the intestinal type are *K-ras* mutations, *erbB-2* gene amplification, loss of heterozygosity and mutations of the *APC* gene, and loss of heterozygosity of the *bcl-2* and *DCC* genes (Gong et al. 1999).

Nicotine and other components of cigarette smoke affect several aspects of gastric physiology (reviewed in detail in the section on "Peptic Ulcer Disease" in Chapter 6). Short-term effects of smoking include increased reflux of duodenal contents into the stomach and mouth, decreased secretion of pancreatic bicarbonate, decreased production of gastric mucus and cytoprotective prostaglandins, and perhaps the increased production of free radicals and release of vasopressin, a potent vasoconstrictor (Endoh and Leung 1994; Eastwood 1997).

Studies have begun to examine whether cigarette smoking influences other environmental risk factors for stomach cancer, particularly *H. pylori* infections (Ley and Parsonnet 2000). Properly designed studies are needed to sort out the causal pathways for stomach cancer and smoking and *H. pylori* infections. Smoking, for example, might act to increase the risk for infection or to synergistically modify the carcinogenic

processes associated with infections. The prevalence of a *H. pylori* infection is reported to be higher among smokers than among lifetime nonsmokers in some cross-sectional studies (Graham et al. 1991; Bateson 1993; Brenner et al. 1997; Goh 1997; Murray et al. 1997; Lin et al. 1998; Phull et al. 1998; Collett et al. 1999), but not in all of them (Maxton et al. 1990; Lindell et al. 1991; Battaglia et al. 1993; EUROGAST Study Group 1993; Tsugane et al. 1994; Shinchi et al. 1997; Russo et al. 1999; Ogihara et al. 2000). Several studies also report that the eradication of an *H. pylori* infection with antibiotics is more difficult in smokers than in nonsmokers (Cutler and Schubert 1993; O'Connor et al. 1995; Goddard and Spiller 1996; Bardhan et al. 1997; Breuer et al. 1997a,b), although at least one study has not found this result (Chan et al. 1997). Thus there is some evidence that cigarette smoking may increase the infectivity of *H. pylori* or decrease host resistance to the infection, although it remains possible that an *H. pylori* infection simply is correlated with smoking in some studies.

The combination of an *H. pylori* infection and cigarette smoking also may be more pathogenic to the gastric mucosa than an *H. pylori* infection alone. Zaridze and colleagues (2000) observed that among men infected with *H. pylori* in Russia, those who ever smoked had a twofold higher risk of stomach cancer than nonsmokers (OR = 2.3 [95 percent CI, 1.1–4.7]). This study found no increase in stomach cancer risks among women who smoked or among male smokers uninfected with *H. pylori* (p value for interaction = 0.07). Another study in Poland found more frequent evidence of intestinal metaplasia in persons infected with *H. pylori* who smoked cigarettes, consumed vodka, or did both than in those with an *H. pylori* infection alone (Jedrychowski et al. 1993, 1999).

H. pylori infections may have differing effects on cancers of the gastric cardia than on noncardia cancers (Fox and Wang 2000). Whereas an *H. pylori* infection is an established risk factor for noncardia stomach cancers, some evidence suggests that *H. pylori* infections actually may be protective against gastric cardia tumors at the gastroesophageal junction (Blaser 1999a,b). Eradication of *H. pylori* results in increased rates of gastroesophageal reflux, a factor contributing to the pathogenesis of Barrett's syndrome and esophageal adenocarcinoma (Labenz et al. 1997; Vicari et al.

1998). Persons who carry particular cagA(+) strains of *H. pylori* experience a marked inflammation of the gastric cardia but have a lower risk of developing adenocarcinoma of either the gastric cardia or the esophagus (Peek et al. 1999; Vaezi et al. 2000).

Compared with nonsmokers, current cigarette smokers have lower plasma and serum concentrations of certain micronutrients, such as beta carotene and ascorbic acid, that may protect against the development of stomach cancer (Smith and Hodges 1987; Stryker et al. 1988; Zondervan et al. 1996). The concentration of these substances in the blood is lower than would be expected from dietary intake (Smith and Hodges 1987; Stryker et al. 1988; Bolton-Smith et al. 1991). It has been proposed that smokers may require a higher dietary intake of certain protective micronutrients than nonsmokers because of a more rapid degradation or excretion of these micronutrients (Stryker et al. 1988; Cross and Halliwell 1993).

Animal models of the carcinogenicity of tobacco smoke to the stomach are limited and largely involve tumors of the rodent forestomach, an organ more analogous to the human esophagus than to the stomach. Specific chemicals found in tobacco smoke and smoke condensate are known to cause cancers of the rodent forestomach when administered orally or by gavage (USDHHS 2000). Substances in cigarette smoke that are listed by the National Toxicology Program as carcinogenic to the rodent forestomach include benz[*a*]anthracene (mouse: gavage), benzo[*a*]pyrene (mouse and hamster: gavage), dibenz(*a,h*)anthracene (mouse: diet), 7H-dibenzo(*c,g*)carbarole (mouse: gavage), n-nitrosodi-n-butylamine (mouse and hamster: diet, drinking water, and gavage), and n-nitrosodiethylamine (mouse: diet and gavage) (USDHHS 2000).

Epidemiologic Evidence

This section considers all published studies (in English) that provide separate data on lifetime nonsmokers and current and former cigarette smokers. Where multiple follow-ups have been reported on the same cohort, data from the longest follow-up are presented. Studies were identified by searching the MEDLINE database (from January 1966 to August 2000) using the medical subject headings "tobacco,"

"smoking," "gastric neoplasms," and "stomach neoplasms," and by examining references cited in published original and review articles (Trédaniel et al. 1997).

Nine cohort studies (Table 2.19) (Nomura et al. 1990; Kneller et al. 1991; Kato et al. 1992; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Engeland et al. 1996; Mizoue et al. 2000; ACS, unpublished data) and 11 case-control studies (Table 2.20) (Correa et al. 1985; Jedrychowski et al. 1986; Boeing et al. 1991; Saha 1991; Agudo et al. 1992; Hansson et al. 1994; Ji et al. 1996; De Stefani et al. 1998; Chow et al. 1999; Inoue et al. 1999; Zaridze et al. 2000) have examined the association between cigarette smoking status and incidence of or death from stomach cancer. Current cigarette smokers consistently have higher incidence or death rates than do lifetime nonsmokers in studies of men (Nomura et al. 1990; Kneller et al. 1991; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Engeland et al. 1996; Mizoue et al. 2000; ACS, unpublished data) and men and women combined (Kato et al. 1992); this finding is less consistent in studies of women (Table 2.19) (Tverdal et al. 1993; Engeland et al. 1996; ACS, unpublished data). The average RR estimate among current smokers compared with lifetime nonsmokers across all of the studies in Tables 2.19 and 2.20, weighted by the number of cases, is 1.6 (1.7 in men and 1.3 in women). Relative risk estimates above 2.0 are seen in several studies of Japanese (Nomura et al. 1990; Kato et al. 1992; Inoue et al. 1999; Mizoue et al. 2000) and other populations with above average risks of stomach cancer (Kneller et al. 1991; Tverdal et al. 1993; De Stefani et al. 1998).

Former smokers have lower incidence or death rates for stomach cancer than do continuing smokers in most studies of men (Tables 2.19 and 2.20) (Nomura et al. 1990; Kneller et al. 1991; Tverdal et al. 1993; Doll et al. 1994; McLaughlin et al. 1995a; Ji et al. 1996; De Stefani et al. 1998; Chow et al. 1999; Inoue et al. 1999; Zaridze et al. 2000; ACS, unpublished data), although one study found a higher risk for former smokers in men and women (Kato et al. 1992). The average RR estimate in former smokers across all studies combined is 1.2 (1.2 in men and 1.3 in women).

Among current smokers, most studies document only a small increase in the risk for stomach cancer with an increasing number of cigarettes smoked per day (Tables 2.21 and 2.22) or years of smoking (Table 2.23). Two prospective studies that do show some gradient of an increased risk with a greater number of cigarettes smoked are the reports by Kneller and colleagues (1991) from Norway and McLaughlin and colleagues (1995a) on United States veterans. The tests for a trend presented in Tables 2.21 and 2.22 are taken from the original papers and do not always specify whether lifetime nonsmokers were excluded from the trend calculations. No significant trend is observed with either the number of cigarettes smoked per day (Table 2.22) or number of years of smoking (Table 2.23) in CPS-II (ACS, unpublished data).

Among former smokers, the risk of stomach cancer consistently decreases below that of continuing smokers with the number of years since cessation (Table 2.24). This trend is clearest in the studies with the largest number of former smokers (De Stefani et al. 1998; ACS, unpublished data). The risk of stomach cancer among former smokers approaches that of lifetime nonsmokers approximately 20 years after quitting.

The epidemiologic studies that have separated cancers of the gastric cardia from noncardia cancers suggest that cancers at both subsites are associated with cigarette smoking (Table 2.25). Two case-control studies (Kabat et al. 1993; Gammon et al. 1997) report stronger associations between smoking and cancers of the gastric cardia than between smoking and noncardia cancers. However, the evidence relating smoking to specific types of stomach cancer is limited (Nomura 1996), as most studies have not been analyzed by anatomic or histologic subsites.

Evidence Synthesis

A large decrease in stomach cancer incidence and death rates occurred in the United States during the time per capita cigarette smoking increased steeply. The timing of these trends and the continuing decrease in gastric cancer incidence and mortality worldwide suggest that cigarette smoking is not, by itself, a major independent cause of stomach cancer. It nevertheless remains possible that cigarette smoking is an important factor in the pathogenesis of both cardia and noncardia stomach cancers.

Many large, well-conducted epidemiologic studies consistently report higher incidence or death rates for stomach cancer among current cigarette smokers than among lifetime nonsmokers. Studies that distinguish between cancers of the gastric cardia and those elsewhere in the stomach generally find that smoking is associated with both sites. Persons who stop smoking have a lower risk of stomach cancer than those who continue. The risk among former smokers diverges progressively away from that of continuing smokers and toward that of lifetime nonsmokers as time elapses after cessation. Among current smokers, the risk of stomach cancer is not strongly associated with either years of smoking or the number of cigarettes smoked per day. In 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the stomach (IARC 2002).

Cigarette smoking may increase the infectivity or add to the pathogenicity of *H. pylori*, a known cause of noncardia stomach cancer. The prevalence of *Helicobacter* infections is inconsistently reported to be higher among cigarette smokers than among lifetime nonsmokers in some studies. The eradication of *H. pylori* infections using antibiotics was more difficult in smokers than nonsmokers in several studies. An *H. pylori* infection in combination with cigarette smoking is associated with more frequent ulcerations (gastric and duodenal combined) (Martin et al. 1989), the progression to metaplasia (Jedrychowski et al. 1993, 1999), and/or gastric cancers (Zaridze et al. 2000) than is an *H. pylori* infection alone. Cigarette smoking is also thought to deplete the plasma and serum concentrations of certain micronutrients that may protect against *Helicobacter* infections or gastric neoplasia.

Two important limitations of most of the epidemiologic studies are that few studies have measured infections with *H. pylori* and cigarette smoking in the same people, and studies have not consistently distinguished between gastric cardia and noncardia cancers. Such information is needed to examine the separate and joint effects of cigarette smoking and an *H. pylori* infection on the main subtypes of stomach cancer. The interaction between smoking and *H. pylori* may vary across different subtypes of gastric cancer. Some evidence suggests that *H. pylori* infections may be negatively associated with cancers of the gastric cardia but positively associated with noncardia gastric cancers (Hansen et al. 1999). The critical exposure for noncardia cancers may be the combination of an *H. pylori* infection and cigarette smoking. If so, then conventional dose-response analyses may misclassify the duration or intensity of the relevant exposure by considering one or both of these factors separately.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and gastric cancers.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and noncardia gastric cancers, in particular by modifying the persistence and/or the pathogenicity of *Helicobacter pylori* infections.

Implications

With inference of a causal association between current and former cigarette smoking and death from gastric cancers, including stomach cancer among the smoking attributable conditions increases the estimated number of deaths caused by smoking by 3,573 in 1990 in the United States, based on CPS-II. The impact of smoking on gastric cancers may be substantially greater in developing countries where the incidence of and mortality from stomach cancer are higher.

Reductions in smoking could help to counteract the increase in cancers of the gastric cardia occurring in the United States and Europe, especially among men. Further research is needed to assess the combined effects of cigarette smoking and an *H. pylori* infection. Of particular interest is the impact of continued cigarette smoking on the infectivity and pathogenicity of *H. pylori*, and the relationship of smoking and other factors to cancers of the gastric cardia.

Table 2.19   Cohort studies on the association between smoking status and the risk of stomach cancer*

Study Location/population	Outcome	Smoking status (number of deaths or cases)
Men		
Nomura et al. 1990 Japanese in Hawaii, United States, 1965–1986 (7,990 men; 150 stomach cancer cases)	Incidence	Never smoked (29) Current smokers (97) Former smokers (24)
Kneller et al. 1991 Norwegians in Norway and United States, 1966– 1986 (17,633 men; 75 stomach cancer deaths)	Mortality	Never smoked (8) Current smokers (22) Former smokers (24)
Tverdal et al. 1993 Norway, 1972–1988 (44,290 men; 66 stomach cancer deaths)	Mortality	Never smoked (8) Current smokers (47) Former smokers (11)
Doll et al. 1994 British physicians, United Kingdom, 1951–1991 (34,439 men; 277 stomach cancer deaths)	Mortality	Never smoked Current smokers (47) Former smokers (11)
McLaughlin et al. 1995a U.S. veterans, United States, 1954–1980 (177,903 men; 1,058 stomach cancer deaths)	Mortality	Never smoked Current smokers Former smokers
Engeland et al. 1996 Norwegian Migrant Study, 1964–1993 (11,863 men; 258 stomach cancer cases)	Incidence	Never smoked (39) Current smokers (169) Former smokers (50)
Mizoue et al. 2000 Fukuoka, Japan, 1986–1996 (4,050 men; 53 stomach cancer deaths)	Mortality	Never smoked (5) Current smokers (26) Former smokers (22)
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982– 1996 (312,332 men; 730 stomach cancer deaths)	Mortality	Never smoked (179) Current smokers (239) Former smokers (312)

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
†RR = Relative risk.
‡CI = Confidence interval.
§Confidence interval was calculated from the original paper using cell counts.
 Number of deaths by smoking category was not reported.

RR[†]	95% CI[‡]	Comments
1.00		Adjusted for age; findings were comparable for intestinal and diffuse histologic types
2.70	1.80–4.10	
1.00	0.60–1.70	
1.00		Adjusted for age; excluded incomplete data
2.60	1.14–5.81	
2.20	0.99–4.91	
1.00		Adjusted for age and geographic area
2.72[§]	1.29–5.75	
1.09[§]	0.44–2.71	
1.00	Data were not	Adjusted for age and calendar period
1.70	reported.	
0.96		
1.0		Adjusted for age and calendar period
1.4	1.2–1.6	
1.0	0.9–1.2	
1.0		Adjusted for age; excluded prevalent cancer
1.3	0.9–1.9	
1.3	0.9–2.0	
1.0		Adjusted for age, study area, and alcohol consumption; excluded prevalent cancer and incomplete data
2.2	0.8–5.7	
2.2	0.8–6.0	
1.00		Adjusted for age; excluded prevalent cancer and incomplete data
2.33	1.91–2.85	
1.60	1.33–1.92	

Table 2.19   Continued

Study Location/population	Outcome	Smoking status (number of deaths or cases)
Women		
Tverdal et al. 1993 Norway, 1972–1988 (24,535 women; 20 stomach cancer deaths)	Mortality	Never smoked (11) Current smokers (4) Former smokers (5)
Engeland et al. 1996 Norwegian Migrant Study, 1964–1993 (14,269 women; 159 stomach cancer cases)	Incidence	Never smoked (119) Current smokers (9) Former smokers (31)
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982–1996 (469,019 women; 469 stomach cancer deaths)	Mortality	Never smoked (282) Current smokers (97) Former smokers (90)
Men and women		
Kato et al. 1992 Aichi, Japan, 1985–1991 (9,753 men and women; 57 stomach cancer deaths)	Mortality	Never smoked (26) Current smokers (25) Former smokers (6)

§Confidence interval was calculated from the original paper using cell counts.

RR	95% CI	Comments
1.00		Adjusted for age and geographic area
0.56[§]	0.18–1.71	
1.44[§]	0.43–4.78	
1.0		Adjusted for age; excluded prevalent cancer
1.0	0.6–1.4	
0.8	0.4–1.6	
1.00		Adjusted for age; excluded prevalent cancer and incomplete data
1.50	1.18–1.90	
1.22	0.96–1.56	
1.00		Adjusted for age, gender, alcohol consumption, cooking methods, and family history of stomach cancer
2.18	1.07–4.43	
2.62	0.97–7.05	

Table 2.20   Case-control studies on the association between smoking status and the risk of stomach cancer*

Study Location/population	Smoking status (cases/controls)	RR[†]	95% CI[‡]
Men			
Agudo et al. 1992 Spain, 1987–1989 (235 stomach cancer cases; 235 hospital controls)	Never smoked (63/58) Current smokers (115/117) Former smokers (50/52)	1.00 0.93 0.93	 0.61–1.70 0.58–1.48
Ji et al. 1996 China, 1988–1989 (770 stomach cancer cases; 819 population controls)	Never smoked (201/281) Current smokers (479/455) Former smokers (90/82)	1.00 1.35 1.26	 1.06–1.71 0.86–1.84
De Stefani et al. 1998 Uruguay, 1992–1996 (331 stomach cancer cases; 622 hospital controls)	Never smoked (31/125) Current smokers (163/217) Former smokers (117/280)	1.0 2.6 1.3	 1.6–3.1 0.8–2.2
Chow et al. 1999 Poland, 1994–1997 (302 stomach cancer cases; 314 population controls)	Never smoked (61/77) Current smokers (130/100) Former smokers (98/136)	1.0 1.7 0.9	 1.1–2.7 0.6–1.4
Inoue et al. 1999 Japan, 1988–1995 (651 stomach cancer cases; 12,041 hospital controls)	Never smoked (68/2,744) Current smokers (378/5,999) Former smokers (203/3,287)	1.00 2.50 1.70	 1.91–3.27 1.28–2.26
Zaridze et al. 2000 Russia, 1996–1997 (248 stomach cancer cases; 292 hospital controls)	Never smoked (62/86) Current smokers (126/154) Former smokers (60/52)	1.0 1.4 1.1	 0.9–2.2 0.6–1.9
Women			
Ji et al. 1996 China, 1988–1989 (354 stomach cancer cases; 632 population controls)	Never smoked (318/567) Current smokers (27/55) Former smokers (9/7)	1.00 0.85 2.01	 0.52–1.40 0.72–5.60
Chow et al. 1999 Poland, 1994–1997 (162 stomach cancer cases; 166 population controls)	Never smoked (77/108) Current smokers (49/38) Former smokers (33/20)	1.0 1.8 1.8	 1.0–3.3 0.9–3.7

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.

Comments

Adjusted for age, area, and hospital; current and former included pipe/cigar smokers; current included former smokers who had quit <5 years before the study

Adjusted for age, income, education, and alcohol intake

Adjusted for age, residence, urban/rural status, and alcohol and vegetable intake

Adjusted for age, education, years lived on farm, and family history of cancer

Adjusted for age; year; season of first hospital visit; family history of gastric cancer; and alcohol, salty food, and fruit intake

Adjusted for age, education, and alcohol consumption

Adjusted for age, income, and education

Adjusted for age, education, years lived on farm, and family history of cancer

Table 2.20 Continued

Study Location/population	Smoking status (cases/controls)	RR	95% CI
	Women		
Inoue et al. 1999	Never smoked (273/26,471)		
	Current smokers (55/4,242)	1.74	1.28–2.36
Japan, 1988–1995 (344 stomach cancer cases; 31,805 hospital controls)	Former smokers (15/1,061)	1.37	0.80–2.34
	Men and women		
Correa et al. 1985	Whites		
	Never smoked (68/73)	1.00	
Louisiana, United States, 1979–1983	Current smokers (75/64)	1.35	0.75–2.41
(391 stomach cancer cases;	Former smokers (39/50)	1.04	0.54–2.03
391 hospital controls)	African Americans		
	Never smoked (32/54)	1.00	
	Current smokers (115/95)	2.66	1.34–5.25
	Former smokers (34/35)	1.85	0.81–4.22
Jedrychowski et al. 1986	Never smoked (52/43)	1.00	
	Current smokers (49/57)	0.68	0.39–1.20
Poland, 1980–1981 (110 stomach cancer cases; 110 population controls)	Former smokers (9/10)	0.79	0.29–2.13
Boeing et al. 1991	Never smoked[§]	1.00	
	Current smokers[§]	0.52	0.30–0.89
Germany, 1958 (143 stomach cancer cases; 238 hospital controls; 251 population controls)	Former smokers[§]	0.61	0.32–1.16
Saha 1991	Never smoked (28/94)	1.00	
	Current smokers (66/86)	2.58	1.22–5.47
United Kingdom, years not given (117 stomach cancer cases; 234 hospital controls)	Former smokers (23/54)	1.43	0.74–3.55
Hansson et al. 1994	Never smoked (120/281)	1.00	
	Current smokers (78/113)	1.72	1.16–2.54
Sweden, 1989–1992 (333 stomach cancer cases; 679 population controls)	Former smokers (85/199)	1.09	0.75–1.59

[§]Numbers of cases and controls by smoking category were not reported.

Comments

Adjusted for age; year; season of first hospital visit; family history of gastric cancer; and alcohol, salty food, and fruit intake

Adjusted for age, gender, alcohol intake, education, and income

Adjusted for residence; analysis did not control for age, gender, or hospital

Adjusted for age, gender, and hospital

Matched for age, gender, and socioeconomic status; current and former included pipe/cigar smokers; current included former smokers who had quit <5 years before the interview

Adjusted for age, gender, socioeconomic status, and other tobacco use

Table 2.21   Cohort studies on the association between the number of cigarettes smoked per day and the risk of stomach cancer*

Study Location/population	Outcome	Cigarettes/day (number of deaths or cases)
Men		
Nomura et al. 1990 Japanese in Hawaii, United States, 1965–1986 (7,990 men; 150 stomach cancer cases)	Incidence	Never smokers (29) 1–10 (15) 11–20 (53) >20 (29)
Kneller et al. 1991 Norwegians in Norway and United States, 1966–1986 (17,633 men; 75 stomach cancer deaths)	Mortality	Never smokers (8) 1–19 (8) 20–29 (7) 30 (7) p value for trend <0.01
Tverdal et al. 1993 Norway, 1972–1988 (44,290 men; 78 stomach cancer deaths)	Mortality	Never smokers (8) 1–9 (12) 10–19 (23) 20 (12)
Doll et al. 1994 British physicians, United Kingdom, 1951–1991 (34,439 men; 277 stomach cancer deaths)	Mortality	Never smokers 1–14 15–24 25 p value for trend = 0.01
McLaughlin et al. 1995a U.S. veterans, United States, 1954–1980 (177,903 men; 1,058 stomach cancer deaths)	Mortality	Never smokers 1–9 10–20 21–39 40 p value for trend <0.01
Mizoue et al. 2000 Fukuoka, Japan, 1986–1996 (4,050 men; 53 stomach cancer deaths)	Mortality	Never smokers (5) 1–24 (20) 25 (6)
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982– 1996 (312,332 men; 730 stomach cancer deaths)	Mortality	Never smokers (179) 1–19 (58) 20 (86) 21–39 (58) 40 (37) p value for trend = 0.5651

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
†RR = Relative risk.
‡CI = Confidence interval.
§Confidence interval was calculated from the original paper using cell counts.
 Number of deaths by smoking category was not reported.

RR[†]	95% CI[‡]	Comments
1.0		Adjusted for age; findings were comparable for intestinal and diffuse histologic types
2.7	1.5–5.1	
2.9	1.9–4.6	
2.4	1.4–4.1	
1.00		Adjusted for year of birth
2.20	0.84–5.97	
2.00	0.73–5.63	
5.80	2.07–16.19	
1.00		Adjusted for age and geographic area
3.00[§]	1.23–7.33	
2.49[§]	1.11–5.56	
3.09[§]	1.26–7.55	
1.00	Data were not reported.	Adjusted for age and calendar period
1.50		
1.80		
1.70		
1.0		Adjusted for age and calendar period
1.3	1.0–1.7	
1.4	1.2–1.6	
1.4	1.2–1.8	
1.9	1.3–2.7	
1.0		Adjusted for age, study area, and alcohol consumption; excluded prevalent cancer and incomplete data
2.2	0.8–6.0	
1.9	0.6–6.4	
1.00		Adjusted for age; excluded prevalent cancer and incomplete data
2.05	1.52–2.76	
2.71	2.09–3.52	
2.62	1.93–3.55	
1.82	1.26–2.61	

Table 2.21 Continued

Study Location/population	Outcome	Cigarettes/day (number of deaths or cases)
Women		
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982–1996 (469,019 women; 469 stomach cancer deaths)	Mortality	Never smokers (282) 1–19 (39) 20 (28) 21–39 (18) 40 (12) p value for trend = 0.3240

RR	95% CI	Comments
1.00		Adjusted for age; excluded prevalent cancer and incomplete
1.39	0.99–1.94	data
1.28	0.86–1.89	
2.05	1.27–3.34	
2.12	1.18–3.81	

Table 2.22   Case-control studies on the association between the number of cigarettes smoked per day and the risk of stomach cancer*

Study Location/population	Cigarettes/day (cases/controls)
Men	
Kato et al. 1990a Japan, 1985–1989 (289 stomach cancer cases; 3,014 hospital controls)	Never smokers[§] 1–19[§] 20[§]
Wu-Williams et al. 1990 United States, 1975–1984 (137 stomach cancer cases; 137 population controls)	Never smokers (21/35) 1–20 (34/25) 21–60 (28/20) >60 (14/5)
Inoue et al. 1999 Japan, 1988–1995 (651 stomach cancer cases; 12,041 hospital controls)	Never smokers (68/2,744) <20 (246/3,610) 20 (132/2,389) p value for trend <0.001
You et al. 1988 China, 1984–1986 (443 stomach cancer cases; 888 population controls)	Never smokers (62/163) <20 (158/326) 20 (223/399)
Women	
Kato et al. 1990a Japan, 1985–1989 (138 stomach cancer cases; 1,767 hospital controls)	Never smokers[§] 1–19[§] 20[§]
Inoue et al. 1999 Japan, 1988–1995 (344 stomach cancer cases; 31,805 hospital controls)	Never smokers (273/26,471) <20 (49/3,847) 20 (6/395) p value for trend <0.05
Men and women	
Ferraroni et al. 1989 Italy, 1983–1987 (397 stomach cancer cases; 1,944 hospital controls)	Never smokers (181/795) <15 (48/267) 15–24 (63/332) 25 (29/159)
Yu and Hsieh 1991 China, 1976–1980 (84 stomach cancer cases; 2,676 population controls)	Never smokers (47/2,369) 1–20 (20/270) 21 (17/37)

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]Numbers of cases and controls by smoking category were not reported.
 Confidence interval was calculated from the original paper using cell counts.

RR[†]	95% CI[‡]	Comments
1.00		Adjusted for age and residence
1.93	1.13–3.30	
2.81	1.83–4.29	
1.0		Adjusted for age, gender, and race; current included cigarette
2.2	1.1–4.7	smokers who also were pipe/cigar smokers
2.1	1.0–4.5	
5.2	1.4–8.6	
1.00		Adjusted for age; year; season of first hospital visit; family history
2.50	1.90–3.49	of gastric cancer; and alcohol, salty food, and fruit intake
2.50	1.84–3.40	
1.0		Adjusted for age, alcohol intake, and family income
1.3	0.9–1.9	
1.5	1.0–2.1	
1.00		Adjusted for age and residence
0.63	0.22–1.79	
1.53	0.63–3.74	
1.00		Adjusted for age; year; season of first hospital visit; family history
1.73	1.25–2.38	of gastric cancer; and alcohol, salty food, and fruit intake; the num-
1.94	0.85–4.47	ber for <20 cigarettes/day is calculated from the table
1.00		Adjusted for age, gender, education, marital status, and coffee and
1.02	0.72–1.44	alcohol consumption
1.01	0.74–1.38	
1.14	0.74–1.75	
1.0		Adjusted for age; gender; income; family history of stomach and
2.1	0.9–4.6	other cancers; tuberculosis; blood type; and intake of alcohol, strong
6.2	2.2–17.0	tea, milk, and fruit

Table 2.22   Continued

Study Location/population	Cigarettes/day (cases/controls)
Men and women	

Hoshiyama and Sasaba 1992
 	
Japan, 1984–1990 (294 stomach cancer cases; 294 population controls;
202 hospital controls)
	Population controls
	  Never smokers (95/110)
	1–29 (108/84)
	  30 (33/26)
	Hospital controls
	  Never smokers (95/88)
	1–29 (108/54)
	  30 (33/22)

RR	95% CI	Comments
		Adjusted for age, gender, and geographic area
1.0		
1.8	1.1–3.0	
1.8	0.9–3.5	
1.0		
1.0	0.5–1.7	
0.7	0.3–1.5	

Table 2.23   Cohort studies on the association between current smoking, years of smoking, and the risk of stomach cancer*

Study Location/population	Outcome	Years of smoking (number of deaths or cases)
Men		
Nomura et al. 1990 Japanese in Hawaii, United States, 1965–1986 (7,990 men; 150 stomach cancer cases)	Incidence	Never smokers (29) <26 (15) 26–35 (24) 36 (58)
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982–1996 (312,332 men; 730 stomach cancer deaths)	Mortality	Never smokers (179) <20 (5) 20–29 (12) 30–39 (73) 40 (149) p value for trend = 0.1081
Women		
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982–1996 (469,019 women; 469 stomach cancer deaths)	Mortality	Never smokers (282) <20 (8) 20–29 (13) 30–39 (41) 40 (35) p value for trend = 0.3666

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.

RR[†]	95% CI[‡]	Comments
1.0		Adjusted for age; findings were comparable for intestinal and
3.5	1.9–6.6	diffuse histologic types
1.5	0.9–2.7	
3.5	2.2–5.6	
1.00		Adjusted for age; excluded prevalent cancer and incomplete data
1.56	0.59–4.11	
1.27	0.68–2.39	
2.19	1.61–2.98	
2.56	2.04–3.21	
1.00		Adjusted for age; excluded prevalent cancer and incomplete data
1.87	0.92–3.81	
1.17	0.65–2.08	
1.86	1.31–2.64	
1.30	0.91–1.86	

Table 2.24 Cohort and case-control studies on the association between years since quitting smoking and the risk of stomach cancer*

Study Location/population	Years since quitting (number of deaths or cases/controls)	RR[†]	95% CI[‡]
Men			
Ji et al. 1996 China, 1988–1989 (770 stomach cancer cases; 818 population controls)	Current smokers (479/455) <5 (33/15) 5–9 (15/22) 10–19 (31/27) 20 (11/18) Never smokers (201/281) p value for trend = 0.10	1.35 2.71 0.94 1.48 0.69 1.00	1.06–1.71 1.36–5.42 0.46–1.94 0.82–2.66 0.30–1.60
De Stefani et al. 1998 Uruguay, 1992–1996 (331 stomach cancer cases; 622 hospital controls)	Current smokers (163/217) 1–4 (40/56) 5–9 (24/53) 10–14 (15/49) 15 (39/121) Never smokers (31/125) p value for trend <0.001	2.6 2.4 1.5 1.0 1.1 1.0	1.6–4.1 1.3–4.3 0.8–2.9 0.5–2.1 0.7–1.9
Chow et al. 1999 Poland, 1994–1997 (302 stomach cancer cases; 314 population controls)	Current smokers (130/100) <10 (28/39) 10–19 (32/43) 20–29 (16/24) 30 (15/27) Never smokers (61/77)	1.7 1.0 0.9 0.8 0.7 1.0	1.1–2.7 0.5–1.8 0.5–1.7 0.4–1.6 0.4–1.5
American Cancer Society, unpublished data Cancer Prevention Study II, United States, 1982–1996 (312,332 men; 730 stomach cancer deaths)	Current smokers (239) <11 (121) 11–19 (95) 20 (96) Never smokers (179) p value for trend = 0.0001	2.33 2.07 1.67 1.21 1.00	1.91–2.85 1.64–2.61 1.30–2.14 0.94–1.55
Women			
Ji et al. 1996 China, 1988–1989 (354 stomach cancer cases; 632 population controls)	Current smokers (27/55) <10 (2/4) 10 (7/3) Never smokers (318/567) p value for trend = 0.48	0.85 0.72 3.66 1.00	0.52–1.40 0.13–4.05 0.91–14.7
Chow et al. 1999 Poland, 1994–1997 (162 stomach cancer cases; 166 population controls)	Current smokers (49/38) <10 (8/7) 10–19 (11/8) 20 (13/5) Never smokers (77/108)	1.8 1.3 1.5 3.0 1.0	1.0–3.3 0.4–4.0 0.5–4.3 1.0–9.2

*Includes only studies that specify lifetime nonsmokers and distinguish current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.

Comments

Adjusted for age, income, education, and alcohol intake

Adjusted for age, residence, urban/rural status, and alcohol and vegetable intake

Adjusted for age, education, years lived on farm, and family history of cancer

Adjusted for age; excluded prevalent cancer and incomplete data

Adjusted for age, income, education, and alcohol intake

Adjusted for age, education, years lived on farm, and family history of cancer

Table 2.24 Continued

Study Location/population	Years since quitting (number of deaths or cases/controls)	RR	95% CI
	Women		
American Cancer Society, unpublished data	Current smokers (97)	1.50	1.18–1.90
	<11 (31)	1.25	0.86–1.82
	11–19 (28)	1.34	0.91–1.99
Cancer Prevention Study II,	20 (31)	1.12	0.77–1.62
United States, 1982–1996 (469,019	Never smokers (282)	1.00	
women; 469 stomach cancer deaths)	p value for trend 0.7258		
	Men and women		
Hansson et al. 1994	Current smokers (78/113)	1.72	1.16–2.54
	1–10 (25/51)	1.27	0.73–2.20
Sweden, 1989–1992 (330 stomach	11–20 (28/59)	1.22	0.72–2.07
cancer cases; 679 population controls)	21–30 (14/41)	0.89	0.46–1.73
	31 (18/48)	0.92	0.52–1.69
	Never smokers (120/281)	1.00	
	p value for trend = 0.02		

Comments

Adjusted for age; excluded prevalent cancer and incomplete data

Adjusted for age, gender, socioeconomic status, and other tobacco use

Table 2.25   Case-control studies on the association between smoking status and the risk of stomach cancer stratified by subsite

Study Location/population	Smoking status	Cardia		
		Number of cases/controls	RR*	95% CI†
Men				
Palli et al. 1992	Never smoked‡	NR§	1.0	
	Current smokers‡		1.1	0.6–2.3
Italy, 1985–1987 (population controls matched for age and gender)	Former smokers‡		1.1	0.5–2.2
Kabat et al. 1993	Never smoked‡	NR	1.0	
	Current smokers‡		2.3	1.4–3.9
United States, 1981–1990 (hospital controls matched for age, gender, race, and hospital)	Former smokers‡		1.9	1.2–3.0
Ji et al. 1996	Never smoked	40/281	1.00	
	Current smokers	83/455	1.22	0.79–3.37
China, 1988–1989 (population controls matched for age and gender)	Former smokers	22/82	1.81	0.97–3.37
Zaridze et al. 2000	Never smoked	12/86	1.0	
	Current smokers	36/154	2.0	0.9–4.5
Russia, 1996–1997 (292 hospital controls)	Former smokers	12/52	1.2	0.5–3.1
Women				
Kabat et al. 1993	Never smoked‡	NR	1.0	
	Current smokers‡		4.8	1.7–14.0
United States, 1981–1990 (hospital controls matched for age, gender, race, and hospital)	Former smokers‡		1.4	0.4–4.4
Men and women				
Gammon et al. 1997	Never smoked	53/244	1.0	
	Current smokers	85/155	2.6	1.7–4.0
United States, 1993–1995 (population controls matched for age and gender)	Former smokers	123/296	1.9	1.3–2.9

*RR = Relative risk.
†CI = Confidence interval.
‡Numbers of cases and controls by smoking category were not reported.
§NR = Data were not reported.
 BMI = Body mass index.

	Noncardia		
Number of cases/controls	RR	95% CI	Comments
NR	1.0 0.9 1.1	0.7–1.1 0.8–1.4	Adjusted for age, geographic area, urban residence, migration from the south, socioeconomic status, familial gastric cancer history, and BMI
NR	1.0 1.7 1.4	1.0–3.0 0.9–2.4	Noncardia = distal stomach; cardia includes esophagus; adjusted for age, education, alcohol intake, hospital, and time period
135/281 339/455 83/82	1.00 1.43 1.08	1.09–1.87 0.69–1.67	Noncardia = distal stomach; adjusted for age, education, income, and alcohol intake
NR	NR	NR	Adjusted for age, education, and alcohol intake
NR	1.0 3.2 2.0	1.3–7.7 0.8–4.9	Noncardia = distal stomach; cardia includes esophagus; adjusted for age, education, alcohol intake, hospital, and time period
106/244 96/155 164/296	1.0 1.8 1.5	1.2–2.7 1.1–2.1	Adjusted for age, gender, geographic area, race, BMI, income, and alcohol intake

Table 2.25 Continued

Study Location/population	Smoking status	Cardia		
		Number of cases/controls	RR	95% CI
Men and women				
Ye et al. 1999				
	Never smoked	34/512	1.0	
Sweden, 1989–1995 (population controls matched for age and gender)	Current smokers	25/415	0.9	0.5–1.6
	Former smokers	31/237	1.7	1.0–3.1
Lagergren et al. 2000				
	Never smoked	43/325	1.0	
Sweden, 1995–1997 (population controls matched for age and gender)	Current smokers	95/181	4.5	2.9–7.1
	Former smokers	124/314	3.4	2.2–5.2

Colorectal Cancer

Together, cancers of the colon and rectum rank as the third most common cancers and cause of cancer deaths among men and women in the United States (ACS 2003). In 2003, an estimated 105,500 cases of cancer of the colon and 42,000 cases of cancer of the rectum were expected to be diagnosed. That same year, 57,100 deaths from both cancers combined were expected to occur (ACS 2003). In the mid-1990s, the lifetime probability of developing colorectal cancer was estimated to be 5.6 percent in the United States (Greenlee et al. 2000).

Worldwide, colorectal cancer incidence and mortality rates vary more than 10-fold among countries; the highest rates occur in western Europe, North America, Australia/New Zealand, and Japan; and the lowest rates occur in countries with developing economies, particularly in Africa and Asia (Parkin et al. 1999; Pisani et al. 1999). Studies of migrants show that, in immigrants moving from countries where the incidence is low to countries where the incidence is high, incidence rates increase within one generation to approximate rates of the new country, suggesting a strong role for environmental causes (Thomas and Karagas 1987; McMichael and Giles 1988).

The average annual age-adjusted population incidence rate of colorectal cancer per 100,000 in the United States from 1996–2000 was 72.4 in black men, 64.1 in white men, 57.2 in Asian/Pacific Islander men, 56.2 in black women, 49.8 in Hispanic men, 46.2 in white women, 38.8 in Asian/Pacific Islander women, 37.5 in American Indian/Alaska Native men, 32.9 in Hispanic women, and 32.6 in American Indian/Alaska Native women (Ries et al. 2003). Incidence rates are consistently higher among men than among women in all racial and ethnic groups (Ries et al. 2003). Colorectal cancer incidence rates increased from 1973 until 1985 and began decreasing steadily in the mid-1980s; mortality rates increased through 1991 and then decreased rapidly through 1997 (Chu et al. 1994; Ries et al. 2000b). The decrease in both incidence and mortality rates has been larger and began earlier in white women than in white men.

	Noncardia		
Number of cases/controls	**RR**	**95% CI**	**Comments**
Distal stomach (intestinal type)			Adjusted for age, gender, geographic area, BMI, socioeconomic status, smokeless tobacco use, and alcohol intake; current/former smokers included pipe/cigar smokers
92/512	1.0		
101/415	1.4	1.0–2.0	
67/237	1.8	1.2–2.7	
Distal stomach (diffuse type)			Adjusted for age, gender, geographic area, BMI, socioeconomic status, smokeless tobacco use, and alcohol intake; current/former smokers included pipe/cigar smokers
61/512	1.0		
46/415	1.3	0.8–2.0	
57/237	2.2	1.4–3.5	
NR	NR	NR	Adjusted for age; gender; education; BMI; reflux symptoms; physical activity; and fruit, vegetable, energy, and alcohol intake; current/former smokers included pipe/cigar smokers

The five-year relative survival rate among whites in the United States is approximately 90 percent when colorectal cancers are diagnosed and treated at the localized stage, but falls below 10 percent when they are diagnosed at the distal stage. Fewer than 40 percent of all cases are diagnosed at the localized stage (Ries et al. 2003). A shift toward an earlier stage at diagnosis occurred among white men and women in the United States between 1975 and 1995 (Troisi et al. 1999), and the resulting improvements in survival have been attributed mostly to the earlier removal of localized carcinomas (Chu et al. 1994; Troisi et al. 1999; Ries et al. 2000b).

Colorectal cancer risk factors include physical inactivity, obesity, and perhaps a diet high in saturated and animal fats and low in vegetables and fruits. These risk factors are still under investigation and uncertainty remains, particularly with regard to the specific dietary factors. The risks also increase for persons with a family history of colorectal cancer or polyps. Factors consistently associated with a reduced risk are the use of aspirin and other nonsteroidal anti-inflammatory drugs, and hormone replacement therapy use among women (Potter 1999).

Colorectal cancer was among the causes of mortality assessed in cohort studies. The hypothesis that prolonged cigarette smoking may contribute to colorectal cancer gained support in the mid-1990s when epidemiologic (particularly cohort) studies reported a higher incidence of adenomatous polyps and/or cancer in long-term smokers (Giovannucci et al. 1994a,b). Uncertainty about the reports of this observed association has primarily come from the possibility of uncontrolled confounding by other lifestyle determinants of risk that are still under study (Doll 1996; Giovannucci and Martínez 1996). Giovannucci and Martínez (1996) and Giovannucci (2001) have provided comprehensive reviews of the literature and the methodologic concerns.

Conclusions of Previous Surgeon General's Reports

Until the 2001 Surgeon General's report on women and smoking (USDHHS 2001), this series of reports had not considered smoking in relation to cancers of the colon and rectum, and colorectal cancers

are not included among the smoking-related cancers by the Centers for Disease Control and Prevention (CDC) (Nelson et al. 1994) or IARC (1986) (Parkin et al. 1994).

Biologic Basis

Most cancers of the colon and rectum are adenocarcinomas (Rosai 1996). These tumors typically develop from clonal expansions of mutated cells through a series of histopathologic stages from single crypt lesions to benign tumors (adenomatous polyp) and then to metastatic carcinomas that take place over a span of 20 to 40 years (Fearon and Vogelstein 1990; Kinzler and Vogelstein 1998). The number and order of genetic and epigenetic changes in tumor suppressor genes (such as *APC*, *p53*, and *DCC*) and oncogenes (such as *ras*) determine the probability of tumor progression (Fearon and Vogelstein 1990; Kinzler and Vogelstein 1998). On the basis of the observation that mutations of the *APC* gene on chromosome 5q are found as frequently in small adenomatous polyps as in cancers, the loss of normal *APC* function is considered an early (and possibly initiating) event in colorectal tumorigenesis (Powell et al. 1992; Morin et al. 1997). Products of the *APC* gene influence cell proliferation, adhesion, migration, and apoptosis (Kinzler and Vogelstein 1998). Activating mutations in codons 12 and 13 of the *ras* oncogene are important in the progression of adenomas but are not directly involved in malignant transformations in the bowel (Bos 1989; Ohnishi et al. 1997; Kinzler and Vogelstein 1998). Approximately 85 percent of colorectal cancers show inactivating mutations of the *p53* tumor suppressor gene on chromosome 17p, resulting in loss of growth arrest and/or apoptosis; these mutations are important at a late stage in malignant transformation (Hollstein et al. 1991; Kinzler and Vogelstein 1998). Clonal expansion of colorectal tumors containing mutant *p53* genes gains a selective survival advantage and becomes increasingly invasive and metastatic (Kinzler and Vogelstein 1998).

Because observational studies consistently show an association between cigarette smoking and adenomatous polyps (IARC 1986; Kikendall et al. 1989; Cope et al. 1991; Monnet et al. 1991; Zahm et al. 1991; Lee et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994b; Peipins and Sandler 1994; Boutron et al.

1995; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000), Giovannucci and others have proposed that cigarette smoking plays a role early in colon and rectum carcinogenesis, likely acting on *APC* genes (Giovannucci et al. 1994a,b; Giovannucci and Martínez 1996). Two large cohort studies found that smoking for two decades or more was associated with large adenomas and that smoking for less than 20 years was associated with small adenomas (Giovannucci et al. 1994a,b). Cigarette smoking for at least three decades also has been associated with an increased risk of colorectal cancer incidence and mortality (Giovannucci et al. 1994a,b; Heineman et al. 1995; Chao et al. 2000). An initiating role of tobacco in the formation of adenomas is further supported by the finding that smokers who quit continue to have an elevated risk of adenoma recurrence after 10 years of smoking cessation (Jacobson et al. 1994). Cigarette smoking has not yet been associated with specific gene mutations or epigenetic changes associated with colorectal cancer.

Cigarette smoke contains many carcinogens, including PAHs, heterocyclic aromatic amines, and *N*-nitrosamines (Hoffmann and Hoffmann 1997), that can reach the large bowel via the circulatory system or by direct ingestion of foods that contain these carcinogens (Giovannucci and Martínez 1996). One small study has documented that DNA adducts to metabolites of benzo[*a*]pyrene, a potent PAH, in colonic mucosa occur more frequently and at higher concentrations in smokers than in nonsmokers (Alexandrov et al. 1996). This study provides direct evidence that tobacco carcinogens bind to DNA in the human colonic epithelium. DNA adduction levels in the colonic epithelium have been found at higher levels in tumor tissue from colorectal cancer cases than from controls (Pfohl-Leszkowicz et al. 1995).

Other genes known to be important in colorectal cancer include mismatch repair genes associated with the hereditary familial syndrome, nonpolyposis colorectal cancer, and with sporadic cases of colorectal cancer (Liu et al. 1995, 1996; Thibodeau et al. 1998). One study has found that cigarette smoking is associated with a mismatch repair deficiency in colorectal cancers, reflected by a sixfold increased risk of microsatellite instability (a genetic marker) in tumors in current smokers compared with nonsmokers (Yang et al. 2000).

To date, the association between cigarette smoking and colorectal cancer has not been found to be modified by polymorphisms of genes important in the detoxification of carcinogens found in tobacco smoke, including glutathione *S*-transferase (GST) *M1*, *T1*, and *N*-acetyltransferase 2 (*NAT2*) (Gertig et al. 1998; Slattery et al. 1998). Studies of colorectal adenomas also have found no modification of the risk of cigarette smoking by polymorphisms of *GSTM1*, *NAT2*, or cytochrome P-4501A1, an enzyme important in the activation of PAHs (Lin et al. 1995; Potter et al. 1999; Inoue et al. 2000). However, one study found that when researchers examined only adenomas 1 cm or larger, current smokers with the *GSTM1* null genotype were at a higher risk compared with those without the null genotype (Lin et al. 1995).

Animal Models

Animal models of tobacco carcinogenicity in the colon and rectum are limited and do not include studies in which the route of exposure is by inhalation. Adenocarcinomas of the colon have been produced in inbred male Syrian hamsters by intrarectal instillation of benzo[*a*]pyrene (Wang et al. 1985). In vivo mutational assay studies show that oral administration of benzo[*a*]pyrene to the *lac*Z transgenic mouse (Muta™ Mouse) induced the highest mutant frequency in the colon compared with other organs tested (Hakura et al. 1998, 1999; Kosinska et al. 1999). In vitro studies show that both rat and human colonic epithelium in cell cultures can enzymatically activate benzo[*a*]pyrene (Autrup et al. 1978).

Epidemiologic Evidence

Published studies on cigarette smoking and colorectal adenomatous polyps and cancer cited in this section were identified by searching the MEDLINE database from 1966 through July 2000 using the headings "tobacco," "smoking," "colorectal adenomas," "colorectal neoplasms," "colonic neoplasms," and "rectal neoplasms," and from the reference lists of published original and review articles in English on cigarette smoking and colorectal adenomas and cancer. The association between cigarette smoking and colorectal adenomas and cancer has been evaluated in a number of prospective and case-control studies since the 1960s. This review focuses on published studies

that exclude cigar and pipe smokers, specify lifetime nonsmokers, and distinguish current from former smokers. If there are multiple reports from the same prospective cohort, results from the longest follow-up period are reported unless otherwise stated.

Table 2.26 presents prospective and retrospective studies of colorectal adenomatous polyps stratified by the cigarette smoking status of participants. Current cigarette smoking was consistently associated with an increased risk of colorectal adenomatous polyps in men and women, with OR estimates ranging between 1.5 and 3.8, adjusting for age and multiple covariates (Cope et al. 1991; Monnet et al. 1991; Zahm et al. 1991; Olsen and Kronborg 1993; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000). Current smokers generally were at a higher risk compared with former smokers (Zahm et al. 1991; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000). Former smokers had a significantly increased risk of colorectal adenomas compared with lifetime nonsmokers in five studies (Monnet et al. 1991; Olsen and Kronborg 1993; Martínez et al. 1995; Nagata et al. 1999; Potter et al. 1999), two of which also found an increased risk in former compared with current smokers (Monnet et al. 1991; Olsen and Kronborg 1993). One Japanese study found no increased risk of adenomas associated with current or former smoking (Kato et al. 1990b), and a randomized clinical trial of antioxidant vitamins in polyp prevention found no association between smoking and the recurrence of colorectal adenomas (Baron et al. 1998). Of two studies that compared adenoma cases to both hospital and population controls, one (Breuer-Katschinski et al. 2000) found an increased risk among current and former smokers only when comparing cases to hospital controls, whereas the other (Almendingen et al. 2000) found a comparably increased risk of adenomas among current and former smokers when comparing cases to either hospital or population controls.

Most studies examining the risk of adenomas in relation to cigarette smoking duration or pack-years have found a significantly positive association (Kikendall et al. 1989; Monnet et al. 1991; Zahm et al. 1991; Olsen and Kronborg 1993; Giovannucci et al. 1994a,b; Boutron et al. 1995; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al.

1999; Almendingen et al. 2000; Inoue et al. 2000). Three prospective studies of the risk of proximal and distal colorectal adenomas have shown a significant dose-response relationship with total duration and with pack-years of smoking in men and women (Giovannucci 1994a,b; Nagata et al. 1999). Both the Health Professionals Follow-Up Study (Giovannucci et al. 1994b) and the Nurses Health Study (Giovannucci et al. 1994a) found that (1) smoking at least 20 years in the past was associated with the prevalence of large distal adenomas and (2) smoking fewer than 20 years was associated with small distal adenomas. Several case-control studies have reported a significant dose-response relationship with pack-years (Kikendall et al. 1989; Martínez et al. 1995; Longnecker et al. 1996; Potter et al. 1999) or with smoking duration (Olsen and Kronborg 1993; Almendingen et al. 2000) in studies of men and women combined. When examined separately by gender, there is a consistently significant dose-response relationship with pack-years and smoking duration among men (Monnet et al. 1991; Zahm et al. 1991; Lee et al. 1993; Boutron et al. 1995; Inoue et al. 2000) but a nonsignificant trend among women (Lee et al. 1993; Boutron et al. 1995). One case-control study reported no association between adenoma risk and pack-years in men or women (Sandler et al. 1993b).

Table 2.27 shows that cohort studies of colon and rectal cancer incidence and mortality among men in the United States consistently report an increased risk associated with current smoking status, with RRs ranging between 1.2 and 1.4 for colon cancer and between 1.4 and 2.0 for rectal cancer, regardless of the number or type of covariates adjusted for (Heineman et al. 1995; Chyou et al. 1996; Hsing et al. 1998; Chao et al. 2000; Stürmer et al. 2000). Two Norwegian studies also report risk estimates within this range (Tverdal et al. 1993; Engeland et al. 1996), but a study of Swedish male construction workers found no increased risk of colon cancer with current smoking (RR = 0.98) or former smoking (RR = 1.02) (Nyrén et al. 1996). More than half of the Swedish cohort was younger than 40 years of age at cohort entry, substantially younger than other cohorts in which an increased risk was observed. The 40-year follow-up of the British Physicians Study reported a RR of 1.36 for colon cancer mortality and 2.30 for rectal cancer mortality (Doll et al. 1994).

CPS-II is the largest cohort study reporting an increased risk of colorectal cancer mortality associated with current smoking status in men (RR = 1.3) and women (RR = 1.4) (Chao et al. 2000). Two Norwegian cohort studies of women have found no increased risk associated with current smoking status (Tverdal et al. 1993; Engeland et al. 1996), similar to the eight-year follow-up report of the Nurses Health Study (Chute et al. 1991); two of these studies included women aged 30 through 55 years at enrollment (Chute et al. 1991; Tverdal et al. 1993). Two other cohort studies of men and women combined found no increased risk of colon or rectal cancer with cigarette smoking (Klatsky et al. 1988; Knekt et al. 1998). The RR estimates associated with former smoking among men and women fall within the range of 1.0 and 1.5 and, with some exceptions (Chute et al. 1991; Heineman et al. 1995; Engeland et al. 1996; Nyrén et al. 1996; Hsing et al. 1998), generally are intermediate between the risks observed among current smokers and lifetime nonsmokers.

Case-control studies of colon and rectal cancer incidence by cigarette smoking status generally have not reported an increased risk among male smokers (Table 2.28) (Kune et al. 1992; D'Avanzo et al. 1995; Le Marchand et al. 1997). The case-control studies are inconsistent for women alone and for women and men combined (Kune et al. 1992; Baron et al. 1994; D'Avanzo et al. 1995; Newcomb et al. 1995; Le Marchand et al. 1997). One study of U.S. women found significantly higher RRs in current smokers compared with lifetime nonsmokers, 1.3 for colon cancer and 1.7 for rectal cancer (Newcomb et al. 1995). When examined by cigarette smoking duration, the risk increased with the number of years the participants had smoked. The risks associated with having smoked 31 to 40 years were 1.7 for colon cancer and 1.5 for rectal cancer (Newcomb et al. 1995); it was the only study to adjust the risk estimates for colorectal cancer screening. Another study has examined the relationship by right and left colon and found a significantly increased risk of cancer in the right colon among former female smokers (OR = 2.4) and a nonsignificantly increased risk of cancer in the left colon and rectum among former male smokers compared with nonsmokers (Le Marchand et al. 1997). This study also reported a significantly increased risk of colon and rectal cancers associated with increments in pack-years of smoking in the distant and recent past among both genders (Le Marchand et al. 1997).

Only more recent epidemiologic studies (since 1994) have examined colorectal cancer incidence or mortality in relation to gradients of smoking duration

and timing, beyond smoking status (Giovannucci et al. 1994a,b; Nyrén et al. 1996; Hsing et al. 1998; Chao et al. 2000). Four recent reports from cohort studies have described an increased risk of colorectal cancer incidence and mortality with increased smoking duration in both men and women (Table 2.29) (Giovannucci et al. 1994a,b; Hsing et al. 1998; Chao et al. 2000). The sole exception is the Swedish study of men in whom no increased risk was observed with an increase in smoking duration (Nyrén et al. 1996). The Health Professionals Follow-Up Study (Giovannucci 1994b) reported a significantly increased risk among men who had smoked at least 40 to 44 years (RR = 1.7); the 16-year follow-up of the Nurses Health Study (Giovannucci 1994a) reported an elevated risk in women who had smoked more than 10 cigarettes a day for 35 to 39 years (RR = 1.5); and another cohort of U.S. men (Hsing et al. 1998) found an increased risk after smoking 20 to 29 years (RR = 2.4).

CPS-II found a statistically significant increase in risk of colorectal cancer mortality among male smokers of 30 to 39 years' duration (multivariate RR = 1.3) and among female smokers of 20 to 29 years' duration (multivariate RR = 1.3) (Chao et al. 2000). Controlling for multiple covariates decreased age-adjusted estimates in currently smoking men but had little net effect on age-adjusted estimates in currently smoking women. Results of cohort studies that assess cigarette smoking status only at cohort enrollment may underestimate the true risk among long-term continuing smokers, because some smokers will have quit smoking during the cohort follow-up period.

Two cohort studies of colorectal cancer mortality have found a consistently increasing risk associated with a younger age at smoking initiation (Table 2.30) (Heineman et al. 1995; Chao et al. 2000). The 26-year follow-up of the veterans cohort reported that initiating smoking before 15 years of age was associated with a RR of 1.4 for colon cancer and 1.5 for rectal cancer (Heineman et al. 1995). CPS-II found that currently smoking men and women who began smoking at 15 years of age or younger had an increased risk of death from colorectal cancer (multivariate RR = 1.4 in men and 1.7 in women) (Chao et al. 2000).

Data from CPS-II show that former smokers experience lower colorectal cancer mortality rates compared with continuing smokers (Table 2.31) (Chao et al. 2000). Risk decreases with a younger age at and a greater number of years since smoking cessation; former smokers who quit 20 or more years before the study were not at an increased risk of death from colorectal cancer compared with nonsmokers. Controlling for multiple covariates reduced the age-adjusted risk estimates in former male smokers but increased the risk estimates in former female smokers. The Leisure World cohort also found that men who had quit smoking more than 20 years ago were at a lower risk of colorectal cancer incidence than those who had quit within the past 20 years (Wu et al. 1987). In the multisite case-control study conducted by Slattery and colleagues (1997), risk remained modestly elevated for those former smokers who had stopped for 15 years or more.

Evidence Synthesis

There is now a strong understanding of the sequence of genetic changes that leads from a normal cell to polyp development and then on to malignancy. Evidence points to an effect of smoking on polyp formation and possibly on the development of malignancy. Recent findings of prospective cohort studies suggest that long-term cigarette smoking is associated with an increased risk of colorectal cancer incidence and mortality in both men and women; risk is highest in current cigarette smokers, intermediate in former smokers, and lowest in nonsmokers. In some studies, the risk of colorectal cancer incidence and mortality tends to increase with longer smoking duration and a younger age at smoking initiation, and decreases with a younger age at and a greater number of years since successful smoking cessation, although the effects of these two factors cannot be readily separated because of their inherent correlation.

The aggregate epidemiologic evidence supports the hypothesis by Giovannucci and colleagues (1994a,b) and Giovannucci and Martínez (1996) that a latent period of several decades is necessary for cigarette smoking to increase colorectal cancer incidence or mortality, and that cigarette smoking likely plays a role in early colon and rectum carcinogenesis. This hypothesis is further supported by the association of smoking with adenomas. A number of studies show a greater risk for polyps in smokers compared with nonsmokers, and some show a dose-response relationship

with the number of cigarettes smoked. Under this hypothesis, the early studies of smoking might have missed an association because of insufficient follow-up time for the necessary tumor growth. This phenomenon would particularly apply to women, since the smoking epidemic began later in women than in men in the United States and most other developed countries. The finding of a declining risk following smoking cessation also suggests that cigarette smoking may affect later stages of the carcinogenic process leading to colorectal cancer.

In assessing whether cigarette smoking plays a causal role in colorectal cancer, consideration needs to be given to nutritional or other factors, such as physical activity and participation in colorectal cancer screening, that may confound the association. Not all recent studies have controlled for colorectal cancer risk factors that may be associated with smoking, such as physical inactivity. However, indirect evidence against confounding comes from the consistent finding of a small but statistically significant increase in risk associated with smoking, regardless of the set of covariates adjusted for in an analysis. Among the prospective cohort studies, three adjusted for physical activity or inactivity (Heineman et al. 1995; Chao et al. 2000; Stürmer et al. 2000). CPS-II analyses further adjusted for the use of estrogen replacement therapy (in women) and aspirin or other nonsteroidal anti-inflammatory drugs (Chao et al. 2000), factors that have been consistently associated with a lower risk of colorectal cancer (Thun et al. 1992; Calle et al. 1995; Potter 1999). Three cohort studies (Giovannucci et al. 1994b; Chao et al. 2000; Stürmer et al. 2000) adjusted for some measure of diet, and four studies (Giovannucci et al. 1994b; Hsing et al. 1998; Chao et al. 2000; Stürmer et al. 2000) adjusted for alcohol consumption. The only study of incidence or mortality that adjusted for screening sigmoidoscopy (as well as other variables) in women reported RR estimates similar to CPS-II results for smoking duration and years since quitting (Newcomb et al. 1995).

Adjusting for measured potential confounders for colorectal cancer in CPS-II affected the association with cigarette smoking differently by gender and by smoking status. Such adjustments increased risk estimates for former female smokers, had little net effect on risk estimates for current female smokers, and decreased the risk estimates for men. The slight decrease in adjusted estimates among men was comparable to that reported from the Health Professionals Follow-Up Study (Giovannucci 1994b), which controlled for saturated fat, folate, and dietary fiber and was one of the few studies that reported age- and multivariate-adjusted risk estimates. Although the possibility of residual confounding cannot be completely excluded, the internal consistency of findings and the fact that adjusting for measured potential confounders actually strengthened the association between smoking and colorectal cancer mortality in former female smokers in CPS-II suggest that the observed associations are unlikely to be explained solely by confounding. While the cohort study data are generally consistent with the hypothesis that smoking causes colorectal cancer, the trends of colorectal cancer incidence in the United States appear to be inconsistent. If smoking causes colorectal cancer after a substantial latent period as hypothesized (Giovannucci 2001), then the temporal patterns of smoking across the twentieth century would predict a decline in incidence in men before a decline in women. The opposite pattern has been observed (Ries et al. 2000b). However, other factors such as changes in risk variables and screening practices would also affect trends in incidence rates. Given the relatively modest effect of smoking on colorectal cancer risks, trends in incidence are an insensitive indicator of any trends in the effects of smoking over time.

Cigarette smoking is associated with a diagnosis of colorectal cancer at a more advanced stage of the disease (Longnecker et al. 1989), leading to a poorer prognosis and a lower survival rate in smokers compared with nonsmokers. However, recent cohort studies have reported similar findings of increased risks among smokers for both colorectal cancer incidence and mortality (Giovannucci et al. 1994a,b; Chao et al. 2000). Although no published reports were found on colorectal cancer screening prevalence by cigarette smoking status, the 1990–1994 National Health Interview Surveys (Rakowski et al. 1999) show that compared with lifetime nonsmokers, women who currently smoke are less likely, and those who are former smokers are more likely, to be screened for breast and cervical cancers. Thus, colorectal cancer mortality

studies cannot exclude the possibility that continuing smokers experienced higher death rates from colorectal cancer than did nonsmokers because of less screening and a later stage of disease at diagnosis. However, the statistically significant increase in risk of colorectal cancer mortality among former female smokers in CPS-II argues against appreciable confounding by differential colorectal cancer screening practices, because these women are perhaps the most likely to be screened. CPS-II results were also similar to those of the one study that adjusted for screening sigmoidoscopy (Newcomb et al. 1995). The consistently observed relationship between cigarette smoking and adenomatous polyps, especially large adenomas (Kikendall et al. 1989; Cope et al. 1991; Monnet et al. 1991; Zahm et al. 1991; Lee et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994a,b; Peipins and Sandler 1994; Boutron et al. 1995; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000), also suggests that confounding by screening is unlikely to explain the increased risk observed in studies of colorectal cancer incidence and mortality.

In 2000, about 23 percent of adults in the United States were current cigarette smokers, and 22 percent were former smokers (CDC 2002b). In 2001, 29 percent of high school students were current cigarette smokers (CDC 2002a). If long-term cigarette smoking is a cause of colorectal cancer (one of the most common cancers in western populations), the multivariate-adjusted RR estimates in CPS-II would indicate that about 12 percent of colorectal cancer deaths among men and 12 percent among women in the general population were attributable to smoking.

Cumulative findings from several recent, large prospective studies show an increased risk of colon and rectal cancer after smoking for two or more decades. The temporal pattern of the effects of smoking suggests that it may act in both earlier and later stages of carcinogenesis.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Implications

The aggregate evidence suggests that cigarette smoking may be one of the avoidable factors that causes colorectal cancer. Current and former smoking should be included with other potential risk factors for this disease in clinical and public health settings, and further research should be directed at smoking and colorectal cancer risk.

The possible inclusion of colorectal cancer among the smoking-related cancers would substantially increase estimates of smoking attributable cancers and deaths worldwide. In the United States, the proportion of colorectal cancer deaths in 1997 attributable to any cigarette smoking (based on CPS-II multivariate-adjusted RRs) would be approximately 12.0 percent among men and 12.3 percent among women, corresponding to an estimated 6,800 deaths. Considering past and future trends in cigarette smoking prevalence in the United States (Pierce et al. 1989) and in colorectal cancer incidence and mortality by gender since the 1950s (Chu et al. 1994), further reductions in smoking among adolescents and adults could accelerate and sustain future reductions in incidence and mortality.

Table 2.26   Epidemiologic studies on the association between smoking status and the risk of colorectal adenoma

Study Location/population	Type of adenoma	Smoking status (case/noncase)
Men		
Monnet et al. 1991 Case-control study, France, 1983–1987 (103 men with colorectal adenoma; 108 male hospital controls with normal colonoscopy)	Colorectal adenomas	Never smoked (17/33) Current smokers (39/43) Former smokers (47/32)
Zahm et al. 1991 Cross-sectional study, United States, 1981–1983 (549 white men from the Pattern Makers League of North America at 11 factories, in a flexible sigmoidoscopy screening program)	Adenomatous polyps	Never smoked (7/178) Current smokers (12/120) Former smokers (12/217)
Honjo et al. 1992 Cross-sectional study, Japan, 1989–1990 (115 cases of men with adenomatous polyps of the sigmoid colon, and 930 male controls with a normal colonoscopy)	Adenomatous polyps of the sigmoid colon	Never smoked (13/244) Former smokers (33/276) Current smokers <25 cigarettes/day (50/280) 25 cigarettes/day (20/130)

Giovannucci et al. 1994b
 	
 Cohort study, United States, 1986–1992 (Health Professionals Follow-up Study data, 626 new cases of colorectal ad-enomas, with pack-year information available for 499 cases and 7,968 of the noncases)
	Small (<1 cm) and large (1 cm) colorectal adenomas	Total pack-years[‡]
		  0 (186/4,085)
		 1–9 (70/970)
		 10–19 (58/917)
		 20–29 (53/727)
		 30–39 (49/454)
		  40 (83/815)

Nagata et al. 1999 Cohort study with cross-sectional analysis, Japan, 1993–1995 (14,427 men aged 35 years, with 181 new cases of colorectal adenoma; smoking informa-tion available for 178 of the cases and 12,260 of the noncases)	Colorectal adenomas	Never smoked (23/2,036) Current smokers (99/6,670) Former smokers (56/3,554)

*CI = Confidence interval.
[†]BMI = Body mass index.
[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Risk estimate	95% CI*	Comments
1.0 1.9 2.7	 0.9–4.0 1.3–5.7	Adjusted for age; excluded men with other bowel diseases (including cancer) or a history of familial adenomatous polyposis
1.0 2.7 1.2	 1.00–7.10 0.50–2.70	Adjusted for age and alcohol intake
1.0 2.2 3.3 2.8	 1.1–4.3 1.8–6.3 1.3–5.9	Estimates were adjusted for drinking (never, former, and current: <30, 30–59, and 60 mL/day, respectively); self-defense forces rank (low, middle, and high), and BMI† (<22.5, 22.5–25.0, and >25.0, respectively); excluded those with prior history of colorectal polypectomy, colectomy or malignant neoplasms, and those having concurrently adenocarcinoma of the large bowel, gastric cancer, or polycythemia vera
1.0 1.53 1.28 1.37 1.93 1.67	 1.14–2.03 0.94–1.74 0.99–1.89 1.37–2.70 1.25–2.22 p for trend = 0.0001	Estimates were adjusted for age, family history of colorectal cancer, BMI, saturated fat intake, dietary fiber, folate, and alcohol intake
1.00 1.44 1.21	 0.93–2.33 0.75–2.01	Adjusted for age; excluded those with a history of colorectal polyps or cancer from self-reports or from colonoscopies (among noncases)

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Men	

Breuer-Katschinski et al. 2000
 	
Case-control study, Germany, 1993–1995 (94 histologically confirmed colorectal adenomas, 88 hospital controls, and 92 population controls free of adenomas, determined by a colonoscopy)
	Colorectal adenomas	Compared with hospital controls
		  Never smoked (NR[§])
		  Current smokers (NR)
		  Former smokers (NR)
		
		Compared with population controls
		  Never smoked (NR)
		  Current smokers (NR)
		  Former smokers (NR)

Inoue et al. 2000 Cross-sectional study, Japan, 1995–1996 (205 histologically confirmed adenomas of the proximal and distal colon, 220 male controls who received a total colonoscopy)	Colorectal adenomas	Never smoked (35/73) Current smokers <25 cigarettes/day (83/51) 25 cigarettes/day (46/24) Former smokers (41/72)
	Women	
Giovannucci et al. 1994a Cohort study with cross-sectional analysis, United States, Nurses Health Study (12,143 women who had a first colonoscopy or sigmoidoscopy between 1980 and 1990, with 498 new cases of adenoma)	Small (<1 cm) and large (1 cm) adenomas of the left colon and rectum	Total pack-years 0 (164/5,382) 1–9 (52/1,498) 10–19 (55/1,280) 20–29 (46/1,166) 30–39 (56/828) 40 (125/1,491)
Nagata et al. 1999 Cohort study with cross-sectional analysis, Japan, 1993–1995 (17,125 women aged 35 years with 78 new cases of colorectal adenomas; smoking information was available for 64 cases and 14,105 noncases)	Colorectal adenomas	Never smoked (46/11,679) Ever smoked (18/2,426)

[§]NR = Data were not reported.

Risk estimate	95% CI	Comments
1.0 2.2 1.2	 0.72–6.8 0.52–2.9	Adjusted for age; gender; social class; relative weight; smoking; and intake of fat, fiber, energy, red meat, vitamin A, carotene, and folate; excluded those with symptoms of irritable bowel syndrome, polyposis, previous colon cancer, resection, adenoma, or any form of colitis
1.0 0.8 0.7	 0.30–2.3 0.29–1.7	
1.0 3.5 3.8 1.1	 2.0–6.1 2.0–7.4 0.6–1.9	Adjusted for hospital, rank in self-defense forces, alcohol use, and BMI; excluded those with a history of colorectomy, polypectomy, or malignant neoplasm
1.0 1.21 1.50 1.33 2.32 2.49	 0.88–1.66 1.10–2.05 0.95–1.86 1.70–3.18 1.95–3.17 p for trend = <0.0001	Estimates were adjusted for age and family history of colorectal cancer; excluded those with previous cancer, as well as those with hyperplastic polyps and adenomas proximal to the descending colon
1.00 2.17	 1.22–3.69	Adjusted for age; excluded those with a history of colorectal polyps or cancer from self-reports or from colonoscopies (among noncases); no current or former smoking status data for women were reported

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)

Women		

Breuer-Katschinski et al. 2000
 	
Case-control study, Germany, 1993–1995 (88 histologically confirmed colorectal adenomas, 90 hospital controls, and 90 population controls free of adenomas, determined by a colonoscopy)
	Colorectal adenomas	Compared with hospital controls
		  Never smoked (NR)
		  Current smokers (NR)
		  Former smokers (NR)
		
		Compared with population controls
		  Never smoked (NR)
		  Current smokers (NR)
		  Former smokers (NR)

Men and women		

Hoff et al. 1987
 	
Cohort study, Norway (159 men and women aged 50–59 years with a 2-year follow-up)
	Polyps in the rectum and sigmoid colon	Men
		  Never smoked (2/12)
		  Current smokers (13/42)
		  Former smokers (1/17)
		Women
		  Never smoked (4/32)
		  Current smokers (2/27)
		  Former smokers (1/6)

Kikendall et al. 1989 Cross-sectional study, United States (Washington, DC; 102 men and postmenopausal women with adenomas at colonoscopy, and 89 colonoscopy-negative controls)	Colonic adenomas	Never smoked (24/31) Current smokers (41/19) Former smokers (33/37) (quit 2 years)
Kato et al. 1990b Case-control study, Japan, 1986–1990 (525 colorectal adenomas and 181 cases with multiple adenomas)	Proximal colon (n = 163) Distal colon (n = 351) Rectum (n = 118)	Never smoked (NR) Current smokers (NR) Former smokers (NR) Never smoked (NR) Current smokers (NR) Former smokers (NR) Never smoked (NR) Current smokers (NR) Former smokers (NR)

Risk estimate	95% CI	Comments
1.0		Adjusted for age; gender; social class; relative weight; smoking; and intake of fat, fiber, energy, red meat, vitamin A, carotene, and folate; excluded those with symptoms of irritable bowel syndrome, polyposis, previous colon cancer, resection, adenoma, or any form of colitis
2.8	0.90–8.6	
1.5	0.62–3.5	
1.0		
0.94	0.36–2.5	
1.8	0.69–4.5	
NR	NR	RR was not reported; for men, former smokers had 1 out of 18 new cases in 2 years (vs. 13 out of 18 for current smokers); for women, frequency of polyps was the same in all 3 smoking categories
1.00	Overall χ^2 = 8.6, p = 0.014;	CI was not reported; excluded those with history of colonic adenomas or cancer, familial polyposis, inflammatory bowel disease, malabsorption, alcoholism, hepatic or renal disease, or recent weight loss
2.79	Mantel-Haenszel χ^2 = 7.2,	
1.15	p = 0.007	
1.00		Adjusted for age, gender, and area of residence; excluded those with self-reported history of colorectal polyps
0.75	0.43–1.29	
1.03	0.57–1.85	
1.00		
0.83	0.55–1.27	
0.93	0.59–1.49	
1.00		
1.06	0.56–2.02	
0.95	0.46–1.94	

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
Men and women		
Cope et al. 1991 United Kingdom, clinic-based study of routine colonoscopies in men and women (66 cases of adenomatous polyps and 86 noncases determined by colonoscopy)	Colonic adenomatous polyps	Never smoked (NR) Current nondrinking smokers (NR) Current drinking smokers (NR)
Olsen and Kronborg 1993 Case-control study within a randomized trial, Denmark, 1986–1990 (171 men and women with colorectal adenomas; 362 controls, with smoking information available for all cases and 266 controls)	Colorectal adenomas	Never smoked (34/34) Current smokers (78/136) Former smokers (59/96)
Jacobson et al. 1994 Case-control study, United States, 1986–1988, New York City (186 recurrent polyp cases [130 men, 56 women] and 330 controls [187 men, 143 women] who had a history of polypectomy but a normal follow-up colonoscopy, with smoking information for all cases and 186 controls)	Recurrent colorectal adenomatous polyps	Men Never smoked (38/76) Current smokers (6/12) Former smokers (12/12) (<5 years) Former smokers (74/86) (5 years) Women Never smoked (14/53) Current smokers (16/21) Former smokers (9/14) (<5 years) Former smokers (17/55) (5 years)
Martínez et al. 1995 Case-control study of men and women in a Houston, Texas, clinic, United States, 1991–1993 (157 cases with colorectal adenomatous polyps and 480 controls without polyps determined by flexible sigmoidoscopy or colonoscopy; included white, black, and Hispanic persons)	Adenomatous polyps	Never smoked (58/257) Current smokers (28/56) Former smokers (71/167)

Risk estimate	95% CI	Comments
1.00		Adjusted for age and gender
2.12	0.54–8.29	
12.70	3.02–53.42	
1.0		Adjusted for age, gender, and dietary fiber; excluded those with a known colorectal cancer or adenoma
2.0	1.1–3.5	
2.1	1.1–3.9	
		Estimates were adjusted for age; p for trend = 0.2 for men and 0.01 for women
1.0		
1.0	0.4–3.0	
2.1	0.8–5.0	
1.7	1.0–2.8	
1.0	1.0	
2.9	1.2–7.0	
2.5	0.9–7.0	
1.1	0.5–2.7	
1.00		Adjusted for age, gender, race, dietary fiber, vitamin C and alcohol intake, BMI, family history of colorectal cancer, physical activity, and use of nonsteroidal anti-inflammatory drugs; excluded those with a history of colorectal polyps, familial polyposis coli, Gardner's syndrome, hereditary nonpolyposis colorectal cancer, any cancer (except nonmelanoma skin), ulcerative colitis, irritable bowel disease, human immunodefiency virus infection, and chronic renal failure
2.29	1.28–4.07	
1.60	1.03–2.49	

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
Men and women		
Longnecker et al. 1996 Case-control study, United States, 1991–1993, southern California HMO-based study of men and women aged 50–74 years undergoing sigmoid-oscopy in southern California (488 cases with colorectal adenomatous polyps and 488 controls without polyps, determined by sigmoidoscopy, including white, black, Asian, and Hispanic persons)	Colorectal adenomatous polyps	Never smoked (168/209) Current smokers (97/55) Former smokers (223/224)

Baron et al. 1998
 	
United States, 1984–1988, men and women participating in a multi-centered clinical trial of antioxidant vitamins to prevent colorectal adenoma recurrence (260 recurrent adenomas and 449 with no recurrence)
	Adenoma recurrence	In right colorectum:
		  Never smoked (NR)
		  Current smokers (NR)
		  Former smokers (NR)
		In left colorectum:
		  Never smoked (NR)
		  Current smokers (NR)
		  Former smokers (NR)

Terry and Neugut 1998
 	
Case-control study, United States (New York City), 1986–1988, 269 incident cases of colorectal adenoma; 508 hospital controls with normal colonoscopy, with smoking informa-tion available for 267 of the cases and 503 of the controls
	Colorectal adenomas	Newly diagnosed adenoma
		  Never smoked (97/215)
		  Ever smoked (170/288)

Risk estimate	95% CI	Comments
1.00		Adjusted for alcohol; race; BMI; vigorous leisure time
2.43	1.56–3.79	activity; and intake of energy, saturated fat, fruits,
1.22	0.90–1.66	and vegetables; excluded persons with significant
		gastrointestinal symptoms
		Adjusted for age, gender, clinical center, dietary fat,
1.00		dietary fiber, energy intake, and colonoscopy interval;
0.89	0.51–1.53	excluded those with a history of familial polyposis,
0.95	0.62–1.44	invasive colorectal cancer, or malabsorption syndromes
1.00		
1.44	0.84–2.49	
1.36	0.88–2.09	
		All estimates were adjusted for gender, age, and Quetelet
1.0		index (weight [kg]/height^2 [m^2]); excluded those with a
1.34	0.97–1.84	history of colorectal cancer

Table 2.26   Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
Men and women		
Potter et al. 1999 Case-control study, United States (Minneapolis, Minnesota), 1991–1994, clinic-based study of men and women aged 30–74 years undergoing colonoscopies (527 with adenomatous polyps and 633 controls without polyps, determined by colonoscopy)	Adenomatous polyps	Never smoked (NR) Current smokers (NR) Former smokers (NR)

Almendingen et al. 2000
 	
Case-control study, Norway (87 adenoma cases and 35 hospital and 35 "healthy" controls without polyps [determined by colonoscopy] aged 50–76 years)
	Colorectal adenomas	Compared with hospital controls
		  Never smoked (20/15)
		  Current smokers (38/5)
		  Former smokers (29/15)
		
		Compared with "healthy" controls
		  Never smoked (20/15)
		  Current smokers (38/7)
		  Former smokers (29/13)

Risk estimate	95% CI	Comments
1.0		Adjusted for age, gender, nonsteroidal anti-inflammatory
2.0	1.4– 2.9	drug use, and hormonal replacement therapy; excluded
1.4	1.1– 1.9	those with genetic syndromes associated with a predisposition to colonic neoplasia, a personal history of ulcerative colitis, Crohn's disease, polyps, and cancer (except nonmelanoma skin)
1.0		Adjusted for BMI; familial colonic cancer; and dietary
3.6	1.1–12.6	intake of energy, fat, fiber, vitamin C, cruciferous
1.4	0.5– 3.9	vegetables, coffee, and alcohol; excluded those with colorectal cancer, irritable bowel disease, renal or heart failure, polyposis coli, or the inability to undergo a
1.0		colonoscopy or dietary assessment
3.8	0.9–14.4	
1.4	0.4– 4.4	

Table 2.27 Cohort studies on the association between current smoking and the risk of colorectal cancer incidence or mortality*

Study Location/population	Type	Smoking status (deaths or cases)
Men		
Tverdal et al. 1993 Norway, 1973–1978 (44,290 men aged 35–49 years; 47 colon cancer deaths; 43 rectal cancer deaths)	Colon (Mortality) Rectal (Mortality)	Never smoked (9) Current smokers (25) Former smokers (13) Never smoked (7) Current smokers (24) Former smokers (12)
Doll et al. 1994 United Kingdom, 1951–1991, British physicians (34,439 men aged 35 years; 437 colon cancer deaths; 168 rectal cancer deaths)	Colon (Mortality) Rectal (Mortality)	Never smoked (NR) Current smokers (NR) Former smokers (NR) Never smoked (NR) Current smokers (NR) Former smokers (NR)
Heineman et al. 1995 United States, 1954–1980, U.S. veterans (248,046 men aged 31–84 years; 2,859 colon cancer deaths; 813 rectal cancer deaths)	Colon (Mortality) Rectal (Mortality)	Never smoked (782) Current smokers (1,213) Former smokers (864) Never smoked (201) Current smokers (383) Former smokers (229)
Chyou et al. 1996 United States, 1965–1995, Honolulu Heart Program (7,945 men aged 45 years; 330 colon cancer cases; 123 rectal cancer cases)	Colon (Incidence) Rectal (Incidence)	Never smoked (88) Current smokers (150) Former smokers (92) Never smoked (28) Current smokers (65) Former smokers (30)
Engeland et al. 1996 Norway, 1964–1993, Norwegian portion of Migrant Study (11,863 men aged 39–73 years; 230 colon cancer cases; 139 rectal cancer cases)	Colon (Incidence) Rectal (Incidence)	Never smoked (41) Current smokers (150) Former smokers (39) Never smoked (20) Current smokers (103) Former smokers (16)

*Includes only studies that specified lifetime nonsmokers and distinguished current from former smoking.
†RR = Relative risk.
‡CI = Confidence interval.
§NR = Data were not reported.

RR[†]	95% CI[‡]	Comments
1.00		Adjusted for age and area of the country, computed from
1.50	NR[§]	Tverdal et al. 1993, Table 1; 1,009 men either reported
1.21	NR	other tobacco use combinations or did not provide
		smoking information and were excluded from the
1.00		analysis
1.82	NR	
1.42	NR	
1.00		Adjusted for age, computed from Doll et al. 1994, Table
1.28	NR	III; analysis did not include men who used tobacco
1.39	NR	products other than cigarettes
1.00		
2.30	NR	
1.50	NR	
1.0		Adjusted for age, year of questionnaire, calendar time,
1.2	1.1–1.4	socioeconomic status, and sedentary job; 953 colon cancer
1.3	1.2–1.4	deaths and 287 rectal cancer deaths were among men
		who either used tobacco products other than cigarettes or
1.0		did not provide smoking information and were excluded
1.4	1.1–1.8	from the analysis
1.4	1.1–1.7	
1.00		Adjusted for age; excluded prevalent colon cancer
1.42	1.09–1.85	
1.27	0.95–1.70	
1.00		
1.95	1.25–3.04	
1.31	0.78–2.20	
1.0		Adjusted for age; excluded prevalent cancer
1.2	0.8–1.6	
1.0	0.6–1.5	
1.0		
1.6	1.0–2.6	
0.8	0.4–1.6	

Table 2.27 Continued

Study Location/population	Type	Smoking status (deaths or cases)
Men		
Nyrén et al. 1996 Sweden, 1971–1991, Swedish construction workers (134,985 men; 713 colon cancer cases; 505 rectal cancer cases)	Colon (Incidence) Rectal (Incidence)	Never smoked (219) Current smokers (314) Former smokers (180) Never smoked (135) Current smokers (235) Former smokers (135)
Hsing et al. 1998 United States, 1966–1986, Lutheran Brotherhood Insurance (17,633 men aged 35 years; 145 colorectal cancer deaths)	Colorectal (Mortality)	Never smoked (26) Current smokers (32) Former smokers (44)
Chao et al. 2000 United States, 1982–1996, Cancer Prevention Study II (312,332 men aged 30 years; 2,156 colorectal cancer deaths)	Colorectal (Mortality)	Never smoked (683) Current smokers (558) Former smokers (915)
Stürmer et al. 2000 United States, 1982–1995, Physicians Health Study I (22,011 men aged 40–84 years; 351 confirmed self-reported colorectal cancer cases)	Colorectal (Incidence)	Never smoked (126) Current smokers (48) Former smokers (177)
Women		
Chute et al. 1991 United States, 1976–1984, Nurses Health Study (118,404 women aged 30–55 years; 191 colon cancer cases; 49 rectal cancer cases)	Colon (Incidence) Rectal (Incidence)	Never smoked (78) Current smokers (55) Former smokers (58) Never smoked (17) Current smokers (13) Former smokers (19)
Tverdal et al. 1993 Norway, 1973–1978 (24,535 women aged 35–49 years; 30 colon cancer deaths; 16 rectal cancer deaths)	Colon (Mortality) Rectal (Mortality)	Never smoked (17) Current smokers (10) Former smokers (3) Never smoked (12) Current smokers (4) Former smokers (0)

BMI = Body mass index.

RR	95% CI	Comments
1.00		Adjusted for age; excluded prevalent colon cancer and incomplete vital status data
0.98	0.82–1.17	
1.02	0.84–1.24	
1.00		
1.16	0.94–1.44	
1.22	0.97–1.54	
1.0		Adjusted for age, alcohol use, and residence (urban/ rural); 43 colorectal cancer deaths among men who were occasional smokers, used other tobacco, or did not provide smoking information were excluded from the analysis
1.0	0.6–1.7	
1.1	0.7–1.8	
1.00		Adjusted for age; race; BMI ; education; family history of colorectal cancer; amount/type of exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.32	1.16–1.49	
1.15	1.04–1.27	
1.00		Adjusted for age, BMI, alcohol use, vigorous exercise, aspirin and -carotene intake, use of multivitamins, and consumption of vegetables and fruits; excluded those with a history of myocardial infarction, stroke, cancer, liver or renal disease, gout, peptic ulcer, or contraindications to aspirin
1.81	1.28–2.55	
1.49	1.17–1.89	
1.0		Adjusted for age; excluded prevalent cancer
1.0	0.7–1.4	
1.2	0.9–1.7	
1.0		
1.1	0.5–1.3	
1.9	1.0–3.6	
1.00		Adjusted for age and area of country, computed from Tverdal et al. 1993, Table 5; 133 women either reported tobacco use other than cigarettes or did not provide smoking information and were excluded from the analysis
1.09	NR	
0.91	NR	
1.00		
0.57	NR	

Table 2.27 Continued

Study Location/population	Type	Smoking status (deaths or cases)
Women		
Engeland et al. 1996 Norway, 1964–1993, Norwegian portion of Migrant Study (14,269 women aged 34–73 years; 300 colon cancer cases; 141 rectal cancer cases)	Colon (Incidence) Rectal (Incidence)	Never smoked (211) Current smokers (63) Former smokers (26) Never smoked (104) Current smokers (24) Former smokers (13)
Chao et al. 2000 United States, 1982–1996, Cancer Prevention Study II (469,019 women aged 30 years; 2,276 colorectal cancer deaths)	Colorectal (Mortality)	Never smoked (1,355) Current smokers (476) Former smokers (445)
Men and women		
Klatsky et al. 1988 United States, 1978–1984, Northern California Kaiser Permanente health maintenance organization cohort (106,203 men and women, 203 colon cancers and 66 rectal cancers)	Colon (Incidence) Rectal (Incidence)	Never smoked (NR) <1 pack/day (NR) 1 pack/day (NR) Former smokers (NR) Never smoked (NR) <1 pack/day (NR) 1 pack/day (NR) Former smokers (NR)
Knekt et al. 1998 Finland, 1966–1972 (56,973 men and women aged 15 years, 241 colon cancers and 216 rectal cancers)	Colon (Incidence) Rectal (Incidence)	Never smoked (144) <15 cigarettes/day (30) 15 cigarettes/day (27) Former smokers (34) Never smoked (120) <15 cigarettes/day (32) 15 cigarettes/day (22) Former smokers (33)

RR	95% CI	Comments
1.0		Adjusted for age; excluded prevalent cancer
1.1	0.8–1.4	
1.3	0.9–2.0	
1.0		
0.8	0.5–1.3	
1.3	0.8–2.4	
1.00		Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; estrogen replacement therapy; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer and incomplete data
1.41	1.26–1.58	
1.22	1.09–1.37	
1.00		Adjusted for age, gender, race, BMI, coffee and alcohol consumption, total serum cholesterol, and education; estimates for current smoking status were available only for packs per day
0.76	0.46–1.26	
1.35	0.78–2.35	
1.03	0.74–1.4	
1.00		
1.05	0.49–2.28	
1.01	0.37–2.79	
1.28	0.71–2.28	
1.00		Adjusted for age, gender, BMI, occupation, geographic area, type of population, and marital status; estimates for current smoking status were available only for cigarettes per day; excluded prevalent cancer; risk estimates for cigar and/or pipe smokers were not presented
1.11	0.72–1.70	
1.37	0.78–2.08	
1.19	0.76–1.85	
1.00		
1.11	0.72–1.70	
0.85	0.51–1.41	
0.87	0.56–1.36	

Table 2.27 Continued

Study Location/population	Type	Smoking status (deaths or cases)
Men and women		
Terry et al. 2001 Sweden, 1961–1977 (17,118 same sex twins; 318 cases of colon cancer; 180 cases of rectal cancer)	Colon (Incidence)	Never smoked (196) 1–10 cigarettes/day (42) 11–20 cigarettes/day (15) 21 cigarettes/day (2) Former smokers (49)
	Rectal (Incidence)	Never smoked (106) 1–10 cigarettes/day (26) 11–20 cigarettes/day (14) 21 cigarettes/day (4) Former smokers (30)

RR	95% CI	Comments
1.0		Adjusted for age, gender, BMI, and physical activity;
1.0	0.7–1.5	excluded those who died prior to assessment and those
1.0	0.6–1.8	with prevalent cancer at baseline; estimates for current
1.7	0.4–7.0	smoking were available only for cigarettes per day; risk
1.1	0.8–1.5	estimates for cigar and pipe smokers were not presented
1.0		
0.9	0.6–1.5	
1.2	0.6–2.4	
5.3	1.9–15.0	
1.0	0.6–1.6	

Table 2.28 Case-control studies on the association between smoking status and the risk of colorectal cancer incidence

Study Location/population	Type	Smoking status (cases/controls)
Men		
Kune et al. 1992 Australia, 1980–1981 (202 colon cancer cases; 186 rectal cancer cases; 398 population controls)	Colon	Never smoked (60/110) Current smokers (46/121) Former smokers (96/167)
	Rectal	Never smoked (47/110) Current smokers (55/121) Former smokers (84/167)
D'Avanzo et al. 1995 Italy, 1985–1991 (875 colorectal cancer cases; 1,863 hospital controls)	Colorectal	Never smoked (269/457) Current smokers (316/837) Former smokers (290/569)
Le Marchand et al. 1997 United States, 1987–1991, Hawaii (multiethnic: Japanese, Caucasian, Filipino, Hawaiian, Chinese; 197 right colon cancer cases/ 197 population controls; 270 left colon cancer cases/270 controls; 221 rectal cancer cases/221 controls)	Right colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Left colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Rectal	Never smoked (NR) Current smokers (NR) Former smokers (NR)
Women		
Kune et al. 1992 Australia, 1980–1981 (190 colon cancer cases; 137 rectal cancer cases; 329 community controls)	Colon	Never smoked (129/197) Current smokers (32/65) Former smokers (29/67)
	Rectal	Never smoked (91/197) Current smokers (26/65) Former smokers (20/67)
D'Avanzo et al. 1995 Italy, 1985–1991 (709 colorectal cancer cases; 1,016 hospital controls)	Colorectal	Never smoked (558/740) Current smokers (101/205) Former smokers (50/71)

*OR = Odds ratio.
†CI = Confidence interval.
‡NR = Data were not reported.
§Based on a diet rich in cereals and poor in vegetables.
 BMI = Body mass index.

OR*	95% CI†	Comments
1.00		Adjusted for age
0.72	NR‡	
1.03	NR	
1.00		
1.03	NR	
1.23	NR	
1.0		Adjusted for age, education, area of residence, family
0.6	0.5–0.8	history of intestinal cancer, food consumption score§ and
0.8	0.6–1.0	intake of fat, calories, meat, and alcohol
1.0		Adjusted for age; family history of colorectal cancer;
0.7	0.3–1.6	physical activity; BMI ; and intake of eggs, fiber, calcium,
1.0	0.5–1.9	calories, and alcohol
1.0		
0.9	0.4–1.9	
1.4	0.9–2.4	
1.0		
0.8	0.4–1.8	
1.4	0.8–2.3	
1.00		Adjusted for age
0.75	NR	
0.64	NR	
1.00		
0.85	NR	
0.64	NR	
1.0		Adjusted for age, education, area of residence, family
0.7	0.5–0.9	history of intestinal cancer, food consumption score and
1.3	0.8–1.9	intake of fat, calories, meat, and alcohol

Table 2.28 Continued

Study Location/population	Type	Smoking status (cases/controls)
Women		
Newcomb et al. 1995

United States, 1990–1991 (526 colon cancer cases; 239 rectal cancer cases; 2,303 population controls) | Colon | Never smoked (276/1,243)
Current smokers (113/517)
Former smokers (137/543) |
| | Rectal | Never smoked (115/1,243)
Current smokers (65/517)
Former smokers (59/543) |
| Le Marchand et al. 1997

United States, 1987–1991, Hawaii (multiethnic: Japanese, Caucasian, Filipino, Hawaiian, Chinese; 164 right colon cancer cases/164 population controls; 194 left colon cancer cases/194 controls; 129 rectal cancer cases/129 controls) | Right colon | Never smoked (NR)
Current smokers (NR)
Former smokers (NR) |
| | Left colon | Never smoked (NR)
Current smokers (NR)
Former smokers (NR) |
| | Rectal | Never smoked (NR)
Current smokers (NR)
Former smokers (NR) |
| **Men and women** | | |
| Baron et al. 1994

Stockholm, 1986–1988 (334 colon cancer cases; 210 rectal cancer cases; 496 population controls) | Colon | Never smoked (163/233)
Current smokers (78/125)
Former smokers (93/138) |
| | Rectal | Never smoked (101/233)
Current smokers (51/125)
Former smokers (58/138) |
| Slattery et al. 1997

United States, 1991–1994, English-speaking members of Kaiser Permanente (1,097 male cases and 892 female cases with first primary colon cancer; 2,410 population controls) | Colon | Men
  Never smoked (336/485)
  Ever smoked (761/805)
Women
  Never smoked (487/636)
  Ever smoked (405/484) |

OR	95% CI	Comments
1.00		Adjusted for age, BMI, alcohol intake, family history
1.33	1.01–1.75	of colon cancer, and sigmoidoscopy; excluded incomplete
1.24	0.96–1.59	data
1.00		
1.70	1.19–2.41	
1.25	0.88–1.77	
1.0		Adjusted for age; family history of colorectal cancer;
1.1	0.4–2.6	physical activity; BMI; and intake of alcohol, eggs, fiber,
2.4	1.0–5.6	calcium, and calories
1.0		
0.7	0.3–1.5	
1.1	0.6–2.0	
1.0		
1.3	0.5–3.7	
1.6	0.7–3.4	
1.00		Adjusted for age, gender, exercise, BMI, and fat and
0.91	0.63–1.31	fiber intake; excluded incomplete data
0.94	0.66–1.34	
1.00		
0.84	0.55–1.28	
0.88	0.58–1.32	
		Estimates were adjusted for age, BMI, long-term vigorous
1.0		activity, energy intake, dietary fiber, dietary calcium,
1.26	1.05–1.51	family history of colorectal cancer, and use of aspirin
		and/or nonsteroidal anti-inflammatory drugs
1.0		
1.08	0.90–1.30	

Table 2.29   Cohort studies on the association between the duration of current smoking and the risk of colorectal cancer incidence or mortality*

Study Location/population	Type	Duration (deaths or cases)
Men		

Giovannucci et al. 1994b
 	
United States, Health Professionals Follow-up Study data (47,935 men; 238 colorectal cancer cases)
	Colorectal (Incidence)	Never smoked (84)
		1–10 cigarettes/day
		  1–19 years (0)
		  20–29 years (9)
		  30–34 years (8)
		  35–39 years (14)
		  40–44 years (26)
		   45 years (43)
		  11 cigarettes/day
		  1–19 years (3)
		  20–29 years (5)
		  30–34 years (3)
		  35–39 years (10)
		  40–44 years (13)
		   45 years (20)

Nyrén et al. 1996 Swedish construction workers (134,985 men; 713 colon cancer cases; 505 rectal cancer cases)	Colon (Incidence)	Never smoked (219) 1–10 years (15) 11–20 years (34) 21–30 years (88) 31–40 years (119) 41 years (53)
	Rectal (Incidence)	Never smoked (135) 1–10 years (7) 11–20 years (26) 21–30 years (69) 31–40 years (94) 41 years (34)
Hsing et al. 1998 United States, Lutheran Brotherhood Insurance (17,633 men; 120 colorectal cancer cases)	Colon (Mortality)	Never smoked (16) 1–19 years (1) 20–29 years (11) 30 years (17)

*Includes only studies that specified lifetime nonsmokers and distinguished current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]NR = Data were not reported.
 BMI = Body mass index.

RR[†]	95% CI[‡]	Comments
1.00		Adjusted for age; BMI ; intake of alcohol, fat, fiber, and folate; and family history of colorectal cancer; excluded prevalent cancer, ulcerative colitis, familial polyposis syndrome, and incomplete data
NR[§]	NR	
1.26	0.60–2.63	
1.28	0.60–2.74	
1.18	0.66–2.13	
1.83	1.15–2.92	
1.60	1.06–2.04	
1.87	0.55–6.31	
0.83	0.32–2.17	
0.77	0.23–2.57	
1.15	0.58–2.31	
1.74	0.92–3.28	
2.55	1.49–4.38	
1.00		Adjusted for age; excluded prevalent colon cancer and incomplete vital status data
0.75	0.43–1.30	
0.74	0.51–1.08	
1.03	0.80–1.33	
1.05	0.83–1.33	
0.99	0.72–1.35	
1.00		
0.76	0.35–1.66	
1.01	0.66–1.55	
1.17	0.87–1.57	
1.26	0.96–1.66	
1.08	0.73–1.60	
1.0		Adjusted for age, alcohol use, and area of residence (urban/rural)
1.3	0.2–9.7	
2.4	1.0–5.3	
1.2	0.6–2.4	
	p value for trend = 0.79	

Table 2.29 Continued

Study Location/population	Type	Duration (deaths or cases)
Men		
Chao et al. 2000 United States, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)	Colorectal (Mortality)	Never smoked (683) <20 years (12) 20–29 years (46) 30–39 years (177) 40 years (323)
Women		
Giovannucci et al. 1994a United States, Nurses Health Study (118,334 women; 586 colorectal cancer cases)	Colorectal (Incidence)	Never smoked (263) 1–10 cigarettes/day 1–19 years (10) 20–29 years (41) 30–34 years (33) 35–39 years (37) 40–44 years (34) 45 years (11) 11 cigarettes/day 1–19 years (2) 20–29 years (32) 30–34 years (26) 35–39 years (49) 40–44 years (33) 45 years (15)
Chao et al. 2000 United States, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer cases)	Colorectal (Mortality)	Never smoked (1,355) <20 years (28) 20–29 years (81) 30–39 years (163) 40 years (204)

RR	95% CI	Comments
1.00		Adjusted for age; race; BMI; education; family history of
1.24	0.68–2.24	colorectal cancer; exercise; aspirin and multivitamin use;
1.33	0.96–1.84	and intake of alcohol, vegetables, high-fiber grain foods,
1.34	1.11–1.62	and fatty meats; excluded prevalent cancer, pipe/cigar
1.31	1.13–1.51	smoking, and incomplete data
	p value for trend = 0.17	

RR	95% CI	Comments
1.00		Excluded prevalent cancer, ulcerative colitis, familial
		polyposis syndrome, and incomplete data; adjusted for
0.79	0.40–1.40	age and BMI
0.98	0.69–1.40	
0.76	0.52–1.10	
0.81	0.57–1.16	
1.03	0.70–1.50	
1.05	0.56–1.99	
0.37	0.11–1.32	
1.06	0.71–1.57	
0.82	0.54–1.24	
1.47	1.07–2.01	
1.63	1.14–2.33	
2.00	1.14–3.49	

RR	95% CI	Comments
1.00		
1.07	0.73–1.58	Adjusted for age; race; BMI; education; family history
1.33	1.05–1.69	of colorectal cancer; exercise; aspirin, multivitamin, and
1.41	1.19–1.68	estrogen replacement therapy use; and intake of alcohol,
1.51	1.29–1.76	vegetables, high-fiber grain foods, and fatty meats;
	p value for trend = 0.17	excluded prevalent cancer and incomplete data

Table 2.30 Cohort studies on the association between the age at initiation of current smoking and the risk of colorectal cancer mortality*

Study Location/population	Type	Smoking initiation (deaths)
Men		

Heineman et al. 1995
 	
United States, U.S. veterans (248,046 men; 3,812 colon cancer deaths; 1,100 rectal cancer deaths)
	Colon	Never smoked (782)
		Started at
		  25 years (219)
		  20–24 years (382)
		  15–19 years (503)
		  <15 years (99)

	Rectal	Never smoked (201)
		Started at
		  25 years (61)
		  20–24 years (108)
		  15–19 years (183)
		  <15 years (30)

Chao et al. 2000
 	
United States, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)
	Colorectal	Never smoked (683)
		Started at
		  20 years (143)
		  16–19 years (258)
		  <16 years (146)

Women		

Chao et al. 2000
 	
United States, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer deaths)
	Colorectal	Never smoked (1,355)
		Started at
		  20 years (225)
		  16–19 years (193)
		  <16 years (54)

*Includes only studies that specified lifetime nonsmokers and distinguished current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]BMI = Body mass index.

RR[†]	95% CI[‡]	Comments
1.0		Adjusted for age, year of questionnaire, calendar time, socioeconomic status, and having a sedentary job
1.1	1.0–1.3	
1.3	1.1–1.5	
1.2	1.1–1.4	
1.4	1.2–1.8	
	p value for trend <0.001	
1.0		
1.2	0.9–1.6	
1.4	1.1–1.7	
1.6	1.3–1.9	
1.5	1.0–2.2	
	p value for trend = 0.006	
1.00		Adjusted for age; race; BMI[§]; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.21	1.01–1.47	
1.36	1.16–1.58	
1.36	1.12–1.64	
	p value for trend = 0.55	
1.00		Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; estrogen replacement therapy; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.36	1.18–1.57	
1.43	1.21–1.67	
1.74	1.31–2.29	
	p value for trend = 0.013	

Table 2.31   Cohort studies on the association between the number of years since or age at smoking cessation and the risk of colorectal cancer incidence or mortality*

Study Location/population	Type	Years since/age at cessation (deaths or cases)
Men		

Wu et al. 1987
 	
United States, 1981–1985 (11,644 retired men and women; 58 male colorectal cancer cases)
	Colorectal (Incidence)	Current smokers (NR[§])
		Years since cessation
		  20 years (NR)
		  >20 years (NR)
		Never smoked (NR)

Chao et al. 2000
 	
United States, 1982–1996, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)
	Colorectal (Mortality)	Current smokers (558)
		Years since cessation
		  <11 (317)
		  11–19 (293)
		  20 (304)
		Never smoked (683)
		
		Current smokers (558)
		Age at cessation
		  61 years (104)
		  51–60 years (235)
		  41–50 years (280)
		  31–40 years (205)
		  <31 years (91)
		Never smoked (683)

Women		

Wu et al. 1987
 	
United States, 1981–1985 (11,644 retired men and women; 68 female colorectal cancer cases)
	Colorectal (Incidence)	Current smokers (NR)
		Years since cessation
		  20 (NR)
		  >20 (NR)
		Never smoked (NR)

*Includes only studies that specified lifetime nonsmokers and distinguished current from former smoking.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]NR = Data were not reported.
 BMI = Body mass index.

RR[†]	95% CI[‡]	Comments
1.80	0.6–5.2	Adjusted for age; excluded those with pre-existing colorectal cancer
2.63	1.3–5.3	
1.71	0.8–3.6	
1.00		
1.32	1.16–1.49	Adjusted for age; race; BMI ; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer and incomplete data
1.28	1.11–1.47	
1.24	1.08–1.43	
0.99	0.86–1.13	
1.00		
	p value for trend = 0.001	
1.32	1.16–1.49	
1.21	0.98–1.50	
1.29	1.11–1.51	
1.19	1.03–1.37	
1.08	0.92–1.26	
0.91	0.73–1.13	
1.00		
	p value for trend = 0.001	
1.35	0.7–1.0	Adjusted for age; excluded those with pre-existing colorectal cancer
0.71	0.3–1.5	
1.61	0.8–3.0	
1.00		

Table 2.31   Continued

Study Location/population	Type	Years since/age at cessation (deaths or cases)
	Women	

Chao et al. 2000
 	
United States, 1982–1996, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer deaths)
	Colorectal (Mortality)	Current smokers (476)
		Years since cessation
		 <11 (317)
		 11–19 (293)
		  20 (304)
		Never smoked (1,355)
		
		Current smokers (476)
		Age at cessation
		  61 years (67)
		 51–60 years (122)
		 41–50 years (93)
		 31–40 years (93)
		 <31 years (70)
		Never smoked (1,355)

RR	95% CI	Comments
1.41	1.26–1.58	Adjusted for age; race; BMI; education; family history of
		colorectal cancer; exercise; aspirin and multivitamin use;
1.39	1.18–1.63	estrogen replacement therapy; and intake of alcohol,
1.10	0.90–1.33	vegetables, high-fiber grain foods, and fatty meats;
1.16	0.98–1.37	excluded prevalent cancer, pipe/cigar smoking, and
1.00		incomplete data
	p value for trend = 0.038	
1.41	1.26–1.58	
1.50	1.16–1.93	
1.54	1.28–1.87	
1.03	0.83–1.27	
1.15	0.93–1.43	
0.98	0.77–1.25	
1.00		
	p value for trend = 0.038	

Prostate Cancer

Prostate cancer is a leading cause of morbidity and mortality among men in the United States. It is more common in African American men than in white men, and the highest recorded rates in the world are among black men in the United States. In 2003, an estimated 220,900 new cases of prostate cancer were diagnosed, and an estimated 28,900 deaths were expected to occur (ACS 2003). Prostate cancer is the leading cause of cancer incidence among men (ACS 2003).

The risk of prostate cancer increases with age. African American men are at an increased risk, whereas Asian men are at a lower risk than white men. Lower vitamin A consumption and higher animal fat intake may increase the risk (Gann et al. 1994; Le Marchand et al. 1994), while a higher intake of lycopene may decrease the risk (Giovannucci et al. 1995; Giovannucci 1999). Having a vasectomy may be associated with an increased risk of prostate cancer 20 or more years after the procedure (Ross and Schottenfeld 1996). Endocrine factors, including testosterone and insulin-like growth factors, have been implicated in the development of this malignancy (Ross and Schottenfeld 1996; Giovannucci et al. 1997; Chan et al. 1998). Variations in the length of the androgen receptor gene *CAG repeat* may explain part of the excess risk in African American men (Platz et al. 2000).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not addressed the relationship between smoking and prostate cancer.

Biologic Basis

During the last several decades there has been an explosion of epidemiologic studies addressing potential risk factors for this common malignancy, including cigarette smoking. Pathogenic mechanisms that may underlie the relationship between smoking and prostate cancer remain unclear. Carcinogens from tobacco can enter and concentrate in prostate cells (Smith and Hagopian 1981). Compared with men who do not smoke, men who smoke cigarettes have higher circulating levels of hormones formed in the adrenal gland (dehydroepiandrosterone, dehydroepiandrosterone sulfate, cortisol, and androstenedione) as well as testosterone, dihydrotestosterone, and sex hormone-binding globulin (Dai et al. 1988; Khaw et al. 1988; Field et al. 1994). This finding supports a potential mechanism for smoking because prospective epidemiologic studies have shown that testosterone is directly related to prostate cancer incidence and mortality (Nomura et al. 1988; Hsing and Comstock 1993; Gann et al. 1996).

Epidemiologic Evidence

The epidemiologic evidence relating smoking to the risk of prostate cancer has been mixed. Studies addressing disease incidence (which include case-control studies and several cohort studies) show an inconsistent increase in risk (Mishina et al. 1985; Honda et al. 1988; Hayes et al. 1994; van der Gulden et al. 1994), or no association between cigarette smoking and prostate cancer (Weir and Dunn 1970; Ross et al. 1987; Fincham et al. 1990; Talamini et al. 1992). Studies of mortality, largely limited to prospective cohort studies, show an increase in risk directly related to the number of cigarettes smoked. Investigators using different approaches to data analysis have attempted to determine whether this finding reflects a delayed diagnosis and treatment of smokers compared with nonsmokers, residual confounding factors, or a direct effect of tobacco smoke. Two studies found that smokers are more likely than nonsmokers to have their cancers diagnosed at a more advanced stage or histologic grade (Hussain et al. 1992; Daniell 1995).

Hsing and colleagues (1991) analyzed data from the follow-up of nearly 250,000 U.S. veterans and observed increased mortality rates for those who were current smokers at baseline. During 26 years of follow-up, approximately 4,600 men died of prostate cancer. Current smokers had a RR of 1.18 (95 percent CI, 1.09–1.28) compared with men who had never smoked, and the risk increased with the number of cigarettes smoked. Men smoking 40 or more cigarettes per day had a RR of 1.51 (95 percent CI, 1.20–1.90) compared with those who had never smoked. In this cohort, risks were higher during the first eight and one-half years of follow-up than during the remainder of the follow-up period, suggesting that recent smoking influenced the risk of prostate cancer mortality.

In an analysis of data from a follow-up of 348,874 men screened for the Multiple Risk Factor Intervention Trial, Coughlin and colleagues (1996) observed similar results. Compared with those who had never smoked, current smokers had a RR of 1.31 (95 percent CI, 1.13–1.52) for prostate cancer mortality. The risk increased with the number of cigarettes smoked; men smoking more than 25 cigarettes per day had a RR of 1.45 (95 percent CI, 1.19–1.97) compared with those who had never smoked.

The Lutheran Brotherhood Cohort Study also provides data on the association between smoking and prostate cancer. Hsing and colleagues (1990b) followed 17,633 white males for 20 years and documented 149 fatal cases of prostate cancer. The RR of prostate cancer mortality was significantly elevated for current smokers. Compared with men who had never smoked, smokers had a RR of 1.8 (95 percent CI, 1.1–2.9). Data from CPS-II were based on 1,748 deaths during nine years of follow-up of 450,279 men (Rodriguez et al. 1997). Current cigarette smoking was related to prostate cancer mortality in this cohort (RR = 1.34 [95 percent CI, 1.16–1.56]), but trends in risk were not observed with the number of cigarettes smoked per day or with the duration of smoking. Among 43,432 men in a prepaid health plan in northern California, Hiatt and colleagues (1994) observed similar results based on 238 deaths from prostate cancer. Men who smoked one or more packs of cigarettes per day had an adjusted RR that was 1.9 (95 percent CI, 1.2–3.1) compared with those who had never smoked.

The Health Professionals Follow-Up Study examined both incidence and mortality in an analysis of the association between smoking and prostate cancer, offering the possibility of considering issues related to etiology, delay in diagnosis, and mortality (Giovannucci et al. 1999). Lifetime cumulative smoking was unrelated to total prostate cancer incidence. However, men who had quit in the past 10 years were at an increased risk of diagnosis with distant metastatic prostate cancer (RR = 1.56 [95 percent CI, 0.98–2.48]) and fatal prostate cancer (RR = 1.73 [95 percent CI, 1.00–3.01]). Men who currently smoked cigarettes had an elevated risk of prostate cancer mortality; however, this risk was not statistically significant (RR = 1.58 [95 percent CI, 0.81–3.10]). Examining pack-years of cigarettes smoked in the preceding 10 years revealed a significant dose-response relationship with metastatic and fatal prostate cancer (p trend = 0.02). Men who smoked 15 or more pack-years in the preceding 10 years were at a higher risk of distant metastatic prostate cancer (RR = 1.81 [95 percent CI, 1.05–3.11]), and fatal prostate cancer (RR = 2.06 [95 percent CI, 1.08–3.90]) compared with nonsmokers. Within 10 years after smoking cessation, the excess risk was eliminated. In this cohort, the investigators also examined the relationship between smoking and survival after diagnosis. Men who smoked cigarettes had a lower survival rate than nonsmokers.

Several cohort studies do not show a significant increase in risk among cigarette smokers (Table 2.32). The British physicians cohort study found no clear association between smoking and prostate cancer mortality in 1951, 1957, 1966, 1972, 1978, and 1990. The heaviest smokers (smoking 25 cigarettes per day) had a RR of 1.24 for fatal prostate cancer compared with men who had never smoked (Doll et al. 1994). A similar association was observed among men followed for 20 years in Sweden (Adami et al. 1996). Current smokers had a RR for prostate cancer mortality of 1.26 (95 percent CI, 1.06–1.50) compared with men who had never smoked. Other studies with a single assessment of smoking status and follow-up periods of up to several decades did not show a clear association between smoking and prostate cancer (Whittemore et al. 1985; Carstensen et al. 1987; Severson et al. 1989).

Other Data

Differential screening and delay in seeking medical care have been hypothesized as possible explanations for the increased risk of prostate cancer mortality among cigarette smokers. In the study by Giovannucci and colleagues (1999), however, screenings for the prostate-specific antigen (PSA) did not differ substantially between groups. Among men younger than 65 years of age, 53 percent of those who had never smoked, 53 percent of the smokers who had quit in the past 10 years, and 50 percent of the current smokers had had at least one PSA test by 1994. For men 65 years of age or older the screening rates were higher: 79 percent of men who had never smoked, 78 percent of those who had quit in the past 10 years, and 70 percent of current smokers.

Smoking may relate to prostate cancer mortality through its impact on tumor characteristics. Two studies have suggested that smokers are more likely to have stage D tumors and to have poorly differentiated tumors (Hussain et al. 1992; Daniell 1995).

Evidence Synthesis

The suggestion of elevated risks for mortality and not for incidence (measured either in case-control studies or in prospective cohort studies) supports an association between smoking and prostate cancer mortality. The association between smoking and prostate cancer mortality rates appears to be reduced within 10 years of smoking cessation. The basis for this association is unclear. It might reflect more advanced disease in smokers, but evidence is limited.

If smoking contributed to the etiology of prostate cancer, an association of smoking with incidence would be anticipated, along with an increase in disease-specific mortality, assuming that cancers in smokers and nonsmokers are similar in clinical features.

Conclusions

1. The evidence is suggestive of no causal relationship between smoking and risk for prostate cancer.

2. The evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers.

Implications

Smoking cessation may reduce prostate cancer mortality. Further research is needed to refine this temporal relationship and to quantify the benefits of smoking cessation after diagnosis with prostate cancer.

Acute Leukemia

In 2003, an estimated 21,900 deaths attributable to leukemia and an estimated 30,600 new cases, evenly divided between acute and chronic leukemia, were expected to occur, affecting 10 times more adults than children (ACS 2003). In adults, the most common types of leukemia are acute myeloid (approximately 10,500 cases were diagnosed in 2003) and chronic lymphocytic (approximately 7,300 cases were diagnosed in 2003). Rates of acute myeloid leukemia among adults are higher in males than in females. In children, the most common type of leukemia is acute lymphocytic, accounting for 2,200 cases in 2003 (ACS 2003).

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted that smoking has been implicated in the etiology of leukemia but the evidence was not consistent, and a conclusion was not reached regarding a possible causal relationship. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that acute myeloid leukemia has been consistently associated with cigarette smoking.

Biologic Basis

Several known leukemogenic substances are contained in cigarette smoke, including benzene and polonium-210 and lead-210 (which emit ionizing radiation). Both benzene and ionizing radiation (NRC 1990) are known causes of human leukemia that are associated with myeloid forms of leukemia and have little, if any, effect on the incidence of chronic lymphocytic leukemia. Radiation also causes acute lymphocytic leukemia in children (NRC 1990). Benzene, classified as a human carcinogen by IARC (1986), induces leukemia both in humans through occupational exposures and in laboratory animal models of this disease. Cigarette smoke is a major source of benzene exposure in the United States, accounting for roughly half of the exposures (Wallace 1996). Among smokers, 90 percent of benzene exposures come from smoking (Wallace 1996).

Data from human and experimental animal studies support the relationship between smoking and leukemia. Known leukemogens have been identified in cigarette smoke, and specific chromosomal abnormalities have been reported among smokers with leukemia. Sandler and colleagues (1993a) reported a higher frequency of smoking in persons with acute myeloid leukemia with specific chromosomal abnormalities (-7 or 7q-, -Y, +13) than in similar patients without these abnormalities. In acute lymphoblastic leukemia the changes found in chromosomes were t(9;22) and (q34;q11).

Epidemiologic Evidence

A possible association between smoking and risk for leukemia was proposed by Austin and Cole (1986), who recommended further analyses of existing data to clarify the relationship between the amount smoked and specific forms of leukemia. Since then, numerous such analyses and new studies have been reported. By 1993, Siegel had systematically reviewed the literature, which included 21 published studies (including several reports from the follow-up of the same population), and concluded, after applying Hill's causal criteria, that smoking was a cause of leukemia (Siegel 1993). Also in 1993, Brownson and colleagues reported a meta-analysis of published studies. They noted a significant association between current or former smoking and leukemia in general, and a stronger association between smoking and myeloid leukemia than with other subtypes (Brownson et al. 1993). Additional studies with similar findings have been published subsequently.

Both case-control and prospective cohort studies support the relationship between cigarette smoking and acute leukemia risk (Tables 2.33 and 2.34). The case-control approach affords the opportunity to quickly develop a series of cases for investigation and to uniformly classify the cases as to the type of leukemia. The results of case-control studies may be subject to information bias, arising from differential reporting of exposure by cases and controls. The prospective cohort studies do not have this limitation, but those using cause-specific mortality as the outcome measure may be affected by misclassification. In spite of these methodologic limitations, the evidence indicates an increased risk for leukemias in smokers. When risk estimates were provided by type, they tended to be higher for acute myeloid leukemia, usually called acute granulocytic leukemia or acute nonlymphocytic

leukemia. A recent, large case-control study that included 807 persons with acute leukemia and 1,593 age- and gender-matched controls showed that the risk was highest among current smokers, and it decreased with years since smoking cessation (Kane et al. 1999).

The association appears stronger among the prospective cohort studies, although not all have shown a positive relationship (Table 2.34). The 20-year follow-up of the British physicians cohort study did not find an association (Doll and Peto 1978); however, with the 40-year follow-up, Doll and colleagues (1994) reported a significant dose-response association among cigarette smokers for myeloid leukemias but not for nonmyeloid leukemias. Men smoking 25 or more cigarettes per day had more than twice the age-standardized mortality rates of those who had never smoked.

In CPS-I, women who smoked had a lower risk of death from leukemia during the follow-up period than those who did not smoke (RR = 0.77) (Garfinkel and Boffetta 1990). A similar gender variation was reported by Friedman (1993) in the follow-up of participants enrolled in the Kaiser Permanente Medical Center multiphasic health check-up study. Among men, the RR of leukemia for current smokers was 2.8 (95 percent CI, 1.2–6.4); the RR for former female smokers compared with women who had never smoked was 0.9 (95 percent CI, 0.4–1.7). By contrast, CPS-II documented a significant positive association between former smoking and leukemia risks in women (RR = 1.34, p <0.05), and a significant dose-response relationship with the amount smoked in both women and men (Garfinkel and Boffetta 1990). These results were based on 327 deaths attributable to leukemia among men and 235 deaths among women.

McLaughlin and colleagues (1989) evaluated smoking and the 26-year risk of mortality from leukemia (based on 1,258 leukemia deaths) among the cohort of U.S. military service veterans for whom there were numerous follow-up reports (Hammond 1966; Kahn 1966; Rogot and Murray 1980; Kinlen and Rogot 1988). In the 26-year follow-up data, these authors found a significant relationship between smoking and all leukemias (with a dose-response association between the number of cigarettes smoked per day and the risk of leukemia). The strongest relationship was for myeloid leukemia (365 cases). The RR for current smokers of more than 20 cigarettes per day compared with persons who had never smoked was 1.95 (p <0.01). In this cohort study, which did not update smoking status after the baseline assessment, risk was

stronger for the first 16 years of follow-up (RR = 1.6 [95 percent CI, 1.3–1.9]) than in the later 10 years (years 15 to 26 of the follow-up) (RR = 1.1 [95 percent CI, 0.9–1.3]) (McLaughlin et al. 1995a). In these data, the overall risk increased with the number of cigarettes smoked per day.

Cohort studies by Linet and colleagues (1991) and by Mills and colleagues (1990) also found a positive dose-response relationship between the number of cigarettes smoked and risk of leukemia. In the Lutheran Brotherhood Cohort Study, Linet and colleagues (1991) reported 74 deaths from leukemia (30 myeloid, 30 lymphatic, and 14 unspecified leukemia cases) among 17,633 white males followed for 20 years. The risk of total leukemia increased with the number of cigarettes smoked per day. Mills and colleagues (1990) followed 34,000 Seventh-Day Adventists for six years and identified 46 histologically-confirmed cases of leukemia. The group that had smoked the highest number of cigarettes in their lifetime had the highest risk of leukemia. These two cohorts were considerably smaller than the U.S. veterans and ACS studies. Other studies supporting a positive dose-response relationship include some of the case-control studies.

Among the prospective studies, the 20-year follow-up of a cohort of construction workers in Sweden shows no relationship between smoking and leukemia (Adami et al. 1998). In this study, 400 cases of leukemia (including 171 myeloid leukemias) were diagnosed during follow-up. Current smokers had a RR for total leukemia of 1.0 (95 percent CI, 0.8–1.2) compared with workers who had never smoked. Similar null results were also observed for myeloid leukemia (RR = 1.0 [95 percent CI, 0.7–1.4]), and there was no evidence of a trend in risks with the number of cigarettes smoked per day.

Evidence Synthesis

A relationship between former or current smoking and the risk of acute myeloid leukemia is supported by evidence of a consistent dose-response relationship with the number of cigarettes smoked per day. The association of the duration of smoking with the degree of risk and an increase in risk among former smokers suggests that the relationship is not dependent on current smoking, but perhaps on the cumulative effects of cigarette smoking. This relationship is observed across diverse populations. The RR for

persons who had ever smoked compared with non-smokers ranged from 1.3 to 1.5. Among those who smoked more than a pack of cigarettes per day the risk increased twofold. In 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and myeloid leukemia (IARC 2002).

Data from human and experimental animal studies provide evidence of a relationship between smoking and leukemia. Known leukemogens have been identified in cigarette smoke, and specific genetic alterations have been reported in smokers with leukemia. Benzene, a known leukemogen (Heath 1990), is found in cigarettes, and is the strongest known chemical leukemogen (Linet and Cartwright 1996). Polonium-210 and lead-210, alpha particle emitters in cigarette smoke, can reach the bone marrow where stem cells are located (Austin and Cole 1986; NRC 1988).

Korte and colleagues (2000) used risk assessment techniques for low-dose extrapolation to assess the proportion of leukemia and acute myeloid leukemia cases that could be attributed to the benzene in cigarettes. On the basis of linear potency models, these authors concluded that benzene in cigarette smoke contributed between 8 and 48 percent of smoking-induced leukemia deaths in total, and from 12 to 58 percent of smoking-induced acute myeloid leukemia deaths.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia.

2. The risk for acute myeloid leukemia increases with the number of cigarettes smoked and with duration of smoking.

Implications

The incidence of leukemia may remain elevated even after smoking cessation. Evidence is limited on the temporal pattern of change in risk after cessation, but a rapid decline in incidence has not been observed. Further research is needed to refine the patterns of risk after smoking cessation.

Table 2.32 Cohort studies on the association between smoking status and behavior and the risk of prostate cancer incidence or mortality

Study	Population/country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI†)		Number of cases
Whittemore et al. 1985	47,271 men Harvard/Penn alumni United States	1962–1966, 1978	243	NR‡	NR	NR
Carstensen et al. 1987	25,129 men Sweden	1963–1979	194	Former smokers Current smokers 1–7 g/day 8–15 g/day >15 g/day	1.0 1.1 0.8 0.9	44 26 31 15
Mills et al. 1989a	±14,000 men Seventh-Day Adventists United States	1977–1982	172	Former smokers Current smokers	1.24 (0.91–1.67) 0.48 (0.16–1.57)	79 3
Severson et al. 1989	8,006 men Japanese Hawaii	1965–1968, 1986	174	Cigarette smokers Former Current	 0.89 (0.61–1.29) 0.87 (0.61–1.23)	 46 65
Thompson et al. 1989	1,776 men Retirement community United States	1972–1974, 1987	54	Current cigarette smokers	1.3 (0.8–2.3)	NR
Ross et al. 1990	5,106 men Retirement community United States	1981–1988	138	Cigarette smokers Former Current	 0.8 0.9	 73 9

*Includes subsequent follow-up if applicable.
†CI = Confidence interval.
‡NR = Data were not reported.

Table 2.32 Continued

Study	Population/country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI)		Number of cases
Doll et al. 1994	34,439 male physicians United Kingdom	1951, 1957, 1966, 1972, 1978, 1990	568		annual mortality	
				Never smokers	68	NR
				Cigarette smokers		
				Former	58	NR
				Current	67	NR
				1–14 cigarettes/day	54	NR
				15–24 cigarettes/day	73	NR
				25 cigarettes/day	84	NR
				Other smokers		
				Former	54	NR
				Current	64	NR
Hiatt et al. 1994	43,432 men Prepaid health plan United States	1978–1985	224	Former smokers	1.1 (0.8–1.5)	94
				Current smokers		
				<20 cigarettes/day	1.0 (0.6–1.6)	24
				20 cigarettes/day	1.9 (1.2–3.1)	25
Le Marchand et al. 1994	8,881 men Random sample Aged 45 years Hawaii	1975–1980, 1989	198	Cigarette smokers		
				Low quartile	1.0	NR
				Intermediate quartile (i)	0.9 (0.6–1.4)	NR
				Intermediate quartile (ii)	1.0 (0.7–1.6)	NR
				High quartile	1.0 (0.6–1.6)	NR
Thune and Lund 1994	1,776 men Retirement community United States	1974–1978, 1991	211	Per 10 cigarettes/day	1.08 (0.90–1.30)	NR
Adami et al. 1996	135,006 male construction workers Sweden	1971–1975, 1991	2,368	Former smokers	1.09 (0.96–1.22)	617
				Current smokers	1.11 (1.01–1.23)	1,069
				Cigarettes/day		
				0	1.00	1,348
				1–4	1.06 (0.93–1.20)	282
				5–14	1.10 (0.99–1.22)	459
				15–24	1.14 (0.99–1.31)	239
				25	1.00 (0.72–1.38)	38
Engeland et al. 1996	11,863 men Norway	1966–1993	703	Former smokers	0.9 (0.7–1.1)	117
				Current smokers	1.1 (0.9–1.37)	451

*Includes subsequent follow-up if applicable.

Table 2.32   Continued

Study	Population/ country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI)		Number of cases
Grönberg et al. 1996	9,680 men Twin register members Sweden	1967, 1970–1989	406	Former smokers	0.91 (0.68–1.21)	92
				Current smokers	1.00 (0.71–1.39)	157
				Tobacco as cigarettes/day (including former smoking)		
				0	1.00 (NR)	117
				1–9	1.06 (0.77–1.48)	112
				10–19	0.96 (0.65–1.39)	86
				20	0.72 (0.42–1.15)	33
Cerhan et al. 1997	1,050 men Rural United States	1982–1993	71	Former smokers	1.2 (0.7–2.1)	30
				Current smokers		
				<20 cigarettes/day	1.8 (0.7–2.4)	6
				20 cigarettes/day	2.7 (1.2–6.0)	9
Hakulinen et al. 1997	4,601 men Finland	1962–1993	209	Former smokers	0.85 (NR)	48
				Current smokers	1.01 (NR)	99
	11,373 men Finland	1972, 1977–1993	109	Former smokers	1.26 (NR)	56
				Current smokers	0.96 (NR)	36
Tulinius et al. 1997	11,366 men Iceland	1968–1995	524	Compared with never smokers, differences for all smoking categories = p 0.1		NR
Veierod et al. 1997	24,051 men Norway	1977–1983, 1992	69	Former smokers	0.6 (0.3–1.1)	20
				Current smokers		
				<10 cigarettes/day	0.5 (0.3–1.1)	11
				10 cigarettes/day	0.6 (0.3–1.2)	14
Giovannucci et al. 1999	47,781 men Health professionals United States	1986–1994	1,369	Former smokers		
				<10 years	1.01 (0.87–1.22)	174
				10 years	0.94 (0.88–1.02)	503
				Current smokers	1.05 (0.85–1.27)	112
Heikkilä et al. 1999	16,481 men Finland	1972–1991	166	Current smokers compared with all others	0.76 (NR)	NR
Parker et al. 1999	1,177 men Iowa United States	1986–1989, 1995	81	Former smokers	1.3 (0.8–2.2)	42
				Current smokers		
				<20 cigarettes/day	1.7 (0.8–3.8)	9
				20 cigarettes/day	1.9 (0.8–4.5)	7

*Includes subsequent follow-up if applicable.

Table 2.33   Case-control studies on the association between smoking and the risk of leukemia

Study	Population	Tobacco exposure	Findings
Williams and Horm 1977	7,518 incident invasive cancer cases For each type of cancer, all other cases comprised the control group United States (nationwide)	• Never smoked • Cigarette level 1: 1–400 cigarette-years[†] (up to 20 pack-years[‡]) • Cigarette level 2: 401–800 cigarette-years (>20 but <40 pack-years) • Cigarette level 3: >800 cigarette-years (40 pack-years) • Men only for cigars and pipes • Cigar level 1: 1–50 cigar-years[§] • Cigar level 2: >50 cigar-years • Pipe level 1: 1–50 pipe-years • Pipe level 2: >50 pipe-years	• No significant associations were found

*CI = Confidence interval.

[†]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

[§]Cigar-years = The number of years of smoking multiplied by the number of cigars smoked per day.

 ALL = Acute lymphocytic leukemia.

[¶]NR = Data were not reported.

**CLL = Chronic lymphocytic leukemia.

[††]AGL = Acute granulocytic leukemia.

Risk estimates (95% CI*)		Comments
<u>Men</u>	<u>Relative odds</u>	The number of all leukemia cases
ALL cigarette use		was not provided; p values and 95%
Never smoked	1.00 (referent)	CIs were not provided
Level 1	0.40	
Level 2	1.48	
Level 3	0.35	
ALL cigar use		
Never smoked	1.00 (referent)	
Level 1	NR[¶]	
Level 2	8.81	
ALL pipe use		
Never smoked	1.00 (referent)	
Level 1	2.03	
Level 2	2.77	
CLL** cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.36	
Level 2	0.84	
Level 3	0.78	
CLL cigar use		
Never smoked	1.00 (referent)	
Level 1	1.32	
Level 2	1.01	
CLL pipe use		
Never smoked	1.00 (referent)	
Level 1	1.13	
Level 2	0.74	
AGL[††] cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.61	
Level 2	1.35	
Level 3	1.14	
AGL cigar use		
Never smoked	1.00 (referent)	
Level 1	0.81	
Level 2	3.19	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Williams and Horm 1977 (risk estimates continued)			

ALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
††AGL = Acute granulocytic leukemia.
‡‡CGL = Chronic granulocytic leukemia.

Risk estimates (95% CI)		Comments
AGL†† pipe use		None
Never smoked	1.00 (referent)	
Level 1	0.61	
Level 2	0.93	
CGL‡‡ cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.80	
Level 2	NR	
Level 3	3.22	
CGL cigar level		
Never smoked	1.00 (referent)	
Level 1	NR	
Level 2	0.82	
CGL pipe level		
Never smoked	1.00 (referent)	
Level 1	NR	
Level 2	2.13	
Women	_Relative odds_	
ALL cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.14	
Level 2	NR	
Level 3	NR	
CLL** cigarette level		
Never smoked	1.00 (referent)	
Level 1	0.84	
Level 2	0.34	
Level 3	0.53	
AGL cigarette level		
Never smoked	1.00 (referent)	
Level 1	1.59	
Level 2	8.76	
Level 3	2.59	
CGL cigarette level		
Never smoked	1.00 (referent)	
Level 1	0.75	
Level 2	3.27	
Level 3	2.59	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Severson 1987	114 incident cases of leukemia (93 with AML[§§]) 133 population controls matched for gender and age Washington state 1981–1984	• Ever smoked • Duration of smoking (years)	• Significant dose-response relationship for duration of smoking with AML
Cartwright et al. 1988	161 cases of acute myeloid leukemia 310 hospital controls matched for gender, age, and hospital Yorkshire, United Kingdom 1979–1986	• Nonsmokers • Smokers	• Marginally significant reduction in risk was associated with smoking
Flodin et al. 1988	111 cases of chronic lymphatic leukemia 431 population controls matched for hospital catchment area Sweden 1975–1984	• Never smoked • Ever smoked	• Ever smoking was a nonsignificant protective factor

[§§]AML= Acute myelocytic leukemia.
  OR = Odds ratio.
[¶¶]RR = Relative risk.

Risk estimates (95% CI)		Comments
<u>OR for AML</u>		None
Never smoked	1.00 (referent)	
Ever smoked	1.78 (1.01–3.15)	
1–9 years	0.93 (0.34–2.51)	
10–19 years	0.79 (0.27–2.29)	
20–29 years	1.70 (0.67–4.27)	
30–39 years	1.80 (0.61–5.35)	
40–49 years	3.03 (1.17–7.83)	
50 years	5.28 (1.73–16.19)	
p value for trend <0.001		
<u>RR[¶]</u>		Crude RR was reported
Nonsmokers	1.0 (referent)	
Smokers	0.6 (0.4–0.96)	
p value = 0.04		
<u>Rate ratio</u>		Crude rate ratio was reported
Never smoked	1.0 (referent)	
Ever smoked	0.71 (0.4–1.2)	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Kabat et al. 1988	342 male and 220 female leukemia cases 9,349 NCC*** and 9,846 CC††† (no matching) United States (9 cities) 1969–1985	• Never smoked • Former smokers • Current smokers • Men only for pipes/cigars • Cigarettes/day (men with ANLL‡‡‡ only)	• Significant negative association with smoking in several categories • No significant positive association with smoking

ALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
***NCC = Noncancer controls.

Risk estimates (95% CI)		Comments
<u>Men</u>	<u>OR</u>	Risk estimates were adjusted for age, duration of smoking, race, gender, education, marital status, type of hospital, and time period
ANLL		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.90 (0.62–1.31)	
CC	1.04 (0.72–1.51)	
Former smokers		
NCC	1.35 (0.90–2.02)	
CC	1.30 (0.87–1.95)	
Current smokers		
NCC	0.63 (0.41–0.97)	
CC	0.91 (0.58–1.41)	
Pipes/cigars only		
NCC	0.67 (0.31–1.44)	
CC	0.57 (0.27–1.21)	
1–14 cigarettes/day		
NCC	0.88 (0.51–1.52)	
CC	1.05 (0.61–1.82)	
15–30 cigarettes/day		
NCC	1.04 (0.69–1.55)	
CC	1.25 (0.83–1.87)	
31 cigarettes/day		
NCC	0.74 (0.44–1.25)	
CC	0.88 (0.52–1.47)	
ALL		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.45 (0.21–0.94)	
CC	0.52 (0.25–1.09)	
CML^{§§§}		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.69 (0.37–1.28)	
CC	0.79 (0.42–1.48)	
CLL**		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.63 (0.33–1.20)	
CC	0.72 (0.37–1.39)	
<u>Women</u>	<u>OR</u>	
ANLL		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.74 (0.49–1.12)	
CC	0.99 (0.65–1.50)	

[†††]CC = Cancer controls.
[‡‡‡]ANLL = Acute nonlymphocytic leukemia.
[§§§]CML = Chronic myelogenous leukemia.

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Brownson 1989	909 white leukemia patients Aged 20 years 3,636 white controls matched for age Missouri 1984–1987	• Never or ever smoked • Cigarettes/day	• For acute leukemias, cigarette smoking was a positive risk factor • For chronic leukemias, cigarette smoking was a negative risk factor

**CLL = Chronic lymphocytic leukemia.
§§AML= Acute myelocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)		Comments
ANLL[‡‡‡]	OR	ORs were adjusted for age and gender
Ever smoked		
No	1.00 (referent)	
Yes	1.43 (1.07–1.90)	
Cigarettes/day		
Never smoked	1.00 (referent)	
<20 cigarettes/day	1.42 (0.81–2.53)	
20 cigarettes/day	1.44 (0.85–1.92)	
ANLL/AML[§§]	OR	
Ever smoked		
No	1.00 (referent)	
Yes	1.42 (1.05–1.90)	
Cigarettes/day		
Never smoked	1.00 (referent)	
<20 cigarettes/day	1.30 (0.67–2.41)	
20 cigarettes/day	1.32 (0.82–1.95)	
ANLL/non-AML	OR	
Ever smoked		
No	1.00 (referent)	
Yes	1.59 (0.56–4.61)	
Cigarettes/day		
Never smoked	1.00 (referent)	
<20 cigarettes/day	2.41 (0.48–10.81)	
20 cigarettes/day	1.54 (0.35–6.65)	
CLL[**]	OR	
Ever smoked		
No	1.00 (referent)	
Yes	0.96 (0.71–1.30)	
Cigarettes/day		
Never smoked	1.00 (referent)	
<20 cigarettes/day	0.70 (0.32–1.48)	
20 cigarettes/day	0.97 (0.61–1.53)	
CML[§§§]	OR	
Ever smoked		
No	1.00 (referent)	
Yes	0.81 (0.50–1.30)	
Cigarettes/day		
Never smoked	1.00 (referent)	
<20 cigarettes/day	1.08 (0.43–2.58)	
20 cigarettes/day	0.29 (0.11–0.73)	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Severson et al. 1990	114 incident cases of leukemia 133 population controls matched for gender and age Washington state 1981–1984	• Ever smoked cigarettes • Pack-years	• Significant risk was associated with ever smoking cigarettes • Significant dose-response relationship with pack-years
Spitz et al. 1990	253 adults with leukemia Cancer controls (number not stated) Texas 1985–1988	• Ever smoked • Never smoked	• No positive associations were found
Brownson et al. 1991	608 men and 523 women with leukemia 1,899 male and 1,742 female hospital controls, frequency matched for age Missouri 1984–1990	• Ever or never smoked • Cigarettes/day	• In men, ever cigarette smoking was a significant risk factor for ANLL • In females, the same relationship was observed, but it was not significant

**CLL = Chronic lymphocytic leukemia.
§§AML= Acute myelocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.
   AANL = Adult acute nonlymphocytic leukemia.

Risk estimates (95% CI)		Comments
<u>OR</u>		Increased risk in smokers appears to be limited to those who inhaled into the chest
Never smoked	1.0 (referent)	
Ever smoked, AANL	2.1 (1.2–3.8)	
Ever smoked, AML[§§]	2.1 (1.2–3.9)	
AANL		
0.7–19.9 pack-years	1.0 (0.4–2.1)	
20.0–39.9 pack-years	2.5 (1.0–6.4)	
40.0 pack-years	3.1 (1.4–7.4)	
p value for trend = 0.0008		
<u>CML[§§§]</u>	<u>OR</u>	There were no adjustments
Never smoked	1.00 (referent)	
Ever smoked	0.81 (0.53–1.25)	
<u>CLL**</u>		
Never smoked	1.00 (referent)	
Ever smoked	0.96 (0.54–1.72)	
AANL/AML		
Never smoked	1.00 (referent)	
Ever smoked	0.75 (0.37–1.54)	
ANLL[‡‡‡]/non-AML		
Never smoked	1.00 (referent)	
Ever smoked	0.62 (0.08–1.28)	
<u>All leukemias</u>		
Never smoked	1.00 (referent)	
Ever smoked	0.78 (0.55–1.12)	
<u>Men</u>	<u>OR</u>	
ANLL		
Never smoked	1.0 (referent)	
Ever smoked	1.5 (1.1–2.0)	
<20 cigarettes/day	1.2 (0.7–2.2)	
20 cigarettes/day	1.2 (0.8–1.8)	
CLL		
Never smoked	1.0 (referent)	
Ever smoked	1.0 (0.7–1.4)	
<20 cigarettes/day	0.9 (0.5–1.9)	
20 cigarettes/day	0.9 (0.2–3.7)	
CML		
Never smoked	1.0 (referent)	
Ever smoked	1.2 (0.8–1.9)	
<20 cigarettes/day	1.8 (0.9–3.7)	
20 cigarettes/day	0.8 (0.4–1.6)	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Brownson et al. 1991 (risk estimates continued)			
Brown et al. 1992	578 white men with leukemia 820 population controls, frequency matched for age, state of residence, and vital status Iowa and Minnesota 1981–1984	• Tobacco users or nonusers • Types of tobacco used • Cigarettes/day • Duration of smoking (years)	• Significant increase in risk for cigarette smokers of the longest duration with CML and CLL

**CLL = Chronic lymphocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)		Comments
<u>Women</u>	<u>OR</u>	None
ANLL[‡‡‡]		
Never smoked	1.0 (referent)	
Ever smoked	1.4 (1.0–1.9)	
<20 cigarettes/day	1.4 (0.8–2.5)	
20 cigarettes/day	1.6 (1.0–2.7)	
CLL**		
Never smoked	1.0 (referent)	
Ever smoked	1.1 (0.7–1.6)	
<20 cigarettes/day	1.1 (0.4–2.1)	
20 cigarettes/day	1.0 (0.5–2.0)	
CML[§§§]		
Never smoked	1.0 (referent)	
Ever smoked	0.8 (0.4–1.4)	
<20 cigarettes/day	0.9 (0.3–2.2)	
20 cigarettes/day	0.5 (0.2–1.4)	
<u>ANLL</u>	<u>OR</u>	Risk estimates were adjusted for age, state of residence, and alcohol consumption
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.4 (0.7–2.9)	
Smokeless only	0.9 (0.2–3.1)	
Pipes/cigars only	0.7 (0.2–2.1)	
Pipes/cigars and smokeless only	1.2 (0.2–5.6)	
Cigarettes only	1.6 (1.0–2.7)	
Cigarettes and other tobacco	1.3 (0.8–2.2)	
<20 cigarettes/day	1.6 (0.9–2.7)	
20 cigarettes/day	1.4 (0.8–2.3)	
>20 cigarettes/day	1.3 (0.7–2.4)	
Duration of smoking		
1–20 years	1.4 (0.8–2.6)	
21–35 years	1.3 (0.7–2.4)	
36–45 years	1.2 (0.6–2.4)	
46 years	1.5 (0.8–2.8)	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Brown et al. 1992 (risk estimates continued)			

ALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)		Comments
CML§§§	OR	
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.7 (0.8–3.8)	
Smokeless only	2.1 (0.4–10.7)	
Pipes/cigars only	0.6 (0.1–5.1)	
Pipes/cigars and smokeless only	2.1 (0.2–18.3)	
Cigarettes only	2.1 (0.9–4.9)	
Cigarettes and other tobacco	1.4 (0.6–3.6)	
<20 cigarettes/day	2.1 (0.8–5.3)	
20 cigarettes/day	1.5 (0.6–3.9)	
>20 cigarettes/day	2.1 (0.8–5.3)	
Duration of smoking		
1–20 years	1.6 (0.6–4.4)	
21–35 years	1.5 (0.6–4.0)	
36–45 years	1.4 (0.4–4.4)	
46 years	3.3 (1.2–9.0)	
CLL**	OR	
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.6 (1.1–2.3)	
Smokeless only	1.9 (0.8–4.3)	
Pipes/cigars only	1.6 (0.8–3.2)	
Pipes/cigars and smokeless only	1.6 (0.5–5.0)	
Cigarettes only	1.6 (1.0–2.5)	
Cigarettes and other tobacco	1.6 (1.1–2.5)	
<20 cigarettes/day	1.9 (1.2–3.0)	
20 cigarettes/day	1.2 (0.7–1.9)	
>20 cigarettes/day	1.7 (1.1–2.8)	
Duration of smoking		
1–20 years	1.9 (1.2–3.1)	
21–35 years	1.3 (0.8–2.1)	
36–45 years	1.6 (0.9–2.6)	
46 years	1.6 (1.0–2.7)	
ALL	OR	
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	0.5 (0.2–1.5)	
Smokeless only	0.0	
Pipes/cigars only	0.8 (0.1–7.2)	
Pipes/cigars and smokeless only	0.0	
Cigarettes only	0.5 (0.1–1.9)	
Cigarettes and other tobacco	0.4 (0.1–1.8)	
<20 cigarettes/day	0.2 (0.00–1.5)	
20 cigarettes/day	0.9 (0.3–3.2)	
>20 cigarettes/day	0.3 (0.1–1.6)	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Brown et al. 1992 (risk estimates continued)			

Risk estimates (95% CI)		Comments
Duration of smoking		
1–20 years	0.4 (0.1–2.0)	
21–35 years	0.3 (0.1–1.6)	
36–45 years	0.8 (0.1–5.0)	
46 years	0.7 (0.1–4.3)	
<u>Myelodysplasia</u>	<u>OR</u>	
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.4 (0.7–2.9)	
Smokeless only	2.7 (0.8–9.4)	
Pipes/cigars only	0.8 (0.2–3.9)	
Pipes/cigars and smokeless only	1.0 (0.1–8.7)	
Cigarettes only	1.6 (0.7–3.5)	
Cigarettes and other tobacco	1.2 (0.5–2.8)	
<20 cigarettes/day	1.0 (0.4–2.5)	
20 cigarettes/day	1.7 (0.7–3.7)	
>20 cigarettes/day	1.1 (0.4–2.8)	
Duration of smoking		
1–20 years	0.4 (0.1–1.6)	
21–35 years	1.4 (0.6–3.6)	
36–45 years	1.5 (0.6–3.8)	
46 years	1.6 (0.7–3.9)	
<u>Other</u>	<u>OR</u>	
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.0 (0.5–2.0)	
Smokeless only	3.0 (0.9–9.2)	
Pipes/cigars only	0.3 (0.0–2.7)	
Pipes/cigars and smokeless only	5.2 (1.5–17.8)	
Cigarettes only	0.7 (0.3–1.6)	
Cigarettes and other tobacco	1.0 (0.5–2.2)	
<20 cigarettes/day	0.7 (0.3–1.8)	
20 cigarettes/day	0.9 (0.4–2.0)	
>20 cigarettes/day	0.9 (0.4–2.0)	
Duration of smoking		
1–20 years	0.4 (0.1–1.3)	
21–35 years	0.9 (0.4–2.1)	
36–45 years	0.7 (0.2–1.0)	
46 years	1.4 (0.6–3.4)	

Table 2.33   Continued

Study	Population	Tobacco exposure	Findings
Mele et al. 1994	Incident adult cases aged 30 years: 28 with ALL ; 55 with RAEB[¶¶¶], preleukemia; 76 with CML[§§§]; and 118 with AML[§§] 1,161 outpatient controls Italy (Rome, Bologna, and Pavia) 1986–1989	• Never smoked • Former smokers • Current smokers • Pack-years	• Significant dose-response relationship with the number of cigarettes/day with AML and RAEB

 ALL = Acute lymphocytic leukemia.
[§§]AML= Acute myelocytic leukemia.
[§§§]CML = Chronic myelogenous leukemia.
[¶¶¶]RAEB = Refractory anemia with excess of blasts.

Risk estimates (95% CI)		Comments
AML	**OR**	Risk estimates were adjusted
Never smoked	1.0 (referent)	for age, gender, education, and
Ever smoked	1.4 (1.0–1.9)	residence outside of study town
Former smokers	1.6 (0.9–2.8)	
Current smokers	1.4 (0.8–2.5)	
1–10 pack-years	1.2 (0.6–2.2)	
11–20 pack-years	1.7 (0.8–3.6)	
>20 pack-years	1.7 (0.9–3.0)	
p value for trend = 0.05		
ALL	**OR**	
Never smoked	1.0 (referent)	
Ever smoked	0.9 (0.5–1.8)	
Former smokers	0.6 (0.2–2.0)	
Current smokers	1.3 (0.5–3.4)	
1–10 pack-years	0.6 (0.2–2.3)	
11–20 pack-years	0.9 (0.2–4.7)	
>20 pack-years	1.3 (0.4–3.7)	
p value for trend = 0.54		
RAEB	**OR**	
Never smoked	1.0 (referent)	
Ever smoked	1.7 (1.0–3.0)	
Former smokers	1.2 (0.4–3.3)	
Current smokers	2.7 (1.2–6.3)	
1–10 pack-years	1.4 (0.5–4.1)	
11–20 pack-years	2.4 (0.7–7.8)	
>20 pack-years	2.4 (1.0–5.8)	
p value for trend = 0.03		
CML	**OR**	
Never smoked	1.0 (referent)	
Ever smoked	1.2 (0.8–1.9)	
Former smokers	1.3 (0.7–2.6)	
Current smokers	1.4 (0.7–2.7)	
1–10 pack-years	1.7 (0.8–3.4)	
11–20 pack-years	1.4 (0.5–3.4)	
>20 pack-years	1.0 (0.5–2.1)	
p value for trend = 0.82		

Table 2.34   Cohort studies on the association between smoking and the risk of leukemia

Study	Population	Tobacco exposure	Outcome
Weir and Dunn 1970	68,153 men aged 35–64 years 482,658 person-years of observation California Began in 1954	• Nonsmokers • All smokers • Packs/day	Death from leukemia (all leukemias)
Paffenbarger et al. 1978	50,000 male alumni of Harvard University (entering 1916–1950) and the University of Pennsylvania (attending 1931–1940) Followed for 35 years Boston and Philadelphia	• Cigarette smokers • Cigarette nonsmokers • 10 cigarettes/day	Death from lymphatic leukemia, myeloid leukemia, or other leukemias
Kinlen and Rogot 1988	U.S. Veterans Cohort Mostly white men United States (nationwide) 1954–1969	• Type of tobacco • Cigarettes/day	Death from lymphatic leukemia, myeloid leukemia, monocytic leukemia, or unspecified leukemias

*CI = Confidence intervals.
†RR = Relative risk.

Findings	Risk estimates (95% CI*)		Comments
• Smokers' risk of dying from leukemia is somewhat greater compared with nonsmokers	**All leukemias** Nonsmokers All smokers About 1/2 pack or less About 1 pack About 1 1/2 packs or more	**RR†** 1.00 (referent) 1.32 0.49 1.73 0.66	Risks were not stratified by leukemia type; p values and 95% CIs were not provided

• Significant risk was associated with both cigarette smoking and smoking 10 cigarettes/day with myeloid leukemia	**Lymphatic leukemia**
	Cigarette nonsmokers
	Cigarette smokers
	  10 cigarettes/day
	
	Myeloid leukemia
	Cigarette nonsmokers
	Cigarette smokers
	  10 cigarettes/day
	
	Other leukemias
	Cigarette nonsmokers
	Cigarette smokers
	  10 cigarettes/day
		RR
		1.00 (referent)
		1.3 (p = 0.57)
		2.7 (p = 0.17)
		
		RR
		1.00 (referent)
		2.4 (p = 0.03)
		3.6 (p = 0.03)
		
		RR
		1.00 (referent)
		1.3 (p = 0.63)
		0.6 (p = 0.65)
			95% CIs were not provided

• 723 outcome events
• Significant dose-response relationship with cigarettes/day and lymphatic and myeloid and mono-cytic leukemias
	Lymphatic leukemia
	Type of tobacco
	  Never smoked
	  Cigarettes
	  Former smokers
	  Cigars
	  Pipes
	Cigarettes/day
	  Never smoked
	  <10 cigarettes/day
	  10–20 cigarettes/day
	   21 cigarettes/day
	χ^2 for trend = 5.02 (p <0.05)
		RR
		
		1.00 (referent)
		1.58 (1.27–1.95)
		1.56 (1.17–2.04)
		2.01 (1.00–3.60)
		0.83 (0.17–2.43)
		
		1.00 (referent)
		1.40 (0.74–2.39)
		1.76 (1.29–2.34)
		1.48 (0.97–2.17)
			No adjustments

Table 2.34   Continued

Study	Population	Tobacco exposure	Outcome
Kinlen and Rogot 1988 (risk estimates continued)			

‡NR = Data were not reported.

Findings	Risk estimates (95% CI)	Comments
	Myeloid and	
	monocytic leukemia RR	
	Type of tobacco	
	Never smoked 1.00 (referent)	
	Cigarettes 1.72 (1.45–2.03)	
	Former smokers 1.54 (1.22–1.92)	
	Cigars 1.78 (0.97–2.98)	
	Pipes 1.18 (0.48–2.57)	
	Cigarettes/day	
	Never smoked 1.00 (referent)	
	<10 cigarettes/day 1.31 (0.78–2.07)	
	10–20 cigarettes/day 1.75 (0.37–2.21)	
	21 cigarettes/day 1.93 (1.45–2.52)	
	χ^2 for trend = 15.48 (p <0.001)	
	Acute leukemia RR	
	Type of tobacco	
	Never smoked 1.00 (referent)	
	Cigarettes 1.51 (1.19–1.89)	
	Former smokers 1.15 (0.81–1.59)	
	Cigars 1.53 (0.66–3.01)	
	Pipes 0.85 (0.17–2.48)	
	Cigarettes/day	
	Never smoked 1.00 (referent)	
	<10 cigarettes/day 1.67 (0.94–2.76)	
	10–20 cigarettes/day 1.54 (1.09–2.10)	
	21 cigarettes/day 1.40 (0.87–2.11)	
	χ^2 for trend = 2.81	
	Unspecified leukemia RR	
	Type of tobacco	
	Never smoked 1.00 (referent)	
	Cigarettes 0.87 (0.55–1.31)	
	Former smokers 1.06 (0.63–1.68)	
	Cigars 0.36 (0.01–2.00)	
	Pipes NR[‡]	
	Cigarettes/day	
	Never smoked 1.00 (referent)	
	<10 cigarettes/day 0.63 (0.13–1.85)	
	10–20 cigarettes/day 0.70 (0.32–1.32)	
	21 cigarettes/day 1.40 (0.70–2.50)	
	χ^2 for trend = 0.13	

Table 2.34   Continued

Study	Population	Tobacco exposure	Outcome
McLaughlin et al. 1989	U.S. Veterans Study (update) 293,658 persons aged 31–84 years (mainly white male World War I veterans) who held active U.S. government life insurance policies in December 1953 Questionnaire administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 26 years of follow-up United States (nationwide)	• Nonsmokers • Ever smoked • Former smokers • Current noncigarette smokers • Current cigarette smokers (cigarettes/day)	Death from leukemia

Findings	Risk estimates (95% CI)		Comments
• Study indicates a positive relationship with smoking, especially for myeloid leukemia	Lymphatic leukemia	RR	95% CIs were not provided
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.09	
	Former smokers	1.21	
	Noncigarette smokers	1.02	
	Current cigarette smokers	1.03	
	<10 cigarettes/day	0.66	
	10–20 cigarettes/day	1.14	
	>20 cigarettes/day	1.10	
	Nonsignificant p value for trend		
	Myeloid leukemia	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.51 (p <0.05)	
	Former smokers	1.31	
	Noncigarette smokers	1.08	
	Current cigarette smokers	1.62 (p <0.01)	
	<10 cigarettes/day	1.48	
	10–20 cigarettes/day	1.45 (p <0.05)	
	>20 cigarettes/day	1.95 (p <0.01)	
	p value for trend = <0.05		
	Acute leukemia	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.27 (p <0.05)	
	Former smokers	1.19	
	Noncigarette smokers	1.01	
	Current cigarette smokers	0.31 (p <0.05)	
	<10 cigarettes/day	1.10	
	10–20 cigarettes/day	1.47 (p <0.01)	
	>20 cigarettes/day	1.16	
	p value for trend = <0.05		
	Other leukemias	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.31	
	Former smokers	1.59 (p <0.05)	
	Noncigarette smokers	0.61	
	Current cigarette smokers	1.16	
	<10 cigarettes/day	1.31	
	10–20 cigarettes/day	0.98	
	>20 cigarettes/day	1.37	

Table 2.34   Continued

Study	Population	Tobacco exposure	Outcome

Garfinkel and Boffetta 1990	2 cohort studies
	  Cancer Prevention Study
	  (CPS) I
	    2,387,252 male and
	    3,318,242 female
	    person-years
	    1959–1965
	  CPS-II
	    1,867,375 male and
	    2,398,772 female
	    person-years
	    1982–1986
	  United States (nationwide)
		• Never smoked cigarettes
		• Ever smoked cigarettes
		• Former cigarette smokers
		• Cigarettes/day
		• Cigar/pipe smokers
		  (men only)
			Death from lymphatic leukemia, myeloid leukemia, or other leukemias

Findings	Risk estimates (95% CI)			Comments
• CPS-I: 477 male and 339 female outcome events • CPS-II: 327 male and 235 female outcome events • In male ever smokers, standardized mortality ratio was significantly larger than 1.0 for all leukemia and myeloid leukemia in both CPS-I and CPS-II; no such relationship was found in female ever smokers	Standardized leukemia mortality ratios			The number of expected deaths was calculated by applying the 5-year, age group-specific mortality rate of the nonsmokers to the denominator of the corresponding age group in the exposed categories; 95% CIs were not provided
	Lymphatic leukemia	**RR**		
		Men	Women	
	CPS-I			
	Ever smoked	1.02	0.80	
	Former smokers	1.25	0.56	
	1–19 cigarettes/day	0.77	0.87	
	20 cigarettes/day	0.99	0.83	
	Cigar/pipe smokers	1.12		
	CPS-II			
	Ever smoked	1.24	1.52	
	Former smokers	1.44	1.94 (p <0.05)	
	1–19 cigarettes/day	0.94	0.67	
	20 cigarettes/day	0.68	1.13	
	Cigar/pipe smokers	1.23		
	Myeloid leukemia			
	CPS-I			
	Ever smoked	2.44 (p <0.05)	0.61 (p <0.05)	
	Former smokers	2.23 (p <0.05)	0.36	
	1–19 cigarettes/day	2.25 (p <0.05)	0.61	
	20 cigarettes/day	2.87 (p <0.05)	0.74	
	Cigar/pipe smokers	1.51		
	CPS-II			
	Ever smoked	1.32 (p <0.05)	1.27	
	Former smokers	1.17	1.33	
	1–19 cigarettes/day	1.65	1.45	
	20 cigarettes/day	1.75 (p <0.05)	0.98	
	Cigar/pipe smokers	0.85		
	Other leukemias			
	CPS-I			
	Ever smoked	1.58 (p <0.05)	0.94	
	Former smokers	1.18	1.44	
	1–19 cigarettes/day	1.53 (p <0.05)	0.88	
	20 cigarettes/day	1.95 (p <0.05)	0.75	
	Cigar/pipe smokers	1.07		
	CPS-II			
	Ever smoked	1.70	0.79	
	Former smokers	1.63 (p <0.05)	0.88	
	1–19 cigarettes/day	2.17 (p <0.05)	0.79	
	20 cigarettes/day	1.75	0.61	
	Cigar/pipe smokers	1.14		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Mills et al. 1990	Seventh-Day Adventist Health Study 34,000 Seventh-Day Adventists California 1977–1982	• Never smoked • Former cigarette smokers • Current cigarette smokers • Greatest number of cigarettes smoked daily • Duration of smoking (years)	Diagnosis of all leukemias and myeloid leukemia

Findings	Risk estimates (95% CI)		Comments
• Significant dose-response relation-ship with all leukemias, but not with myeloid leukemia	<u>All leukemias</u>	<u>RR</u>	RRs were adjusted for age and gender
	Never smoked	1.00 (referent)	
	Former smokers	2.00 (1.01–3.95)	
	Current smokers	2.10 (0.48–9.23)	
	Greatest number of cigarettes smoked daily		
	Never smoked	1.00 (referent)	
	1–14 cigarettes/day	1.01 (0.34–2.99)	
	15–24 cigarettes/day	2.44 (0.93–6.38)	
	25 cigarettes/day	3.00 (1.25–7.22)	
	p value for trend = 0.009		
	Duration of smoking		
	Never smoked	1.00 (referent)	
	<5 years	1.28 (0.39–4.32)	
	5–14 years	1.69 (0.56–5.14)	
	15 years	2.55 (1.18–5.53)	
	p value for trend = 0.03		
	<u>Myeloid leukemia</u>	<u>RR</u>	
	Never smoked	1.00 (referent)	
	Former smokers	2.24 (0.91–5.53)	
	Current smokers	2.04 (0.25–16.65)	
	Greatest number of cigarettes smoked daily		
	Never smoked	1.00 (referent)	
	1–14 cigarettes/day	1.94 (0.60–6.27)	
	15–24 cigarettes/day	1.49 (0.32–6.94)	
	25 cigarettes/day	3.55 (1.14–11.07)	
	p value for trend = 0.10		
	Duration of smoking		
	Never smoked	1.00 (referent)	
	<5 years	2.39 (0.65–8.77)	
	5–14 years	1.45 (0.31–6.71)	
	15 years	2.69 (0.94–7.72)	
	p value for trend = 0.19		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Linet et al. 1991	Lutheran Brotherhood Cohort Study 17,633 white male policy-holders of the Lutheran Brotherhood Insurance Society Followed for 20 years (286,731 person-years) United States (nationwide) 1967–1986	• Type of tobacco • Cigarettes/day	Death from leukemia

Findings	Risk estimates (95% CI)		Comments
• 74 outcome events • No significant relationship with any of the leukemias • Most of the myeloid leukemia risk estimates were less than 1.0	Myeloid leukemia Type of tobacco used Never Any Cigarettes only Pipes/cigars only Cigarettes and other tobacco	RR 1.0 (referent) 0.8 (0.3–1.7) 0.3 (0.1–1.6) 1.1 (0.2–5.0) 1.0 (0.4–2.2)	Poisson regression was used to calculate RRs; risk estimates were adjusted for age
	Cigarettes/day Never smoked Ever smoked 10 cigarettes/day 11–20 cigarettes/day >20 cigarettes/day p value for trend = 0.68	 1.0 (referent) 0.8 (0.3–1.8) 0.5 (0.2–1.6) 0.8 (0.3–2.1) 1.3 (0.5–3.8)	
	Lymphatic leukemia Type of tobacco used Never Any Cigarettes only Pipes/cigars only Cigarettes and other tobacco	RR 1.0 (referent) 1.4 (0.5–3.5) 2.7 (0.9–8.3) 0.7 (0.1–6.1) 1.5 (0.6–4.2)	
	Cigarettes/day Never smoked Ever smoked 10 cigarettes/day 11–20 cigarettes/day >20 cigarettes/day p value for trend = 0.11	 1.0 (referent) 1.7 (0.6–4.4) 1.5 (0.5–4.6) 1.7 (0.6–5.2) 1.9 (0.5–7.2)	
	Other leukemias Type of tobacco used Never Any Cigarettes only Pipes/cigars only Cigarettes and other tobacco	RR 1.0 (referent) 1.5 (0.3–6.8) 1.5 (0.2–10.3) NR NR	
	Cigarettes/day Never smoked Ever smoked 10 cigarettes/day 11–20 cigarettes/day >20 cigarettes/day p value for trend = 0.06	 1.0 (referent) 1.7 (0.4–7.6) 0.4 (0.0–4.5) 2.5 (0.5–12.5) 3.0 (0.5–18.2)	

Table 2.34   Continued

Study	Population	Tobacco exposure	Outcome
Friedman 1993	Kaiser Permanente study 57,224 never smokers 20,928 former smokers 64,839 current smokers 24 years of follow-up Oakland and San Francisco Began in 1964	• Never smoked • Former smokers • Current smokers • Packs/day (men with acute nonlymphocytic leukemia only)	Diagnosis of leukemia
Doll et al. 1994	34,439 British male doctors United Kingdom 1951–1991 (40 years of follow-up)	• Never smoked • Former smokers • Current smokers • Cigarettes/day	Mortality from myeloid leukemia or nonmyeloid leukemia

Findings	Risk estimates (95% CI)			Comments
• Cigarette smoking was significantly associated with the development of acute nonlymphocytic leukemia in men	<u>Acute nonlympho- cytic leukemia</u>	<u>RR</u>		RRs were adjusted for age
		Men	Women	
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	2.3 (0.9–5.7)	1.3 (0.6–2.8)	
	Current smokers	2.8 (1.2–6.4)	0.9 (0.4–1.7)	
	<1 pack/day	1.0 (referent)		
	1–2 packs/day	1.5 (0.6–3.6)		
	>2 packs/day	1.6 (0.5–5.1)		
	p value for trend = 0.31			
	<u>Acute myeloid leukemia</u>	<u>RR</u>		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	1.6 (0.6–4.7)	1.4 (0.6–3.1)	
	Current smokers	2.0 (0.8–5.0)	0.9 (0.4–1.8)	
	<u>Chronic myeloid leukemia</u>	<u>RR</u>		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	0.5 (0.0–4.2)	1.0 (0.2–4.5)	
	Current smokers	3.5 (0.9–13.0)	0.6 (0.2–2.2)	
	<u>Chronic lymphocytic leukemia</u>	<u>RR</u>		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	1.0 (0.5–1.8)	0.6 (0.1–1.7)	
	Current smokers	0.8 (0.5–1.5)	0.6 (0.3–1.3)	
• "...(myeloid leuke-mia) showed a marginally significant relation with the amount smoked." (p. 903)	Annual mortality per 100,000 men			Mortality rates were standardized for age and calendar period; p value was not provided
	<u>Myeloid leukemia</u>	<u>Number</u>		
	Nonsmokers	4		
	Former smokers	8		
	Current smokers	7		
	1–14 cigarettes/day	3		
	15–24 cigarettes/day	9		
	25 cigarettes/day	10		
	<u>Nonmyeloid leukemia</u>	<u>Number</u>		
	Nonsmokers	14		
	Former smokers	9		
	Current smokers	12		
	1–14 cigarettes/day	16		
	15–24 cigarettes/day	8		
	25 cigarettes/day	13		

Table 2.34   Continued

Study	Population	Tobacco exposure	Outcome
Engeland et al. 1996	26,000 men Norway 1966–1993	• Never smoked • Former smokers • Current smokers	Diagnosis of leukemia
Engeland et al. 1997	502,496 cancer cases Norway 1953–1993	• Ever/never smoked	Diagnosis of leukemia before or after diagnosis of another smoking-associated cancer (SAC)
Nordlund et al. 1997	26,000 women Sweden 1963–1989	• Never smoked • Former smokers • Current smokers • Cigarettes/day • Age at smoking initiation	Diagnosis of leukemia
Tulinius et al. 1997	11,580 women 11,366 men Iceland 1968–1995	• Never smoked • Former smokers • Cigarettes/day	Diagnosis of leukemia (all leukemias)

Findings	Risk estimates (95% CI)		Comments
• No significant associations	<u>Men</u> <u>RR</u> Never smoked 1.0 (referent) Former smokers 0.9 (0.4–1.9) Current smokers 0.6 (0.4–1.2) <u>Women</u> <u>RR</u> Never smoked 1.0 (referent) Former smokers 0.3 (0.0–2.2) Current smokers 1.3 (0.7–2.5)		No adjustments
• Significantly increased mortality among men and women who smoked for developing leukemia before developing other SACs	<u>Standardized incident ratios for smokers</u> (observed/expected) <u>Men</u> <u>Women</u> Leukemia before 1.6 (1.2–2.0) 1.9 (1.2–2.8) another SAC Leukemia after 1.3 (1.0–1.6) 1.3 (0.9–2.0) another SAC		Estimates of the expected number were based on gender-specific incidence rates from the entire Norwegian population during 8 time periods

• No significant risks	<u>RR</u>
	Never smoked 1.00 (referent)
	Former smokers 1.03 (0.32–3.29)
	Current smokers 1.24 (0.71–2.18)
	
	1–7 cigarettes/day 1.52 (0.80–2.91)
	8–15 cigarettes/day 0.93 (0.33–2.59)
	  16 cigarettes/day 0.69 (0.09–4.99)
	
	Age at smoking initiation
	  19 years old 1.25 (0.38–4.16)
	  20–23 years old 1.56 (0.85–2.86)
	p value for trend = 0.154
			RRs were adjusted for age and place of residence

• Significant risk associated with smoking 15–24 cigarettes/day	<u>RR</u> Never smoked 1.0 (referent) Former smokers 2.08 (0.68–6.35) 1–14 cigarettes/day 1.14 (0.34–3.78) 15–24 cigarettes/day 3.96 (1.52–10.3) 25 cigarettes/day NR		RRs were adjusted for age

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Adami et al. 1998	334,957 male construction workers Sweden 1971–1991	• Never smoked • Former smokers • Current smokers • Cigarettes/day • Duration of smoking (years) • Pipe tobacco • Snuff dipping	Diagnosis of leukemia

Findings	Risk estimates (95% CI)		Comments
• No significant association	Myeloid leukemias	RR	RRs were adjusted for age
	Never smoked	1.0 (referent)	
• No indication of a dose-response relationship	Former smokers	0.7 (0.5–1.2)	
	Current smokers	1.0 (0.7–1.4)	
	1–14 cigarettes/day	1.3 (0.9–1.7)	
	15 cigarettes/day	0.8 (0.5–1.3)	
	Duration of smoking		
	Former smokers		
	1–10 years	0.6 (0.3–1.3)	
	11–20 years	1.0 (0.6–1.9)	
	21 years	0.7 (0.3–1.4)	
	Current smokers		
	1–10 years	0.8 (0.4–1.7)	
	11–20 years	0.7 (0.4–1.3)	
	21–30 years	1.4 (0.8–2.2)	
	31 years	1.2 (0.8–1.9)	
	Pipe tobacco		
	<30 g/week	1.0 (0.6–1.7)	
	30 g/week	1.2 (0.8–1.7)	
	Ever dipped snuff	1.0 (0.7–1.4)	
	Acute leukemias	RR	
	Never smoked	1.0 (referent)	
	Former smokers	0.8 (0.5–1.3)	
	Current smokers	1.1 (0.8–1.6)	
	1–14 cigarettes/day	1.4 (1.0–2.0)	
	15 cigarettes/day	1.1 (0.7–1.8)	
	Duration of smoking		
	Former smokers		
	1–10 years	0.7 (0.3–1.5)	
	11–20 years	0.7 (0.3–1.5)	
	21 years	1.0 (0.5–2.0)	
	Current smokers		
	1–10 years	1.4 (0.8–2.7)	
	11–20 years	0.7 (0.4–1.5)	
	21–30 years	1.5 (0.9–2.4)	
	31 years	0.9 (0.5–1.5)	
	Pipe tobacco		
	<30 g/week	1.0 (0.6–1.8)	
	30 g/week	1.1 (0.7–1.7)	
	Ever dipped snuff	1.0 (0.7–1.4)	

Liver Cancer

There are strong geographic variations in liver cancer incidence around the world. Although liver cancer is a relatively infrequent cause of cancer mortality in the United States, it is a leading cause of cancer deaths in the world (London and McGlynn 1996). In the United States, less than 1.5 percent of incident cancers are primary cancers of the liver and bile ducts. However, cancer of the liver ranks eighth (by deaths) on a worldwide basis, with three-quarters of the cases occurring in developing countries where hepatitis B and aflatoxin ingestion are prevalent causal exposures (Parkin et al. 1993). In the United States, an estimated 17,300 new cases of liver cancer and 14,400 deaths attributed to this cancer were expected to occur in 2003 (ACS 2003). Liver cancer is more common among men than women, in part reflecting the greater alcohol intake by men. Liver cancer incidence and mortality rates have increased since the 1980s in the United States (McKean-Cowdin et al. 2000). Hypotheses for this increase include the increasing frequency of hepatitis C virus and hepatitis B virus (HBV) infections.

Interpretation of the relationship between smoking and liver cancer is complicated by the potential for confounding by alcohol and HBV infections. First, alcohol intake is an established risk factor and smokers tend to drink more than nonsmokers, and this exposure has not been measured routinely in all studies that include information on smoking history. Second, chronic HBV infections are recognized as a major cause of this malignancy (IARC 1988). As for alcohol, not all epidemiologic studies that have addressed smoking have also assessed the hepatitis status of study participants. Hence, the unconfounded contribution of smoking to risks for liver cancer has been difficult to assess. Considerable epidemiologic evidence indicates, however, that smokers are at an increased risk for this cancer.

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted an association between smoking and hepatocellular cancer that persisted after controlling for potentially confounding lifestyle factors including alcohol intake. That report also noted that HBV infections may modify the effects of smoking on the risk of liver cancer. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that smoking might be a contributing factor to the development of liver cancer.

Biologic Basis

Circulating carcinogens from tobacco smoke are metabolized in the liver, thus exposing the liver to many absorbed carcinogens. A long-term exposure to these carcinogens may therefore lead to cellular damage in the liver and the development of cancer. Carcinogens may act directly on the genes of the hepatocytes.

Epidemiologic Evidence

Epidemiologic data come from a wide range of studies in both low- and high-incidence countries (Table 2.35). Many of these studies have evaluated smoking, alcohol, and viral causes of liver cancer thoroughly, although some of the larger cohort studies have not controlled for each of these causal agents in assessing smoking's effect. Cigarette smoking was directly related to the risk of liver cancer as the number of cigarettes smoked per day increased in some case-control studies (Yu et al. 1983; Trichopoulos et al. 1987b; Kuper et al. 2000) but not in others (Tanaka et al. 1992).

In a cohort study of U.S. veterans, Hsing and colleagues (1990a) noted a significant trend in increased risks with an increasing number of cigarettes smoked, but their analysis did not control for alcohol consumption or hepatitis viral status. On the other hand, Doll and colleagues (1994) did not observe a trend in risk with higher levels of cigarette smoking in the 40-year report of the British physicians cohort study, and concluded that smoking is not related to liver cancer. In a 12-year cohort study of 14,397 residents of Taiwan aged 40 years and older, cigarette smoking was positively related to mortality from liver cancer (Liaw and Chen 1998). Among men, 110 deaths from liver cancer were identified, and for current smokers the RR was 2.2 (95 percent CI, 1.4–3.6) compared with persons who had never smoked. These authors adjusted for alcohol consumption and the presence of HBV surface antigens.

For persons smoking more than a pack a day, the RR for liver cancer has been 2 or more in both case-control and cohort studies, compared with the risk for persons who had never smoked (Yu et al. 1983; Hsing et al. 1990a; Doll et al. 1994; Kuper et al. 2000). However, not all studies have found an effect of this magnitude (Tanaka et al. 1992; Chiesa et al. 2000; Mori et al. 2000a). This inconsistency may be in part due to the study design and to the relative contribution of HBV infection to the risk of malignancy. For example, Lam and colleagues (1982) observed a RR of 3.3 (95 percent CI, 1.0–13.4) among current smokers, but the association was confined to those who were HBV-negative. Similarly, Trichopoulos and colleagues (1980, 1987b) observed significant associations among HBV-negative persons. In contrast, in a cohort of HBV-positive men and women in China, Tu and colleagues (1985) observed a RR of 4.6. One explanation for the varying results is the dominant role of hepatitis viral infection and the extent to which its effects have been considered in the studies on smoking. The higher RRs that were observed in several studies of persons who were negative for HBV compared with those who were positive suggest that this explanation is plausible.

Evidence Synthesis

A substantial body of epidemiologic evidence supports a relationship between smoking and liver cancer, but a positive association was not found in all studies considered. The metabolism in the liver of the many carcinogens from tobacco smoke leads to an exposure of hepatocytes to these carcinogens. The strength of an association between cigarette smoking and liver cancer varies according to HBV infection status, with stronger associations among those who are negative for HBV. In many of the studies, risk increases with the number of cigarettes smoked per day. Although confounding by alcohol and HBV infection status may bias the findings of some studies, controlling for these causes does not remove the strong association between smoking and liver cancer seen in several of the studies summarized in this report. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the liver (IARC 2002).

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer.

Implications

The global burden of liver cancer may increase if smoking increases around the world. Further research is needed to resolve the relationship of smoking to liver cancer with further consideration of the history of hepatitis infection and alcohol use.

Table 2.35   Studies on the association between smoking and the risk of liver cancer

Study	Location	Cases
Case-control studies		
Trichopoulos et al. 1980	Greece	79
Lam et al. 1982	Hong Kong	107
Stemhagen et al. 1983	United States	265
Yu et al. 1983	United States	78
Hardell et al. 1984	Sweden	102
Filippazzo et al. 1985	Italy	120
Kew et al. 1985	South Africa	240
Austin and Cole 1986	United States	86
Trichopoulos et al. 1987b	Greece 1976–1984	194
La Vecchia et al. 1988	Italy	151
Lu et al. 1988	Taiwan	131
Yu et al. 1988	United States	165

*RR = Relative risk.
†CI = Confidence interval.
‡HBV = Hepatitis B virus.
§HBsAg = Hepatitis B surface antigen.

RR* (95% CI†) compared with never smokers	Comments
5.5 (2.0–15.6)	The association was confined to persons who were HBV‡-negative
3.3 (1.0–13.4)	The association was confined to persons who were HBV-negative
Men: 0.7 (0.4–1.1) Women: 1.0 (0.6–1.7)	None

Current
    1 pack/day: 1.2 (0.6–2.5)
  >1 pack/day: 2.6 (1.0–6.7)
	RR in heavy smokers (>1 pack/day) compared with light smokers (1 pack/day) = 1.8 (0.1–4.6); RR for the >1 pack/day low-alcohol intake group = 1.8 (0.7–5.0)

1.1 for current and former smokers (no CI was reported)	RR was calculated from smokers (73.5%) and 66% of the never smokers (controls)
0.8 (0.4–1.5)	None
<1.0 (no CI was reported) for heavy smokers; compared with nonsmokers; no current HBV = 1.3 for heavy smokers compared with nonsmokers	Heavy smoking = 20 cigarettes/day
1.0 (0.5–1.8)	None
7.3 for smokers of 30 cigarettes/day	The association was confined to persons who were HBV-negative; slope for a trend with the number of cigarettes smoked was significantly higher in persons negative for HBsAg§ than the corresponding slope for persons positive for HBsAg
0.9 (0.6–1.5)	None
Odds ratio = 1.33 for smokers compared with nonsmokers; χ^2 for trend = 0.88 (p >0.05) adjusted for gender and HBsAg	Smoking behaviors, duration in years, or number of cigarettes smoked per day were not associated with hepatocellular carcinoma in the multivariate models
3.3, p <0.05	None

Table 2.35   Continued

Study	Location	Cases
Case-control studies		
Tanaka et al. 1992	Japan	204
Kuper et al. 2000	Greece 1995–1998	333
Cohort studies		
Oshima et al. 1984	Japan	20
Tu et al. 1985	China	70
Shibata et al. 1986	Japan	22
Kono et al. 1987	Japan	51
Hsing et al. 1990a	United States veterans	289
Doll et al. 1994	United Kingdom	76
McLaughlin et al. 1995a	United States veterans	363
Liaw and Chen 1998	Taiwan	Men: 110 Women: 18
Mori et al. 2000a	Japan	22

[‡]HBV = Hepatitis B virus.
[§]HBsAg = Hepatitis B surface antigen.
 Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

RR* (95% CI†) compared with never smokers	Comments
Current smokers: 1.5 (0.9–2.5) Former smokers: 1.6 (0.9–2.8)	There was no significant trend in risks with pack-years smoked
Current smokers <2 packs/day: 1.2 (0.8–1.9) 2 packs/day: 1.6 (0.9–2.9)	Risks were strongest in persons without both HBsAg§ and antibodies to hepatitis C virus (RR = 2.8 [1.1–6.9] for smokers of 2 packs/day; trend p = 0.03)
5.8 (1.0–34.2)	None
4.6 (p <0.05)	HBV‡-positive cohort
Standard mortality ratio (observed/expected) = >4.8 (p <0.001) among cigarette smokers in fishing area	There was no clear dose-response relationship; risks were insignificant after adjusting for shahi drinking

Current compared with never and former smokers
  1–19 cigarettes/day: 1.14 (0.59–2.20)
   20 cigarettes/day: 1.04 (0.49–2.23)
	There was no association with smoking

Cigar/pipe smokers: 3.1 (2.0–4.8)
Cigarettes
  Current smokers: 2.4 (1.6–3.5)
  Former smokers: 1.9 (1.2–2.9)
	Risks increased with the number of cigarettes/day: <10 (2.2); 10–20 (2.0); 21–39 (2.9); >39 (3.8 [1.9–8.0]); there was a strong dose-response relationship (p <0.001); did not control for alcohol intake or HBV status

2.0 for persons who smoked 25 cigarettes/day	There was no significant trend for the number of cigarettes smoked per day
Current smokers: 1.8 (1.4–2.3) Former smokers: 1.5 (1.2–2.0)	The mortality study did not control for alcohol or viral status
Men Current smokers: 2.2 (1.4–3.6)	Results were adjusted for alcohol intake and HBsAg status; risks increased with more years of smoking, and decreased with an older age at initiation
2.10 (0.61–7.23)	Results were adjusted for age and gender; a small number of cases precluded an informative analysis of the interactions

Adult Brain Cancer

Brain cancer incidence is higher in men than in women. In 2003, an estimated 18,300 new cases (10,200 among men and 8,100 among women), and an estimated 13,100 deaths attributed to brain cancer were expected to occur (ACS 2003).

The systematic epidemiologic study of brain cancer is hampered by the grouping of clinicopathologic entities and by problems with the accurate diagnosis of intracranial lesions. Further, it often is difficult to distinguish primary from secondary or metastatic lesions. Risk factors for brain cancers include working in petrochemical, rubber, and agricultural industries. Radiation exposure also has been related to the risk of brain cancer (NRC 1990; Preston-Martin and Mack 1996).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not reviewed brain cancer and smoking.

Biologic Basis

Exposure to nitroso compounds has been related to the risk of brain cancer, stimulating interest in cigarette smoke as a source of exposure. Two major subcategories of nitroso compounds include nitrosamines, which require metabolic activation, and nitrosamides, which do not. The nitrosamides, particularly nitrosoureas, are effective nervous system carcinogens in many species (Preston-Martin and Mack 1996). Nitrosamides have been shown to damage DNA by the production of adducts. The major sources of exposure to nitrosamines in the United States are tobacco smoke, cosmetics, automobile interiors, and cured meats.

Epidemiologic Evidence

Both case-control and cohort studies have evaluated the relationship between smoking and cancer of the brain. In the 26-year follow-up of the U.S. veterans cohort (Hsing et al. 1991), no relationship was observed between smoking and mortality from brain cancer. In a population-based case-control study in Los Angeles County, California, that included 94 women with intracranial gliomas, no relationship was observed between cigarette smoking and the risk of brain cancer (Blowers et al. 1997). In a comparable study from the San Francisco Bay area that included 434 adults with incident glioma, men but not women were at an increased risk of cancer if they had smoked unfiltered cigarettes. Among the men, those who reported using filter-tipped cigarettes had no increase in risks compared with men who had never smoked (RR = 0.8 [95 percent CI, 0.5–1.2]), and those who smoked unfiltered cigarettes had an increased RR of 1.8 (95 percent CI, 0.9–3.4) (Lee et al. 1997). Among the women, an increased risk was not observed, although the prevalence of smoking unfiltered cigarettes was substantially lower. An Australian case-control study also failed to show any relationship between smoking and glioma in women, but did show a suggestive relationship in men (Ryan et al. 1992). On the basis of 416 cases (166 women and 250 men), Hurley and colleagues (1996) reported that men who had smoked had a RR for glioma of 1.64 (95 percent CI, 1.10–2.45) compared with men who had never smoked, while for women who had smoked the RR was 0.99 (95 percent CI, 0.62–1.62) compared with women who had never smoked. In this study, there was no evidence of an increase in risk among either women or men with increased durations of smoking or pack-years of smoking.

Eight other studies, all smaller than those reviewed above, have also failed to find an association between smoking and glioma (Musicco et al. 1982; Ahlbom et al. 1986; Burch et al. 1987; Brownson et al. 1990; Hochberg et al. 1990; El-Zein et al. 1999; Bondy et al. 2001; Zheng et al. 2001). In several of these studies, controls were limited to hospitalized patients— a potential source of bias when evaluating smoking-related risks (Musicco et al. 1982; Burch et al. 1987). Ahlbom and colleagues (1986) studied 78 cases and observed no association between smoking and astrocytoma when using population controls (RR = 1.2 [95 percent CI, 0.6–2.5]). Musicco and colleagues (1982) observed a nonsignificant increase in risk when comparing heavy smokers with persons who had never smoked (RR = 1.5, p = 0.71). Burch and colleagues (1987) compared 215 cases with 215 hospital controls, and observed an overall RR of 1.44 (95 percent CI, 0.94–2.21) comparing smokers of plain cigarettes with

nonsmokers, and a RR of 0.98 (95 percent CI, 0.66–1.46) comparing smokers of filter-tipped cigarettes with nonsmokers. There was a significant increase in risk with an increased amount smoked for those smoking plain cigarettes (p = 0.026) but not for those smoking filter-tipped cigarettes (p = 0.64).

Evidence Synthesis

Overall, the epidemiologic evidence shows no consistent relationship between smoking and glioma. Duration of smoking, the number of cigarettes smoked per day, and pack-years of smoking have been evaluated in different studies. None of these measures of exposure shows a strong or consistent relationship.

Conclusion

1. The evidence is suggestive of no causal relationship between smoking cigarettes and brain cancer in men and women.

Implications

Epidemiologic research using both case-control and cohort designs has not found an association between smoking and brain cancer in adults. Any new studies on this topic will need to have large sample sizes and careful characterizations of the tumors.

Breast Cancer

Breast cancer is the most frequently diagnosed nonskin cancer among women (ACS 2003). In 2003, an estimated 212,600 new cases and 40,200 deaths attributed to breast cancer were expected to occur. From 1996–2000, the average annual age-adjusted population incidence rate of breast cancer per 100,000 in the United States was 140.8 in white women, 121.7 in black women, 97.2 in Asian/Pacific Islander women, 89.8 in Hispanic women, and 58.0 in American Indian/Alaska Native women (Ries et al. 2003). The possibility that cigarette smoking is associated with breast cancer has been a topic of substantial research, given the high prevalence of exposure to this harmful agent, the high incidence of breast cancer, and the relative difficulty of modifying many established breast cancer risk factors.

The relationship between active smoking and breast cancer has been investigated since 1960 (MacMahon and Feinleib 1960) in many large, well-designed epidemiologic studies (Palmer and Rosenberg 1993; Terry and Rohan 2002). Most of these studies have found overall associations close to the null: some RRs for the association with smoking have been modestly inverse, whereas some have been modestly positive. Investigators have hypothesized that smoking may have antiestrogenic effects as well as carcinogenic effects on breast tissue, and thus may exert countervailing influences on breast cancer risks (Palmer and Rosenberg 1993). If both of these effects have a role in breast cancer development, the increase in risk may become apparent only when women are classified according to characteristics related to their susceptibility to the antiestrogenic or carcinogenic effects. In the absence of such stratification, the hypothesized effects of cigarette smoke might be expected to lead to null findings overall in a single study and to inconsistency across studies, depending on the characteristics of the participants.

Conclusions of Previous Surgeon General's Reports

The 2001 Surgeon General's report on women and smoking (USDHHS 2001) reviewed the scientific data on the association between cigarette smoking and breast cancer, concluding that "Thus, active smoking does not appear to appreciably affect breast cancer risk overall. However, several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS[2] exposure affects risk" (p. 217). A more detailed review of the evidence is

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[2]ETS = Environmental tobacco smoke.

provided in this section, including evidence on the above three points. Since the 2001 report, IARC has concluded that the evidence is indicative of no association between smoking and breast cancer (IARC 2002).

Biologic Basis

Because smokers have a higher incidence of cancers at sites that do not have direct contact with cigarette smoke, including the cervix, pancreas, and bladder (USDHHS 1982), researchers have hypothesized that constituents of cigarette smoke may reach distant tissues, including breast tissue. Biomarkers have now provided evidence supporting this hypothesis. Mutagens from cigarette smoke have been found in the nipple aspirates of nonlactating women (Petrakis et al. 1980), indicating that mutagenic tobacco smoke components do reach breast tissue. Thus, prolonged exposure to these substances may initiate and promote benign and malignant breast disease. In a small case-only study, Perera and colleagues (1995) found DNA adducts characteristic of cigarette smoke in four out of seven breast tumors from smoking women, but not in any of the tumors from eight nonsmokers. In a larger case-only study, Li and colleagues (1996) similarly found such adducts in breast tissues of all current smokers (17 out of 17) and in some (5 out of 8) former smokers, even 18 years after smoking cessation. They found the same adducts in 4 out of 52 nonsmokers. The data from former smokers suggest that smoking-induced DNA damage might persist for a long time.

Whereas the research described above suggests that breast tissue of smokers is exposed to tobacco-smoke carcinogens, some researchers (MacMahon et al. 1982) have proposed that smokers would have a reduced risk of breast cancer, based on a hypothesis that breast cancer is an estrogen-related disease and that cigarette smoking has antiestrogenic effects. However, the biologic foundations underlying both of the postulated mechanisms of this hypothesis (carcinogenic exposure and antiestrogenic effects) are not firmly established.

Empirical support for the hypothesis that cigarette smoking exerts antiestrogenic effects and therefore might lower the risk for breast cancer comes from several sources, including laboratory studies of rodents and studies of hormones in smokers and nonsmokers. Rats exposed to cigarette smoke develop fewer mammary tumors than do unexposed rats (Davis et al. 1975; Dalbey et al. 1980), although this finding may be the result of differences in weight or survival. Findings

from this animal model also are interpreted in light of the uncertain relevance of the mammary tumor model in rodents for breast cancer in humans. For instance, mammary cancer in rats is prolactin-dependent (Kleinberg 1987), and the lower risk of tumors may reflect a lowering of prolactin levels from long-term exposure to tobacco smoke (Ferry et al. 1974; Andersson 1985).

Smoking has also been hypothesized as affecting estrogen levels. Researchers are uncertain about how smoking might affect the biology of estrogen-related events in women not taking oral estrogens. However, several possible mechanisms have been proposed. Polycyclic aromatic hydrocarbons in tobacco smoke may induce cytochrome P-450 enzymes that metabolize sex hormones (Conney 1967; Lu et al. 1972). Michnovicz and colleagues (1986) suggested that smoking increases the 2-hydroxylation of the estradiol metabolic pathway, thus decreasing the availability of active estrogens to tissues. Cigarette smoking leads to an early menopause, and disturbances in estrogen-dependent processes before menopause could be due to a toxic impact on the developing graafian follicle (Mattison 1980). Also, the lower body weight of smokers would result in lower estrone and estradiol levels than nonsmokers of similar age. Finally, smoking increases the levels of the adrenal androgen hormones androstenedione and dihydroepiandrosterone (Baron et al. 1990; Law et al. 1997), which could explain some (but hardly all) of the hormone effects.

Whereas initial comparisons of estrogen levels between smokers and nonsmokers documented differences, more recent studies have generally shown similar levels. Among premenopausal women, studies of urinary excretion of estrogens have tended to yield different findings from studies of plasma levels of reproductive hormones. MacMahon and colleagues (1982) were among the first to examine estrogens and smoking, and reported that premenopausal women who smoked had lower urinary excretions of estrone, estriol, and estradiol during the luteal phase of the menstrual cycle than women who had never smoked. Former smokers did not manifest this pattern, however, nor were there differences in urinary excretion during the follicular phase of the menstrual cycle. Michnovicz and colleagues (1986) found results similar to those of MacMahon and colleagues for both the luteal and follicular phases. In another study of premenopausal women, Westhoff and colleagues (1996) found that smokers had, on average, lower levels of midcycle and luteal-phase urinary estradiol levels than nonsmokers.

However, comparisons of endogenous serum estrogen levels between smokers and nonsmokers have clearly shown that among both premenopausal and postmenopausal women smokers do not have lower levels of the major estrogens than nonsmokers (Baron et al. 1990; Law et al. 1997; USDHHS 2001). Three studies of premenopausal women (Longcope and Johnston 1988; Key et al. 1991; Thomas et al. 1993) found no differences in plasma concentrations of reproductive hormones between smokers and nonsmokers. Although the study conducted by Thomas and colleagues (1993) consisted of a small number of women (26 smokers, 24 nonsmokers), it was more detailed than other similar studies. These researchers took multiple blood samples from participants over the course of a menstrual cycle, equally timed from the date of the previous cycle, and also examined the effects of smoking on luteinizing hormone pulsatility, enabling them to explore possible differences in the length of the follicular and luteal phases between smokers and nonsmokers. Thomas and colleagues (1993) concluded that smoking did not result in major alterations in cyclicity; secretion of gonadotropins, estradiol, and progesterone; metabolism of estradiol; or secretion of androgens. They noted that these data confirm those of Longcope and Johnston (1988) and Key and colleagues (1991), suggesting that the antiestrogenic properties of cigarette smoking act through mechanisms other than alterations in hormone levels.

Several studies have examined hormone levels in postmenopausal women (Friedman et al. 1987; Trichopoulos et al. 1987a; Khaw et al. 1988; Longcope and Johnston 1988; Kabat et al. 1997). Again, some studies measured hormone levels in urine; others measured levels in plasma. None found lower levels of circulating estrogens among women who smoked compared with women who did not smoke. It is possible that a failure to detect differences in estrogen levels between smoking and nonsmoking women who are postmenopausal could be due to limitations in measurement, because estrogen levels in postmenopausal women are often at the limits of detection. Differences in postmenopausal estrogen levels between smokers and nonsmokers could be due, at least in part, to body fat levels. Smokers tend to be leaner than nonsmokers, and in postmenopausal women, an important source of estrogen is the peripheral conversion of androgen precursors that occurs in fat cells.

The interpretation of differences in estrogen levels between smokers and nonsmokers, and relating them to differences in the risk of breast cancer, is complex because the effects of specific estrogens likely vary by organ site, and smoking may affect only specific estrogens (Rohan and Baron 1989). For example, Michnovicz and colleagues (1986) proposed that smoking may shift the metabolism of estrone and estradiol toward the production of catechol estrogens. This shift would leave estrogen and estradiol concentrations unchanged, but would increase catechol estrogen production at the expense of estriol. If the breast were equally sensitive to estriol and catechol estrogens, this change would not affect breast cancer risk, although it would affect organs that react differently to estriol and catechol estrogens. The estrogenic hormone dependence of breast cancer is not well defined. It is clear, however, that the estrogen dependence of breast cancer is not as marked as that of endometrial cancer, and any antiestrogenic effects of smoking might be unimportant with respect to this weaker estrogen-related disease (Rohan and Baron 1989).

Epidemiologic Evidence

This section discusses all studies of active and passive smoking in relation to breast cancer that were considered in a 1993 epidemiologic review (Palmer and Rosenberg 1993), and any additional epidemiologic studies on this topic published from September 1992 to the end of 1999, identified through a MEDLINE search. Several additional relevant reports beyond this inclusive review are also cited. A review of the observational epidemiologic literature was then used to identify articles in the fields of biology, pathology, and endocrinology that examined the biologic basis for potential positive and negative causal links between exposure to cigarette smoking and breast carcinogenesis.

Cigarette Smoking and Breast Cancer Risk

Palmer and Rosenberg (1993) reviewed all of the studies on smoking and breast cancer published in the scientific literature before September 1992 (Tables 2.36, 2.37, 2.38, and 2.39). They excluded studies of prevalent breast cancer, studies providing insufficient methodologic detail (e.g., those lacking CIs or definitions of the reference categories [all of the studies excluded for this reason had fewer than 300 cases]), and case-control studies in which patients with smoking-related diagnoses were included in the control series. These studies, with likely overestimates of the prevalence of smoking in the general population represented by the control groups, would have found spuriously reduced RR estimates if smoking truly did increase the risk for breast cancer. For each of the 19 studies deemed

informative, Palmer and Rosenberg (1993) provided detailed qualitative summaries in the four tables in their review, noting where the data were available in individual studies, RR estimates for former and current smokers overall stratified by age at commencement of smoking, and for the highest categories of smoking intensity or duration.

In four case-control studies included in this review (Rosenberg et al. 1984; Baron et al. 1986; Stockwell and Lyman 1987; Palmer et al. 1991), controls were selected from among hospital patients or cancer registry patients, and only patients with conditions judged to be unrelated to cigarette smoking were included (Table 2.36). All of these studies were large (all had more than 1,700 cases; one [Stockwell and Lyman 1987] had more than 5,000 cases), and controlled for many of the known risk factors for breast cancer including age at menarche, age at birth of first child, and parity. Two of the four studies also controlled for alcohol consumption, obesity, menopausal status, and other potential confounding factors as they are risk factors for breast cancer and are associated with smoking (Rosenberg et al. 1984; Palmer et al. 1991). Relative risk estimates for the heaviest current smoking categories (i.e., one or more packs per day) were close to 1.0, ranging from 0.93 to 1.3. None of these four studies showed a dose-response gradient of risk with the number of cigarettes smoked per day.

In seven other case-control studies (O'Connell et al. 1987; Adami et al. 1988; Rohan and Baron 1989; Chu et al. 1990; Ewertz 1990, 1992; Palmer et al. 1991; Field et al. 1992), the general community was used as a source of controls (Table 2.37). All of these studies controlled for major reproductive risk factors; some also controlled for alcohol consumption and obesity. The estimated RR for heavy smoking was 0.57 in the smallest study (O'Connell et al. 1987); in the other studies, estimates ranged from 0.75 to 1.59, with no evidence of dose-response relationships.

Three studies of screened populations (Brinton et al. 1986; Meara et al. 1989; Schechter et al. 1989) compared women with incident cases (detected after the first screening) of breast cancer with women who were screened the same number of times without any detection of breast cancer (Table 2.38). All of the studies adjusted for reproductive risk factors and obesity, and one study (Meara et al. 1989) also adjusted for alcohol consumption. These studies generally found ORs between 1.2 and 1.3 for heavy smokers and long-term smokers, compared with women who had never smoked. Meara and colleagues (1989) found higher ORs but CIs were wide.

All five cohort studies (Table 2.39) (Hiatt and Fireman 1986; Hiatt et al. 1988; London et al. 1989; Schatzkin et al. 1989; Vatten and Kvinnsland 1990) controlled for obesity and alcohol consumption in addition to reproductive factors. Relative risk estimates for the heaviest current smoking categories ranged from 0.86 to 1.19. The largest study (London et al. 1989), which assessed repeated measures of smoking during follow-up, found that the RR comparing those currently smoking 25 or more cigarettes per day with women who had never smoked was 1.02.

Palmer and Rosenberg (1993) concluded their 1993 review by stating that the existing body of epidemiologic evidence neither supported the hypothesis that cigarette smoking has a net effect of reducing the risk of breast cancer nor supported the hypothesis that cigarette smoking increases the risk of breast cancer, even among specific subgroups of women who might be assumed to be at an especially high risk from the carcinogenic effects of smoking, such as heavy smokers who began smoking as teenagers.

Since 1993, additional large, well-designed case-control studies of smoking and breast cancer (Table 2.40) have provided detailed analyses of the amount smoked, duration of smoking, and (in two of the three studies) years since smoking cessation. The largest study (Baron et al. 1996) is a population-based, case-control study with 6,888 cases and 9,529 controls from Maine, Massachusetts, New Hampshire, and Wisconsin, conducted from 1988–1991. This study investigated the effects of smoking among women at very high levels of exposure: heavy smokers, long-term smokers, and those who began smoking very early in life. The current understanding of the processes of breast cell development and differentiation has led some scientists to hypothesize that the timing of exposure to tobacco smoke relative to the stage of breast tissue development may be an important determinant of susceptibility to the carcinogenic effects of smoking. Exposure at very young ages and before a first pregnancy may more strongly increase the risk of breast cancer than exposure at older ages, because breast cells are undifferentiated before pregnancy and are therefore believed to be more susceptible to mutagenesis.

In this large study, the number of cigarettes usually smoked per day was not related to risk for breast cancer. Very heavy smokers (those who smoked >2 packs per day) were not at a higher risk than lifetime nonsmokers; the OR was 1.09 (95 percent CI, 0.79–1.49). Duration of smoking was also unassociated with risk; among women who had smoked cigarettes for more

than 50 years compared with women who had never smoked, the OR was 1.07 (95 percent CI, 0.84–1.37). Risk of breast cancer was also not related to the duration of smoking among heavy smokers (>2 packs per day), to the average amount smoked per day among long-term smokers (>20 years), or to pack-years of smoking. There was no overall relationship between age at initiation of smoking and risk of breast cancer. Women who began smoking at an early age (before 15 years of age) were not at an increased risk compared with women who had never smoked; the OR was 1.13 (95 percent CI, 0.97–1.31). This finding was true even among women who began smoking at an early age and who usually smoked more than 20 cigarettes per day (OR = 1.04 [95 percent CI, 0.81–1.33]). No evidence was found of an effect of smoking within subgroups of the study population. The ORs for current and former smokers within high- and low-risk strata for the various covariates, including menopausal status, family history status, history of benign breast disease, and alcohol intake, were all close to 1.0. Thus, in this large population-based study, the researchers found little evidence that cigarette smoking either increases or decreases the risk for breast cancer. Neither early age at smoking initiation, heavy smoking, nor long-term smoking demonstrated an association with an altered risk. This study had several important methodologic strengths that enhanced the validity of the findings. First, the large sample size permitted estimates of the effects of higher exposures with considerable precision. Second, the population-based design of the study, together with a high response rate (>80 percent for both cases and controls), made major response biases unlikely. Finally, substantial confounding of the findings is unlikely, because the RR estimates presented by Baron and colleagues (1996) were adjusted for the main known breast cancer risk factors, with little change over those adjusted only for the matching factors of age and geographic area.

In 1998, Gammon and colleagues published results from another large population-based, case-control study of women under the age of 55 years. This study consisted of 2,199 cases and 2,009 controls surveyed during 1990–1992 from central New Jersey; Seattle, Washington; and Atlanta, Georgia. The objective was similar to that of Baron and colleagues (1996): to examine the effects of smoking on the risk for breast cancer among women at extreme exposure levels, those who were heavy smokers as teenagers or those who were long-term smokers. Similar to Baron and colleagues, Gammon and colleagues (1998) found little evidence for increased breast cancer risk associated

with smoking in their large study. Risk was significantly reduced among current smokers who reported smoking for more than 21 years (OR = 0.70 [95 percent CI, 0.52–0.94]), compared with women who had never smoked. Risk was also reduced for women who began smoking at 15 years of age and younger among both current smokers (OR = 0.59 [95 percent CI, 0.41–0.85]) and former smokers (OR = 0.76 [95 percent CI, 0.50–1.15]). Gammon and colleagues found no significant effect modification by selected hormone-related characteristics including menopausal status, oral contraceptive use, hormone replacement therapy use, body size as an adult, and usual alcohol consumption. They also found no significant heterogeneity in breast cancer risk in relation to the age at beginning smoking.

In a national case-control study of breast cancer in the United Kingdom conducted among young women aged 35 years and younger, Smith and colleagues (1994) found no effects of cigarette smoking on the risk for breast cancer. The RR comparing women who had smoked for 10 or more years with women who had never smoked was 1.0 (95 percent CI, 0.79–1.25), whereas the RR comparing women who had started smoking at 16 years of age or younger was 1.11 (95 percent CI, 0.87–1.43).

The most recent combined analyses on smoking and breast cancer were reported in 2002 by the Collaborative Group on Hormonal Factors in Breast Cancer (2002). Data were analyzed at the individual level from 53 studies, including 58,515 cases and 95,067 controls; information on both tobacco and alcohol was included in all of these studies. The analysis of the risk associated with smoking was limited to the 22,255 cases and 40,832 controls who reported drinking no alcohol. Compared with lifetime nonsmokers, the pooled RR for breast cancer was 0.99 for current smokers and 1.03 for former smokers. Only one study found a significantly increased risk (Figure 2.7).

In conclusion, hypotheses that women with higher levels of exposure to cigarette smoking (i.e., heavy smokers and those who have been smoking since an early age) would have elevated risks of breast cancer have not been supported by data from large studies. The weight of the epidemiologic evidence supports the conclusion that smoking is not associated with breast cancer risk. This null relationship is consistent with the two hypothesized mechanisms, antiestrogenic effects and carcinogenic exposures, that imply countervailing consequences of smoking that both increase and decrease the risk for breast cancer.

Genotype-Smoking Interactions

Recent advances in molecular biology and genetics, in terms of both scientific understanding of and technological applications to large populations, have enabled epidemiologists to examine the relationship between smoking and breast cancer in subgroups of women hypothesized to differ with respect to genetic susceptibility to the carcinogenic or antiestrogenic effects of cigarette smoke. Some of the genes involved in the metabolism of carcinogens play a role in the risks for various human cancers, including breast cancer, and reviews of the growing literature on these genes, known as metabolic susceptibility genes, have been published (Idle et al. 1992; Daly et al. 1994; Hirvonen 1995; Raunio et al. 1995; Rothman 1995; Vineis 1995). By definition, these genes function only in the context of interactions with the environment, because the substrates of their gene products are xenobiotic chemicals (foreign to the biologic system) or their metabolites (Garte et al. 1997).

Cigarette smoking results in exposure to aryl aromatic amine carcinogens that are metabolized and detoxified by the cytochrome P-4501A2 (*CYP1A2*) and *NAT1* and *NAT2* genes. The *NAT2* gene has four major alleles (Lin et al. 1993; Hunter et al. 1997). Persons who are homozygous for any combination of the three slow acetylator alleles have a slow acetylation phenotype (slow acetylators), whereas those who have at least one copy of the rapid acetylator allele have a rapid acetylation phenotype (rapid acetylators) (Lin et al. 1993; Hunter et al. 1997). Women who are rapid acetylators are hypothesized to be less vulnerable to potential carcinogenic effects on the breast from smoking than women who are slow acetylators, because members of the former group more rapidly metabolize or "clear" the toxic agents from their tissues. Approximately 50 percent of whites and a lower proportion of African Americans inherit a polymorphism in the *NAT2* gene that leads to decreased acetylator activity (i.e., *NAT2*-"slow" genotype) (Bell et al. 1993; Lin 1996). The *NAT1* enzyme participates in *N*-acetylation of a variety of carcinogenic arylamines, as does the *NAT2* enzyme. However, the link between *NAT1* alleles and enzyme function has not been directly established, and investigations are ongoing to determine the functional importance of *NAT1* gene variants (Deitz et al. 1997; Grant et al. 1997; Hughes et al. 1998; Millikan et al. 1998).

In a case-control study of 304 cases and 327 controls, Ambrosone and colleagues (1996) found that among premenopausal women, being a slow acetylator did not strengthen the effect of smoking on the risk for breast cancer. In fact, risk associated with smoking increased more sharply among rapid acetylators than among slow acetylators, although all ORs were imprecise. Among postmenopausal women, Ambrosone and colleagues (1996) found an association between smoking and breast cancer risk only among women with the *NAT2*-slow genotype. Among women who were slow acetylators, those in the highest category of number of cigarettes smoked per day (>20) were at an increased risk for breast cancer (OR = 4.4 [95 percent CI, 1.3–14.8]), but there were only 11 cases and 5 controls in this high-exposure stratum. The response rates among cases and controls were low, raising concerns about selection biases with regard to smoking status. These methodologic problems may explain, in part, why the finding of an interaction between smoking and slow acetylator genotype has not been replicated in subsequent larger studies. Results from a case-control study nested within the Nurses Health Study cohort with 466 incident cases and 466 matched controls (Hunter et al. 1997) suggest that current smoking was associated with a slight increase in the risk for breast cancer among women with the *NAT2* slow genotype, but this same slight increase was also observed among women with the rapid acetylator genotype. The OR comparing currently smoking women with the slow acetylator genotype to women with the rapid acetylator genotype who had never smoked was 1.4 (95 percent CI, 0.7–2.6); the OR comparing currently smoking women with the rapid acetylator genotype to women who had never smoked with this same "low risk" genotype was 1.2, thus providing no evidence of a genotype-smoking interaction.

To examine the specific hypothesis that smoking before a first pregnancy is an especially strong risk factor for breast cancer, Hunter and colleagues (1997) limited analyses to parous women with complete information on early-life smoking. Women with the rapid acetylator genotype who ever smoked before their first pregnancy were at an increased risk relative to women with the rapid acetylator genotype who had never smoked (OR = 1.7 [95 percent CI, 1.0–2.6]), but there was no dose-response relationship with the duration of smoking before a first pregnancy. Similarly, among women with the slow acetylator genotype, there was an increased risk for breast cancer among women who had smoked for one to five years before their first pregnancy (OR = 2.0 [95 percent CI, 1.1–3.8]), relative to the reference group of women with the rapid acetylator genotype who had never smoked, but the risk of breast cancer was not increased among women who had smoked for five or more years before their first pregnancy (OR = 0.9 [95 percent CI, 0.6–1.5]). Again, there

was no evidence for a genotype-smoking interaction in this analysis.

The Carolina Breast Cancer Study, a population-based case-control study of breast cancer among white and African American women living in North Carolina, found no main effect of smoking (OR = 1.0 for current smokers [95 percent CI, 0.7–1.4], and OR = 1.3 for former smokers [95 percent CI, 0.9–1.8], both relative to lifetime nonsmokers) (Millikan et al. 1998). These results were not modified by the presence of either the *NAT2* or the *NAT1* gene. Among postmenopausal women, those who had smoked within the past three years and had the *NAT1*10* genotype had an OR of 9.0 (95 percent CI, 1.9–41.8) and those with the *NAT2* rapid genotype had an OR of 2.8 (95 percent CI, 0.4–8.0) compared with nonsmokers.

Other research into potential gene-environment interactions has considered genes related to polycyclic aromatic hydrocarbons, which are carcinogens found in cigarette smoke. The *CYP1A1* gene product is involved in the metabolism of these hydrocarbons and is polymorphic, although the exact functional importance of the polymorphisms is unclear (Cosma et al. 1993; Kawajiri et al. 1993; Crofts et al. 1994; Landi et al. 1994; Wedlund et al. 1994; Jacquet et al. 1996; Zhang et al. 1996; Persson et al. 1997; Ishibe et al. 1998). Studies of potential gene-environment interactions have been small and results have been inconsistent. Ambrosone and colleagues (1995) found an interaction between smoking and the *CYP1A1* genotype only among light smokers (for whom the OR comparing the high-risk to low-risk genotype was 5.22 [95 percent CI, 1.16–23.56]); however, among heavy smokers, the high-risk genotype was not associated with an increased risk (OR = 0.86 [95 percent CI, 0.24–3.09]). This somewhat contradictory finding (that no increased risk was found in the subgroup of heavy smokers, despite an increase among light smokers) was based on a small number of cases and noncases in the relevant strata; for instance, the OR of 5.22 was based on only seven cases and three controls in the high-risk genotype stratum.

To date, the largest study of the *CYP1A1* genotype, smoking, and a risk for breast cancer was conducted among 900 women (cases and controls combined) nested within the Nurses Health Study cohort (Ishibe et al. 1998). In this study, current smokers with a high-risk variant at the *MspI* nucleotide had an OR of 7.36 (95 percent CI, 1.39–39.0) relative to lifetime nonsmokers with a low-risk variant; the corresponding OR for a variant at the exon 7 nucleotide was 1.51 (95 percent CI, 0.55–4.13). The OR of 7.36 was based on nine cases and two controls in the high-risk stratum. On the basis of the low prevalences of the

high-risk genotypes in *CYP1A1*, Ishibe and colleagues (1998) estimated that only 2.5 percent of breast cancer cases that occurred in the Nurses Health Study cohort over a five-year period could be attributed to the combination of cigarette smoking and a high-risk genotype.

The gene *GSTM1* is also involved in the metabolism of carcinogens, including polycyclic aromatic hydrocarbons (Mannervik and Danielson 1988; Nebert 1991). Ambrosone and colleagues (1995) found that the null effect of cigarette smoking was not modified by the high-risk *GSTM1* genotype.

Scientists are continuing to pursue research into how genetic factors might interact with cigarette smoking to determine a risk for breast cancer, but so far few clear patterns have emerged. Currently, it is not possible to differentiate subgroups of women who are genetically "susceptible" to the carcinogenic effects of cigarette smoking from those women who are not.

Brunet and colleagues (1998) have pursued a different line of genetic research, speculating that the antiestrogenic effects of smoking might be especially potent in women at very high risk of breast cancer; that is, those who carry mutations in the *BRCA1* or *BRCA2* gene. It has been estimated that the risk for breast cancer associated with mutations in either gene exceeds 80 percent by the time a carrier reaches 70 years of age (Easton et al. 1995; Tonin et al. 1995), although some researchers have estimated the risk to be lower (Struewing et al. 1997). Some factors that are believed to influence penetrance (i.e., frequency of expression of a genotype) include parity (Narod et al. 1995) and, with respect to the *BRCA2* gene, the position of the mutation (Gayther et al. 1997). Brunet and colleagues (1998) speculated that cigarette smoking, because of its hypothesized antiestrogenic effects, also may be associated with a lower penetrance. In their case-control study of women in Canada who were carriers of *BRCA1* or *BRCA2* gene mutations (186 cases, 186 controls), the risk of breast cancer in smokers was about half of that in nonsmokers. The reduction in risk associated with smoking was significant for a carrier of *BRCA1* mutations who had smoked the equivalent of four or more pack-years in her life (OR = 0.47 [95 percent CI, 0.26–0.86]). For *BRCA2* gene carriers the magnitude of reduction was somewhat greater (OR = 0.39 [95 percent CI, 0.10–1.49]). There was evidence of a dose-response trend: the degree of breast cancer protection associated with cigarette smoking increased with the number of pack-years smoked. The OR was 0.65 for women with four or fewer pack-years of smoking and 0.46 for those with more than four pack-years of smoking.

Contrasting findings were reported by Couch and colleagues (2001) who carried out a retrospective cohort study of women from high-risk breast cancer families. Of the sisters and daughters in the families, those who had smoked had an increased risk of breast cancer compared with those who had never smoked (RR = 2.4 [95 percent CI, 1.2–5.1]). These studies differ substantially in design, and the case-control approach of Brunet and colleagues (1998) is subject to several potential sources of bias (Baron and Haile 1998).

Passive Smoking, Active Smoking, and Breast Cancer Risk

The involuntary inhalation of tobacco smoke by nonsmokers has also been examined as a risk factor for breast cancer. Exposure to secondhand smoke and breast cancer risk has been considered relevant to understanding active smoking and breast cancer risk because passive exposure involves a lower dose of the same agents inhaled by the active smoker. The literature on passive smoking and breast cancer was reviewed in the 2001 Surgeon General's report with the conclusion that "the totality of the evidence does not support an association between smoking and the risk for breast cancer" (USDHHS 2001, p. 13). Recently, epidemiologists have also investigated the relationship between active and passive exposures to cigarette smoke and breast cancer, and attempted to use a truly "unexposed" reference group; that is, women who have been neither active smokers nor exposed passively to another's cigarette smoke. According to some researchers (Morabia et al. 1996), only by comparison with such a truly unexposed group will the effects of active smoking be assessed without bias.

The studies of passive smoking and breast cancer contrast somewhat with the findings of the far larger number of studies of active smoking that are consistent in showing no relationship of active smoking with breast cancer. Morabia and colleagues (1996) hypothesized that this apparent contradiction stemmed from the failure of most studies to separate passive smokers from the "unexposed" reference group when assessing the effects of active smoking. They tested this hypothesis in a population-based, case-control study conducted among women living in Geneva, Switzerland. The researchers obtained a detailed lifetime history of exposure to active and passive smoking from all participants, and defined their unexposed reference group as those women never regularly exposed to either passive or active smoking. Passive smokers were women who reported having been exposed to secondhand smoke at least one hour per day for at least 12 consecutive months during their lifetime.

The study included 244 cases and 1,032 controls, with 126 cases and 620 controls who were never active smokers. Among these never active smokers, only 28 cases and 241 controls were also never passive smokers, forming the referent "unexposed" group. The ORs comparing ever active smokers with the referent group were 2.2 for smoking an average of 1 to 9 cigarettes per day, 2.7 for 10 to 19 cigarettes per day, and 4.6 for 20 or more cigarettes per day. Among current active smokers the dose-response trend was even stronger. The ORs did not vary in magnitude when women were stratified according to whether they began smoking before or after their first pregnancy. To examine the effect of removing passive smokers from the reference group, Morabia and colleagues (1996) computed the ORs after considering all never active smokers (including those exposed to secondhand smoke) as the reference group, as in most other studies. The ORs corresponding to the three categories of active smoking given above were reduced in magnitude from 2.2, 2.7, and 4.6 to 1.2, 1.7, and 1.9, respectively. Using this same reference group, Morabia and colleagues (1996) also found an association of breast cancer risk with passive smoking.

A caution that must be raised in reference to this study relates to potential confounding. In this study of women living in Geneva, Switzerland, those with a higher formal education smoked more than women with lower educational levels, unlike the situation in the United States where the prevalence of smoking is now higher in lower socioeconomic groups. Women of a higher socioeconomic status tend to have higher risks for breast cancer because of a higher prevalence of reproductive risk factors (e.g., later age at first birth and lower parity). Thus the findings of elevated risks associated with active and passive smoking in this study of Swiss women could be confounded, in part, by the known reproductive risk factors. Although Morabia and colleagues (1996) controlled for some of these known factors (e.g., age at menarche and at first live birth), as well as for family history of breast cancer, body mass index, and alcohol consumption, there may have been residual confounding because of the control for factors in relatively crude categories and the omission of some factors from the model (e.g., parity, postmenopausal hormone use, and age at menopause). Failure to fully adjust for the higher risks associated with a higher socioeconomic status in this study could explain, in part, the relatively high ORs comparing active smokers and the unexposed control group.

Cigarette Smoking and Breast Cancer Hormone Receptor Status

It is not yet clear if breast cancers with a different hormone receptor status represent etiologically distinct forms of the disease with different risk factor profiles. Researchers have hypothesized that breast cancer tumors that have both estrogen and progesterone receptors (ER-positive/PR-positive) are most closely related to risk factors that are likely mediated by endogenous hormones, whereas tumors without these receptors (ER-negative/PR-negative) would be unrelated to these risk factors (Kelsey et al. 1993; Potter et al. 1995). Receptor status-discordant tumors might exhibit intermediate risk factor profiles. It is not clear from this hypothesis, however, whether smoking, because of its antiestrogenic properties, should decrease the risk of ER-positive/PR-positive tumors, increase the risk of ER-negative/PR-negative tumors, or do both. Findings have been inconsistent.

Several studies have examined whether smoking increases the risk of breast cancers with a particular ER status. A case-control study of Japanese women (1,154 cases, 21,714 controls) found a slightly elevated OR for all breast cancers combined associated with ever smoking (Yoo et al. 1997). This OR elevation was confined to PR-positive tumors (OR = 1.73 [95 percent CI, 1.22–2.45]) and was not observed in PR-negative tumors (OR = 1.06 [95 percent CI, 0.73–1.54]). In this study, there was no difference in estrogen receptor status (OR = 1.42 for ER-positive tumors, 1.33 for ER-negative tumors). However, estrogen receptor status was known for only 40 percent of the cases, and progesterone receptor status was known for only 39 percent of the cases.

In a cohort study reported by London and colleagues (1989), heavy smoking was associated with a small increase in the risk of ER-positive tumors (OR = 1.38 [95 percent CI, 1.04–1.84]). Smoking was not associated with either ER-positive or ER-negative tumors in a case-control analysis by McTiernan and colleagues (1986). In another study, researchers found an increased risk of ER-negative tumors among smokers (Cooper et al. 1989).

Each of the above-cited studies examined active smoking in relation to ER status, without removing passive smokers from the reference group (of lifetime nonsmokers). Morabia and colleagues (1998b) examined the relationship between passive smoking, active smoking, and ER status in their previously described case-control study of women in Geneva, Switzerland, again using a reference group of never active, never passive smokers. They divided smokers into three

mutually exclusive categories: ever passive, ever active with fewer than 20 cigarettes per day on average, and ever active with 20 or more cigarettes per day on average. They found elevated ORs for both ER-negative and ER-positive tumors in each of the three smoking categories, relative to the reference group. The ORs were slightly higher for the ER-negative tumors, but the numbers of ER-negative cases in the various smoking strata were small, and thus the ORs were imprecise.

Cigarette Smoking and Breast Cancer Mortality

All of the previously discussed studies have examined the relationship between cigarette smoking and breast cancer incidence. Calle and colleagues (1994) examined smoking as a predictor of breast cancer mortality in CPS-II. During the six-year follow-up period, these researchers found that women who were current smokers at baseline were more likely to die of breast cancer than lifetime nonsmokers (RR = 1.26 [95 percent CI, 1.05–1.50]), whereas former smokers were slightly less likely to die of breast cancer than lifetime nonsmokers (RR = 0.85 [95 percent CI, 0.70–1.03]). The association of current smoking with risk for fatal breast cancer increased with a greater number of cigarettes smoked per day, as well as with the total number of years of smoking. The ORs for 1 to 9, 10 to 19, 20 to 29, 30 to 39, and 40 or more cigarettes smoked per day were 0.58, 1.19, 1.32, 1.44, and 1.74, respectively, all relative to lifetime nonsmokers. The ORs for breast cancer mortality for less than 10, 10 to 19, 20 to 29, 30 to 39, and 40 or more years of smoking were 1.10, 1.04, 1.10, 1.26, and 1.38, respectively, again all relative to lifetime nonsmokers.

Because the weight of the epidemiologic evidence does not support a strong etiologic relationship between smoking and breast cancer incidence, these findings on breast cancer mortality likely reflect a poorer survival experience among smokers who develop breast cancer, which might be expected for several reasons. First, smokers are more likely than nonsmokers to have comorbid conditions, such as respiratory and cardiovascular diseases, that could deleteriously affect survival. Second, smokers do not seek a screening mammography as often as nonsmokers, and therefore their disease might tend to be diagnosed at later stages. Data from the 1987 National Health Interview Survey Cancer Control Supplement indicate that current smokers are less likely than lifetime nonsmokers to receive screening mammograms and that the screening disadvantage is greatest among heavy smokers. In contrast, former smokers are more likely to receive

mammograms than lifetime nonsmokers (Calle et al. 1994). These differences in screening behavior support the possibility that the results observed by Calle and colleagues (1994) are due in part to later diagnoses among current, and especially heavy, smokers and to earlier diagnoses among former smokers.

Evidence Synthesis

Since the 1960s many large, well-conducted studies of the relationship between active cigarette smoking and breast cancer have been completed, as have laboratory studies of the relationship between smoking and ovarian hormone levels. The epidemiologic evidence provides no support for an overall relationship, neither causal nor protective, between active cigarette smoking and breast cancer. The studies have been conducted in diverse populations around the world and involved thousands of participants.

Evidence for an increased susceptibility to the carcinogenic effects of cigarette smoking on the breast in subgroups of women (e.g., defined by genotype, menopausal status, age at starting smoking) has been inconsistent. The inconsistency in RRs for subgroup analyses among the various studies is not surprising given the small numbers of women in the relevant strata of many of these analyses. For some subgroups, an initial finding from one study regarding an elevated risk in a particular subgroup of women (e.g., Ambrosone and colleagues' 1996 report of a strong positive relationship between smoking and breast cancer among women with the slow acetylator *NAT* genotype) has not been replicated in subsequent studies. Similarly, Brunet and colleagues (1998) observed that women with mutations in *BRCA1* or *BRCA2* genes who smoked had a significantly lower risk of breast cancer than women with such mutations who did not smoke, but this observation was not replicated in the study conducted by Couch and colleagues (2001).

In light of the evidence showing no overall association between active smoking and breast cancer, passive smoking would also be expected not to be associated with breast cancer risks, assuming that the same mechanisms apply to both active and passive smoking. Although most studies of smoking and breast cancer did not remove passive-only smokers from the reference group of lifetime nonsmokers (Morabia and colleagues [1996] were the first to do so), one would still expect to find a dose-response gradient in analyses of active smoking because active smokers are also

the most heavily exposed passive smokers. The hypothesis put forth by Morabia and colleagues (1996, 1998a) and Wells (1991, 1998), that the true (positive) relationship between active smoking and breast cancer will become apparent only when passive-only smokers are removed from the reference group, implicitly assumes that the effects of passive-only smoking are at least as great as those from active smoking. Consider a hypothetical, but realistic, study that shows a RR of 1.0 comparing current smokers who have smoked for 10 or more years and the reference group of never active smokers. If the argument is made that the "true" RR is 2.0, and that it will not become apparent unless passive-only smokers are removed from the reference group, then there is an assumption that the RR of current smokers who have smoked 10 or more years compared with passive-only smokers is 1.0, or, equivalently, that the risk conveyed by passive smoking alone is equal to that conveyed by long-term active smoking. This comparability of risks seems implausible on a biologic basis.

Conclusions

1. The evidence is suggestive of no causal relationship between active smoking and breast cancer.

2. Subgroups of women cannot yet be reliably identified who are at an increased risk of breast cancer because of smoking, compared with the general population of women.

3. Whether women who are at a very high risk of breast cancer because of mutations in *BRCA1* or *BRCA2* genes can lower their risks by smoking has not been established.

Implications

In contrast to evidence for many other chronic diseases, epidemiologic evidence suggests that cigarette smoking does not contribute to the burden of breast cancer. It would be false to tell women that they will prevent breast cancer if they quit smoking. Similarly, no woman should ever be advised to smoke to lower her breast cancer risk, given the lack of evidence and the extremely high health risks for other diseases known to be associated with smoking.

Figure 2.7   Results on tobacco consumption and breast cancer in women who reported drinking no alcohol

Study (country)	Number of cases/controls	% ever smoked (cases/controls)	Relative risk of breast cancer in ever smokers vs. never smokers (SE)*	Relative risk and 99% CI[†] of breast cancer in ever smokers vs. never smokers
Cohort studies:				
Willett et al. 1987 (USA)	1,224/5,599	49/49	1.01 (0.07)	
Friedenreich et al. 1993 (Canada)	181/662	35/35	1.25 (0.23)	
Feigelson et al. 2001 (USA)	213/922	34/33	1.07 (0.19)	
van den Brandt et al. 1995 (Netherlands)	119/504	27/30	0.89 (0.23)	
Gapstur et al. 1992 (USA)	679/2,765	25/26	0.93 (0.10)	
Million Women Study Collaborative Group 1999 (UK)	324/1,291	50/44	1.24 (0.15)	
Other[‡]	1,923/7,655	4/5	0.78 (0.12)	
All cohort studies	**4,663/19,398**	**25/26**	**1.00 (0.04)**	
Case-control, population controls:				
Harvey et al. 1987 (USA)	649/872	29/26	1.12 (0.14)	
Chu et al. 1989 (USA)	1,817/1,821	49/43	1.28 (0.08)	
Enger et al. 1999 (USA)	336/317	50/48	1.18 (0.20)	
Siskind et al. 1989 (Australia)	248/514	32/29	1.31 (0.26)	
Rohan and McMichael 1988 (Australia)	188/213	35/32	1.06 (0.31)	
Ewertz 1991 (Denmark)	227/198	59/57	0.88 (0.27)	
Bowlin et al. 1997 (USA)	153/208	37/34	0.99 (0.32)	
Rosenberg et al. 1990 (Canada)	114/211	40/42	0.88 (0.31)	
Sneyd et al. 1991 (New Zealand)	538/1,058	43/41	1.09 (0.13)	
White et al. 1994 (USA)	211/286	42/42	0.87 (0.21)	
Longnecker et al. 1995b (USA)	578/590	53/52	1.02 (0.13)	
Smith et al. 1994 (UK)	655/662	47/45	1.08 (0.13)	
Longnecker et al. 1995a (USA)	1,507/2,247	39/39	1.07 (0.09)	
Rookus and van Leeuwen 1994 (Netherlands)	247/247	52/51	0.90 (0.21)	
Yang et al. 1992 (Canada)	505/517	48/44	1.15 (0.17)	
Primic-Zakelj et al. 1995 (Slovenia)	115/128	29/30	0.67 (0.38)	
Rossing et al. 1996 (USA)	152/181	52/49	0.79 (0.26)	
Swanson et al. 1997 (USA)	353/241	59/68	0.63 (0.21)	
Magnusson et al. 1999 (Sweden)	1,311/1,312	32/33	0.91 (0.08)	
McCredie et al. 1998; Hopper et al. 1999 (Australia)	774/518	38/36	1.03 (0.15)	
Kropp et al. 2001 (Germany)	168/251	46/52	0.94 (0.25)	
Johnson et al. 2000 (Canada)	974/1,110	42/40	1.14 (0.11)	
Other[§]	2,851/3,567	11/13	0.99 (0.12)	
All case-control, population controls	**14,671/17,269**	**36/35**	**1.07 (0.03)**	
Case-control, hospital controls				
Meara et al. 1989 (UK)	154/171	44/53	0.71 (0.30)	
La Vecchia et al. 1987; Ferraroni et al. 1998 (Italy)	831/1,025	31/31	1.01 (0.12)	
(France)	492/923	18/24	0.82 (0.16)	
La Vecchia et al. 1989 (Italy)	980/1,034	28/30	0.82 (0.10)	
Katsouyanni et al. 1994 (Greece)	219/462	21/24	1.28 (0.29)	
Other[¶]	245/550	20/26	0.72 (0.25)	
All case-control, hospital controls	**2,921/4,165**	**27/29**	**0.89 (0.06)**	
All studies	**22,255/40,832**	**33/30**	**1.03 (0.02)**	

0   0.5   1.0   1.5   2.0

*SE = Standard error.
[†]CI = Confidence interval.
[‡]Hiatt and Bawol 1984; Mills et al. 1989b; Land et al. 1994; Thomas et al. 1997.
[§]Lee et al. 1987; Adami et al. 1988; Yuan et al. 1988; Ursin et al. 1992; Wang et al. 1992; Morabia et al. 1996; Viladiu et al. 1996; Gao et al. 2000.
 Le et al. 1986; Richardson et al. 1989; Clavel-Chapelon et al. 1997.
[¶]Ferraroni et al. 1993; Levi et al. 1996.
Source: Collaborative Group on Hormonal Factors in Breast Cancer 2002. Reprinted with permission.

Table 2.36 **Case-control studies on the association between smoking and the risk of breast cancer that used hospital or cancer registry controls**

Study	Population	Cases	Controls
Rosenberg et al. 1984	Hospital patients in the United States, mostly from the northeast 1976–1982	2,160	717; cancers of the ovary, colon, rectum, and lymphoreticular system; malignant melanoma
Baron et al. 1986	Hospital patients in New York 1957–1965	1,741	2,118; nonmalignant conditions, excluding diseases of the respiratory or circulatory system
Stockwell and Lyman 1987	Florida cancer registry 1981	5,246	3,921; cancers (colorectal and endocrine; malignant melanoma)
Palmer et al. 1991	Hospital patients in northeastern United States 1982–1986	1,955	805; cancers (colorectal, bone, and connective tissue; malignant melanoma; lymphoma)

*RR = Relative risk.
†CI = Confidence interval.
‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
§BMI = Body mass index.

Measure of cigarette smoking	RR* (95% CI†) compared with never smokers		Comments
Former smokers	1.1	(0.8–1.3)	Controlled for geography, age, education, age at menarche, age at first pregnancy, parity, BMI§, alcohol intake, oral contraceptive use, estrogen use, benign breast disease, and family history
Current smokers	1.1	(0.9–1.3)	
1–14 cigarettes/day	1.3	(0.9–1.8)	
15–24 cigarettes/day	1.0	(0.8–1.4)	
25 cigarettes/day	1.1	(0.8–1.6)	
1–14 pack-years‡	0.91	(0.75–1.10)	Controlled for age, marital status, number of pregnancies, and BMI
15 pack-years	0.93	(0.76–1.13)	
Former smokers	1.0	(0.8–1.1)	Controlled for age, race, and marital status
Current smokers			
<20 cigarettes/day	1.3	(1.1–1.5)	
20–40 cigarettes/day	1.2	(1.0–1.5)	
>40 cigarettes/day	1.3	(1.0–1.8)	
Former smokers	1.1	(0.9–1.4)	Controlled for age, age at menopause, age at menarche, age at first birth, parity, family history, benign breast disease, oral contraceptive use, education, alcohol intake, and BMI
Current smokers	1.3	(1.1–1.6)	
25 cigarettes/day	1.2	(0.9–1.8)	
Age started			
<16 years	1.8	(1.0–3.4)	

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.37   Case-control studies on the association between smoking and the risk of breast cancer that used healthy controls drawn from population sources

Study	Population	Cases	Controls
O'Connell et al. 1987	North Carolina hospital patients 1977–1978	276	1,519 from community
Adami et al. 1988	Swedish cancer registry Aged <45 years only 1984–1985	422	527 from population register
Rohan and Baron 1989	Australian cancer registry 1982–1984	451	451 from electoral rolls
Chu et al. 1990	Cancer and Steroid Hormone Study U.S. cancer registries 1980–1982	4,720	4,682 from random-digit telephone dialing
Ewertz 1990	Denmark Population-based 1983–1984	1,480	1,332 from age-stratified population sample
Palmer et al. 1991	Canada Cases from tertiary care hospital 1982–1986	607	1,214 from neighbors matched for age
Field et al. 1992	New York state Population-based 1982–1984	1,617	1,617 from driver's license lists

*RR = Relative risk.

†CI = Confidence interval.

‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

§Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

 BMI = Body mass index.

Measure of cigarette smoking	RR* (95% CI†) compared with never smokers	Comments
Former smokers	1.16 (0.80–1.69)	Controlled for age, race, oral contraceptive use, estrogen use, and alcohol intake
Current smokers		
1–20 cigarettes/day	0.75 (0.52–1.09)	
>20 cigarettes/day	0.57 (0.30–1.08)	
20 cigarettes/day	1.1 (0.7–1.8)	Controlled for age, age at menarche, age
20 years' duration	1.2 (0.8–1.7)	at first pregnancy, menopause, education,
Age started		benign breast disease, family history, oral
<15 years	1.3 (0.7–2.5)	contraceptive use, and alcohol intake
Former smokers	1.04 (0.73–1.48)	Controlled for family history, menopausal
Current smokers	1.37 (0.95–1.96)	status, BMI , alcohol intake, benign
1–15 cigarettes/day	1.15 (0.72–1.86)	breast disease, and the practice of self-
>15 cigarettes/day	1.59 (0.99–2.57)	examination
Ever smokers	1.2 (1.1–1.3)	Controlled for age, reproductive factors,
Former smokers	1.1 (1.0–1.3)	family history, benign breast disease, and
Current smokers	1.2 (1.1–1.3)	estrogen replacement therapy
25 cigarettes/day	1.2 (1.1–1.4)	
40 pack-years‡	1.1 (0.9–1.4)	
Age started		
<17 years	1.1 (1.0–1.2)	
Former smokers	0.98 (0.80–1.24)	Controlled for age and place of residence
Current smokers	0.93 (0.78–1.10)	
500 cigarette-years§	0.91 (0.69–1.18)	
20 cigarettes/day	0.75 (0.56–1.00)	
Age started		
<15 years	0.87 (0.42–1.77)	
Former smokers	1.0 (0.7–1.3)	Controlled for age, age at menopause, age
Current smokers	1.1 (0.9–1.4)	at menarche, age at first birth, family
25 cigarettes/day	1.2 (0.9–1.6)	history, benign breast disease, BMI, oral
Age started		contraceptive use, education, and alcohol
<16 years	1.7 (1.0–2.9)	intake
Ever smokers	1.03 (0.9–1.19)	Controlled for birth year, race, menopausal
>2 packs/day	1.16 (0.68–1.96)	status, age at first birth, family history of
40 years' duration	1.04 (0.84–1.29)	breast cancer, and alcohol intake
40 pack-years	1.05 (0.81–1.35)	
Age started		
<14 years	1.15 (0.51–2.61)	

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.38 Case-control studies on the association between smoking and the risk of breast cancer conducted among screening program participants

Study	Population	Cases	Controls	Measure of cigarette smoking	RR* (95% CI[†]) compared with never smokers

Brinton et al. 1986	U.S. screening program 1977–1980	1,547	1,930	Ever smokers
				Current smokers
				Former smokers
				  40 years' smoking
				  40 cigarettes/day
				Age started
				  <17 years
					1.20 (1.0–1.4)
					1.18 (0.9–1.4)
					1.24 (1.0–1.5)
					1.26 (0.9–1.7)
					1.15 (0.8–1.6)
					
					1.30 (1.0–1.6)

Meara et al. 1989	Edinburgh (UK) screening program	118	118	Former smokers
				Current smokers
				  1–14 cigarettes/day
				  15 cigarettes/day
					0.99 (0.42–2.33)
					
					1.75 (0.65–4.72)
					2.90 (1.16–7.25)

Schechter et al. 1989	Canadian screening program 1981–1987	317	951	Ever smokers >500 cigarette-years[‡]	1.1 (0.9–1.6) 1.2 (0.9–1.9)

*RR = Relative risk.
[†]CI = Confidence interval.
[‡]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Comments

Controlled for age; results were unchanged after adjusting for body mass index (BMI), age at menarche, age at first birth, family history, benign breast biopsies, and exogenous hormone use

Controlled for age, menopausal status, age at first pregnancy, age at menarche, family history, oral contraceptive use, BMI, alcohol intake, and socioeconomic status

Controlled for age, age at menarche, age at first birth, parity, age at menopause, family history, benign breast disease, oral contraceptive use, estrogen use, height, weight, ethnicity, breast self-examination, mammograms, education, and marital status

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.39   Cohort studies on the association between smoking and the risk of breast cancer

Study	Population	Cases	Measure of cigarette smoking	RR* (95% CI[†]) compared with never smokers

Hiatt and Fireman 1986	California health plan members; 84,172 women aged 20–84 years, followed for 8–16 years	1,363	Former smokers
			Current smokers
			  1–2 packs/day
			  >2 packs/day
				1.21 (1.02–1.42)
				
				1.22 (1.05–1.43)
				1.19 (0.88–1.60)

Hiatt et al. 1988	California health plan members; 68,674 women examined 1978–1984, followed for up to 6 years	303	Former smokers Current smokers 2 packs/day	0.65 (0.47–0.89) 1.15 (0.47–2.83)

London et al. 1989	Nurses Health Study participants; 117,557 enrolled in 1976, aged 30–55 years, followed for 10 years	1,788	Former smokers
			Current smokers
			  15–24 cigarettes/day
			  25 cigarettes/day
			Age started
			  <17 years
				1.08 (0.96–1.20)
				
				0.99 (0.85–1.15)
				1.02 (0.86–1.22)
				
				1.07 (0.91–1.25)

Schatzkin et al. 1989	Framingham Heart Study; 2,636 women aged 31–64 years, followed for up to 32 years	143	10–19 cigarettes/day 20 cigarettes/day	1.1 (0.7–2.0) 1.0 (0.6–1.7)
Vatten and Kvinnsland 1990	Residents of 3 counties in Norway; 24,329 women followed for 11–14 years; aged 35–51 years at the beginning of this study	242	Current smokers of >10 cigarettes/day vs. former smokers and never smokers	0.86 (0.62–1.19)

*RR = Relative risk.
[†]CI = Confidence interval.

Comments

Controlled for age, race, education, age at menarche, parity, marital status, body mass index (BMI), and alcohol intake; results were unchanged when age at menopause was controlled

Controlled for age, race, BMI, and alcohol intake

Controlled for age, age at first birth, parity, menopausal status, age at menarche, family history, oral contraceptive use, benign breast disease, alcohol intake, and BMI

Controlled for age, parity, menopausal status, education, BMI, height, and alcohol intake

Controlled for age, occupation, and BMI; reference category included former smokers

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.40   Large case-control studies on the association between smoking and the risk of breast cancer published after 1993

| Study | Total number of cases and controls | OR* compared with never smokers (adjusted) | | | | | |
| | | Ever smokers | | Current smokers | | Former smokers | |
		OR	95% CI[†]	OR	95% CI	OR	95% CI
Smith et al. 1994	755/755	1.01	0.81–1.26	NR[‡]	NR	NR	NR
Baron et al. 1996	6,888/9,529	NR	NR	1.0	0.92–1.09	1.10	1.01–1.19
Gammon et al. 1998	2,199/2,009	NR	NR	0.82	0.67–1.01	0.99	0.81–1.21

*OR = Odds ratio.
[†]CI = Confidence interval.
[‡]NR = Data were not reported.

OR compared with never smokers (adjusted)								
Number of years of smoking			Cigarettes per day			Number of years since quitting		
Years	OR	95% CI	Amount smoked	OR	95% CI	Years	OR	95% CI
1–9	1.09	0.80–1.47	15	0.96	0.76–1.23	NR	NR	NR
10	1.00	0.79–1.25	16	1.16	0.89–1.50	NR	NR	NR
10	0.96	0.83–1.10	10	1.04	0.95–1.14	3	1.39	1.14–1.68
11–20	1.02	0.90–1.15	11–20	1.07	0.98–1.17	4–10	1.23	1.08–1.40
21–30	1.12	1.00–1.25	21–30	1.06	0.90–1.24	11–20	1.08	0.95–1.20
31–40	1.12	1.00–1.25	31–40	1.04	0.87–1.24	21–30	0.94	0.81–1.10
41–50	1.01	0.89–1.15	>40	1.09	0.79–1.49	>30	0.92	0.75–1.12
>50	1.07	0.84–1.37	NR	NR	NR	NR	NR	NR
Current Smokers			Current Smokers					
8	0.63	0.34–1.15	<10	0.69	0.47–1.02	NR	NR	NR
9–14	0.98	0.68–1.41	10–19	0.91	0.65–1.28	NR	NR	NR
15–21	0.92	0.68–1.23	20	0.78	0.58–1.04	NR	NR	NR
>21	0.70	0.52–0.94	>20	0.95	0.66–1.38	NR	NR	NR
Former Smokers			Former Smokers					
8	0.98	0.76–1.28	<10	0.96	0.70–1.31	0.5–5	1.02	0.73–1.43
9–14	0.98	0.71–1.35	10–19	1.21	0.84–1.74	6–10	0.95	0.67–1.34
15–21	0.91	0.57–1.44	20	0.84	0.61–1.16	11–15	1.01	0.70–1.44
>21	1.27	0.58–2.77	>20	1.05	0.66–1.68	>15	0.97	0.67–1.40

Summary

A systematic review of new epidemiologic evidence adds new inferences for a causal relationship between smoking and a number of cancers. This report draws several new conclusions. Specifically, it concludes that evidence is sufficient to infer a causal relationship between smoking and cancers of the cervix, kidneys, pancreas, and stomach. Also, it infers a causal relationship between smoking and acute myeloid leukemia. Although there is evidence that smoking is not related to the risk of developing prostate cancer, this report also concludes that it is probable that smoking contributes to a higher mortality rate from prostate cancer. Finally, this report concludes that active smoking is not causally related to breast cancer.

Conclusions

Lung Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and lung cancer.

2. Smoking causes genetic changes in cells of the lung that ultimately lead to the development of lung cancer.

3. Although characteristics of cigarettes have changed during the last 50 years and yields of tar and nicotine have declined substantially, as assessed by the Federal Trade Commission's test protocol, the risk of lung cancer in smokers has not declined.

4. Adenocarcinoma has now become the most common type of lung cancer in smokers. The basis for this shift is unclear but may reflect changes in the carcinogens in cigarette smoke.

5. Even after many years of not smoking, the risk of lung cancer in former smokers remains higher than in persons who have never smoked.

6. Lung cancer incidence and mortality rates in men are now declining, reflecting past patterns of cigarette use, while rates in women are still rising.

Laryngeal Cancer

7. The evidence is sufficient to infer a causal relationship between smoking and cancer of the larynx.

8. Together, smoking and alcohol cause most cases of laryngeal cancer in the United States.

Oral Cavity and Pharyngeal Cancers

9. The evidence is sufficient to infer a causal relationship between smoking and cancers of the oral cavity and pharynx.

Esophageal Cancer

10. The evidence is sufficient to infer a causal relationship between smoking and cancers of the esophagus.

11. The evidence is sufficient to infer a causal relationship between smoking and both squamous cell carcinoma and adenocarcinoma of the esophagus.

Pancreatic Cancer

12. The evidence is sufficient to infer a causal relationship between smoking and pancreatic cancer.

Bladder and Kidney Cancers

13. The evidence is sufficient to infer a causal relationship between smoking and renal cell, renal pelvis, and bladder cancers.

Cervical Cancer

14. The evidence is sufficient to infer a causal relationship between smoking and cervical cancer.

Ovarian Cancer

15. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and ovarian cancer.

Endometrial Cancer

16. The evidence is sufficient to infer that current smoking reduces the risk of endometrial cancer in postmenopausal women.

Stomach Cancer

17. The evidence is sufficient to infer a causal relationship between smoking and gastric cancers.

18. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and noncardia gastric cancers, in particular by modifying the persistence and/or the pathogenicity of *Helicobacter pylori* infections.

Colorectal Cancer

19. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Prostate Cancer

20. The evidence is suggestive of no causal relationship between smoking and risk for prostate cancer.

21. The evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers.

Acute Leukemia

22. The evidence is sufficient to infer a causal relationship between smoking and acute myeloid leukemia.

23. The risk for acute myeloid leukemia increases with the number of cigarettes smoked and with duration of smoking.

Liver Cancer

24. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer.

Adult Brain Cancer

25. The evidence is suggestive of no causal relationship between smoking cigarettes and brain cancer in men and women.

Breast Cancer

26. The evidence is suggestive of no causal relationship between active smoking and breast cancer.

27. Subgroups of women cannot yet be reliably identified who are at an increased risk of breast cancer because of smoking, compared with the general population of women.

28. Whether women who are at a very high risk of breast cancer because of mutations in *BRCA1* or *BRCA2* genes can lower their risks by smoking has not been established.

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Chapter 3
Cardiovascular Diseases

Introduction

Heart disease and stroke—the main types of cardiovascular disease caused by smoking—are the first and third leading causes of death in the United States, respectively (American Heart Association [AHA] 2002; Anderson 2002). More than 61 million people in the United States suffer from some form of cardiovascular disease (CVD), including high blood pressure, coronary heart disease (CHD), stroke, congestive heart failure (CHF), and other conditions. Nearly 950,000 Americans die each year as a result of CVD, accounting for 39.4 percent of all deaths in 2000 (AHA 2002). This chapter reviews the evidence on the relationship between smoking and CVD. In particular, it examines the associations between smoking and subclinical atherosclerosis, CHD and sudden death, stroke, and abdominal aortic aneurysm (AAA).

Conclusions of Previous Surgeon General's Reports

One of the first topics addressed in the Surgeon General's reports was smoking and CVD, although the 1964 report focused primarily on the relationships between smoking and respiratory diseases, including cancer and chronic lung diseases (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). The report noted that male cigarette smokers had higher death rates from CHD than nonsmoking males. In 1967, the second Surgeon General's report on smoking concluded that the evidence "strongly suggests that cigarette smoking can cause death from coronary artery disease" (USDHEW 1967, p. 27). With a growing number of studies addressing other cardiovascular endpoints, the 1971 and 1974 reports highlighted the associations between smoking and peripheral vascular disease, aortic atherosclerosis, and cerebrovascular disease, including stroke (USDHEW 1971, 1974). The 1979 report concluded that smoking was not only one of the main risk factors for CHD (nonfatal and fatal myocardial infarctions [MIs] and sudden death), but was a causal factor supported by evidence considered to be proved beyond a "reasonable doubt" (USDHEW 1979, p. 4-63). In addition, that report presented evidence of strong associations with morbidity from peripheral vascular disease and aortic aneurysms. In contrast, the association between smoking and stroke was considered "not conclusive" (USDHEW 1979, p. 1-14).

Subsequent Surgeon General's reports reviewed the evidence linking cigarette smoking to CHD. The conclusions in the 1983 Surgeon General's report reaffirmed that cigarette smoking is one of the major independent causes of CHD and, given the prevalence of smoking, "should be considered the most important of the known modifiable risk factors for coronary heart disease" (U.S. Department of Health and Human Services [USDHHS] 1983, p. iv). The evidence considered included a large number of epidemiologic, clinical, and experimental studies carried out with a variety of methods and research designs. Until the 1980s, though, there had been limited evidence related to the reduction of risk after maintained cessation. In an extensive review of updated data on the benefits to cardiovascular health from smoking cessation, the 1990 Surgeon General's report found that "smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking" (USDHHS 1990, p. 11). Other conclusions from that report include the following:

> The excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked.

> Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies, this reduction in risk of recurrence or premature death has been 50 percent or more.

Smoking cessation substantially reduces the risk of peripheral artery occlusive disease compared with continued smoking.

Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival (USDHHS 1990, p. 260).

The 1998 Surgeon General's report focused on the impact of smoking in ethnic and racial minority populations in the United States (USDHHS 1998) and concluded that even though more data would be helpful, existing data indicated that the association of tobacco use with CHD did not differ between whites and four major racial and ethnic minority groups. A similar conclusion was reached for women in the 2001 Surgeon General's report on women and smoking (USDHHS 2001).

This chapter is not an exhaustive review of the now vast literature on tobacco smoking and heart and vascular disease, although it does include an update of recent clinical and epidemiologic studies on the subject. The primary focus, however, is a review of the evidence relevant to smoking and subclinical measures of atherosclerosis, including what is understood about the role of smoking in the pathophysiologic processes that cause atherosclerosis and its clinical manifestations (i.e., CVD syndromes including coronary artery disease, AAA, peripheral vascular disease, and stroke). These advances in understanding of pathogenesis deepen the understanding of smoking as a cause of CVD.

Search strategies for this chapter included reviewing previous Surgeon General's reports on smoking, publications originating from the largest observational studies on CVD, and reference lists from important publications; consulting with content experts; and conducting focused literature searches on specific topics including the new literature on subclinical measures.

Biologic Basis

When the association between cigarette smoking and CVD was first identified in epidemiologic studies, the underlying biologic mechanisms were not yet well understood. The injury hypothesis of atherosclerosis, formally proposed in the mid-1970s (Ross and Glomset 1976a,b), provided a framework for considering the atherosclerotic effects of smoking, even though the specific tobacco components and the precise mechanisms for the injury to the endothelium (the inner cellular layer of the arterial wall) were unknown. During the 1990s, research further clarified the pathophysiology of the atherosclerotic effects of cigarette smoking. In addition, in the last three decades a large body of evidence has accumulated, demonstrating that smoking increases the risk for thrombosis (USDHHS 1990; Meade et al. 1993; Miller et al. 1998). This evidence provides an additional framework for understanding the pathophysiologic effects of smoking on the basic underlying processes of CVD. Recent experimental work, including in vitro studies, animal studies, and controlled experiments in humans, has added to the understanding of these mechanisms. This evidence is reviewed in the following section.

Smoking, Atherogenesis, and Thrombosis

The development of atherosclerosis is the main underlying pathophysiologic process of the most clinically significant manifestations of CVD, namely CHD, stroke (cerebrovascular disease), and peripheral arterial disease. Atherosclerosis is a process of hardening of the arteries characterized by deposition of lipid in the inner layers of the arteries, by fibrosis, and by thickening of the arterial wall. Atherosclerotic plaques develop over time, slowly progressing from the early lipid deposition that characterizes fatty streaks, through the more advanced raised fibrous lesions that decrease the space inside the artery (the arterial lumen), to the complicated lesions that are usually associated with clinical events. The process of plaque destabilization and complications is thought to be associated with inflammatory changes and thrombotic complications that obstruct the blood flow and result in clinical manifestations such as MI or stroke. There are underlying complex interactions of the blood (serum and blood cells) with the arterial wall as well as between cellular elements within the arterial wall itself. Table 3.1 offers a basic summary of the stages

Table 3.1 Basic pathogenic mechanisms in atherogenesis

Stage of change	Mechanism
Interactions between blood components and the arterial wall (endothelium)	Hypercholesterolemia (increased low-density lipoprotein [LDL] cholesterol) Endothelial dysfunction Leukocyte and platelet activation and adherence to the endothelium Migration of leukocytes through the endothelium
Changes within the arterial wall	LDL modification (oxidation) LDL accumulation in monocytes, turning them into foam cells Accumulation of LDL and collagen in intercellular space Smooth muscle cell proliferation
Advanced changes, complications	Plaque inflammation Endothelial denudation Platelet activation, micro- and macro-thrombosis Fibrinolysis of thrombi Plaque/thrombi rupture—emboli

and related mechanisms of the complex multistage phenomenon of atherogenesis. Each of these processes is mediated by a variety of chemotactic molecules and cytokines (Ross 1993, 1999).

The following section presents evidence showing that cigarette smoking affects a number of these processes. The evidence demonstrates that this delicate and highly regulated physiologic interface between blood and arterial wall components is adversely and strongly affected by the toxic products added to the bloodstream from cigarette smoke. These toxins then become part of the complex atherothrombotic process underlying CVD (Powell 1998).

Smoking and Endothelial Injury or Endothelial Dysfunction

The critical role of endothelial dysfunction in the early stages of atherosclerosis is now well recognized (Ross 1993, 1999). Endothelial dysfunction is associated with an increased adhesion of circulating monocytes and T lymphocytes to the endothelium as well as with their subsequent migration into the intimal layer of the arterial wall, the layer of cells and tissue innermost to the arterial wall. These cells, in the presence of modified low-density lipoprotein (LDL) cholesterol (e.g., oxidized LDL cholesterol), become foam cells and accumulate in the intima, constituting a key

element in the early phases of atherogenesis. Endothelial dysfunction has been experimentally linked to atherosclerosis in animal models (Moore 1973) as well as in humans (Celermajer et al. 1992; Corretti et al. 1995).

Early reports on the possible detrimental effects of cigarette smoking on the endothelium focused mainly on morphologic changes in the endothelium (Pittilo 1990; USDHHS 1990). This research included animals experimentally exposed to nicotine at serum levels similar to those of human smokers, and observational and experimental human studies. The findings included the following:

- Umbilical arteries from cords of infants born to smoking mothers showed endothelial changes absent in cords from nonsmoking mothers (Asmussen and Kjeldsen 1975; Asmussen 1982a,b; Pittilo 1990). These changes included subendothelial edema or swelling, widening of the intercellular junctions between cells, distension of the endoplasmic reticulum, and increased numbers of mitochondria. Similarly, morphologic examinations of uterine arteries in smoking women showed significantly more inter- and intracellular holes in the endothelium than did arteries in nonsmoking women (Bylock et al. 1979).

- Short-term experimental studies in healthy non-smokers demonstrated that cigarette smoking is associated with an acute increase in the endothelial cell count in circulating blood. Compared with the minimal effects of nontobacco cigarettes, smoking two tobacco cigarettes more than doubled the number of damaged endothelial cells (anuclear carcasses) in the circulating blood of healthy persons (Davis et al. 1985). This effect was not modified by the previous administration of aspirin or rutosides (semisynthetic derivatives of rutin, a naturally occurring flavonoid) (Davis et al. 1986, 1989).

- Other laboratory data support the biologic plausibility of the above effects: cultured rat peritoneal mesothelial cells were exposed to plasma obtained from nonsmoking persons and from persons who had just smoked two cigarettes (Pittilo et al. 1985). Whereas the plasma from nonsmokers had little effect on the cultured cells, the plasma from smokers produced marked morphologic alterations, including blebbing or bubble formation of the luminal membrane. Pittilo and colleagues (1984) reported that exposure of rat endothelium to the blood from a person who had recently smoked two cigarettes resulted in the deposition of large numbers of platelets on the endothelial surface, an effect that was not observed when exposing the endothelium to human blood obtained before smoking. Likewise, in the absence of morphologic changes, cigarette smoke exposure in dogs resulted in an increased endothelial permeability to the coagulable protein fibrinogen (Allen et al. 1988). Pittilo (1990) reviewed animal studies that further supported these observations. A number of experiments with rabbit and rat models conducted during the 1980s consistently found that cigarette smoking was associated with morphologic changes in the endothelium, including cell loss and the formation of blebs and microvillous-like projections into the luminal cell surfaces.

In recent years, more subtle functional changes in the endothelium have been associated with smoking. Even in the absence of morphologic changes, a dysfunctional endothelium can secrete growth factors, chemotactic molecules that draw in inflammatory cells, and cytokines that stimulate the inflammatory process of atherosclerosis. The cytokines and other molecules can stimulate smooth muscle cell proliferation, monocyte/lymphocyte adhesion, and subendothelial migration leading to atherosclerosis and the loss of the endothelium's normal antithrombotic properties (Pittilo 1990; Vogel 1997; Hutchison 1998).

The endothelium regulates the vascular tone by secreting vasodilators (e.g., nitric oxide) and vasoconstrictors (Arnal et al. 1999). The functional status of the endothelium can be studied by examining arterial diameter changes in response to stimuli whose effects depend on the integrity of the endothelium. Quantitative angiography, for example, can measure changes in the coronary artery diameter in response to varying concentrations of acetylcholine, an endothelium-dependent vasodilator. Plethysmography can record changes in the diameter of the brachial artery in response to stimuli from an endothelium-dependent vasodilator (e.g., reactive hyperemia induced by blood flow increase) by measuring the pressure or by ultrasound (Celermajer et al. 1992; Corretti et al. 1995). Using these techniques, young and middle-aged cigarette smokers without disease had a significant reduction in endothelium-dependent vasodilatation compared with nonsmoking controls (Celermajer et al. 1993). This association was dose-dependent (vasodilatation decreased with more pack-years[1] of exposure) and seemed to be potentially reversible (a weaker association was observed in former smokers). Similar effects were seen in young persons who reported exposures to secondhand smoke, also in a dose-dependent fashion (Celermajer et al. 1996). Further studies have confirmed these findings and suggest a synergism between smoking and hypercholesterolemia (Heitzer et al. 1996), raising the possibility that smoking potentiates endothelial dysfunction by enhancing LDL oxidation.

Clinical studies that used measures of endothelial dysfunction in the coronary arteries have also confirmed these results. For example, a 1999 report showed that smokers had no increases in coronary myocardial blood flow (measured with positron emission tomography) in response to a cold pressor test (Campisi et al. 1999). However, after administration of L-arginine (the precursor of nitric oxide), the myocardial blood flow response in smokers normalized, becoming indistinguishable from that of nonsmokers. This observation suggests that the abnormal flow response in smokers is related to endothelial dysfunction (Campisi et al. 1999). Further evidence of the deleterious effects of smoking on endothelial function

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[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

comes from human experiments showing steady increases in the von Willebrand factor (vWF), a possible marker of endothelial damage, 10 and 30 minutes after smoking two cigarettes (Blann et al. 1998). Compared with nonsmokers, smokers also released smaller amounts of tissue plasminogen activator (TPA) when stimulated by substance P, suggesting another mechanism whereby endothelial cell dysfunction may increase thrombosis (Newby et al. 1999).

Smoking and Thrombosis/Fibrinolysis

In a pathology study of plaque tissue obtained from samples of diseased arteries removed by surgery, plaques from smokers were more frequently complicated by thrombosis along the walls of the arteries than were plaques from nonsmokers (Spagnoli et al. 1994). Proper balance of the tightly regulated coagulation-fibrinolytic systems is critical to plaque stability and blood flow in the later phases of atherosclerosis. This balance between clotting and dissolution of clots depends on extremely complex interactions involving all of the cellular components in the blood-arterial wall interface, especially the endothelial cells and platelets. When this complex system is disturbed, pathologic thrombosis may occur, leading to vascular occlusion by thrombus fragments that could result in clinically manifest infarcts. The association between cigarette smoking and changes in blood vessels that are conducive to thromboses has been previously described (USDHHS 1990; Miller et al. 1998). Evidence suggests that these prothrombotic effects of smoking may be most important to the natural history of atherosclerosis, and probably are the main underlying factors associating smoking with sudden cardiac death (Burke et al. 1997).

The prothrombotic effects associated with cigarette smoking stem partially from the effects of smoking on the endothelium, as discussed in the preceding section. Endothelial denudation exposes circulating plasma coagulation factors to the prothrombotic matrix of arterial and plaque tissue. Moreover, impaired endothelial function results in disturbances of the tightly regulated physiologic interface between blood components and vessel walls, leading, for example, to homeostatic disruptions and increased levels of plasma vWF (Blann et al. 1998). Recent experimental evidence in smoke-exposed animals concurs with parallel comparisons of human carotid artery specimens from smokers and nonsmokers (Matetzky et al. 2000), indicating that smoking increases tissue factor expression (a small molecular-weight glycoprotein that initiates the extrinsic clotting cascade [Toschi et al. 1997]).

Together, these animal and human findings suggest yet another mechanism whereby smoking may increase the risk for acute arterial thrombosis (Matetzky et al. 2000).

Furthermore, the direct effects of smoking on the properties of platelets, platelet activation, and platelet adhesion are well proven (Lassila et al. 1988; Lakier 1992), and even nonsmokers exposed to cigarette smoke experience acute increases in platelet aggregability (Davis et al. 1985). As in the endothelial damage discussed above, neither aspirin nor rutosides prevented these acute effects on platelet activity (Davis et al. 1986). Smoking also elevates the plasma concentration of beta-thromboglobulin and the platelet factor, thereby increasing the tendency toward clot formation (Davis et al. 1986).

More recent experiments reinforce and further clarify these earlier results. In controlled experiments using habitual smokers with stable CHD (Hung et al. 1995), blood obtained five minutes after smoking two cigarettes had increases in platelet thrombus formation and whole blood platelet aggregation compared with blood obtained five minutes before smoking. In another experiment, the increased aggregability of platelets in smokers was related to increases in fibrinogen and platelet-fibrinogen binding (Fusegawa et al. 1999).

With regard to fibrinolytic activity, studies have shown that compared with the endothelium of nonsmokers, the endothelium of smokers has a reduced ability to release TPA in response to an infusion of substance P, an endothelium-dependent vasodilator (Newby et al. 1999, 2001). This impaired TPA response may be critical in the acute phase of coronary thrombosis by slowing the conversion of fibrin into soluble products. In combination with the prothrombotic effects of smoking, the imbalance in the coagulation-fibrinolytic systems may precipitate the propagation of microthrombi in the surface of atheromatous plaques, leading to arterial occlusion and clinical manifestations of thrombosis (Newby et al. 1999). Evidence also strongly suggests that smoking has synergistic effects with some pharmacologic substances (e.g., oral contraceptives) in its thrombogenic potential (Lidegaard 1999; Roy 1999).

Fibrinogen is an acute-phase protein that rises quickly in response to a number of stimuli (Gabay and Kushner 1999), and in cross-sectional studies, smoking is strongly associated with increased plasma levels of fibrinogen (Ernst et al. 1987; Folsom et al. 1991, 1992; Miller et al. 1998). In addition, prospective cohort studies show that persons who start or continue to smoke have larger increases in plasma fibrinogen

over time than do nonsmokers (Meade et al. 1987; Folsom et al. 2000), findings supported by a short-term experiment showing decreases in plasma fibrinogen following smoking cessation (Rothwell et al. 1991). Thus, the smoking-associated increase in plasma levels may reflect a chronic inflammatory response associated with the insult to the arterial tissue and other organs (e.g., bronchitis) from long-term smoking. Numerous studies have demonstrated that the fibrinogen level is an independent cardiovascular risk factor (Wilhelmsen et al. 1984; Kannel et al. 1987; Ernst and Resch 1993; Danesh et al. 1998), and the deleterious effects of smoking on CVD risk may be partially mediated by the rise in fibrinogen.

The profound alterations of the fibrinolytic system associated with smoking are also reflected in the strong association between cigarette smoking and plasma levels of certain hemostatic factors. Smoking is associated with increased antithrombin III activity (Folsom et al. 1992) and decreased levels of protein C (Conlan et al. 1993b), factor VIII (Conlan et al. 1993a), factor IX activation peptide, factor X activation peptide, and prothrombin fragment 1+2 (Miller et al. 1998). In contrast to the increases in vWF levels experimentally induced by cigarette smoking (Blann et al. 1998), cross-sectional studies do not show a significant independent association between cigarette smoking status and average vWF plasma levels (Conlan et al. 1993a). The results for factor VIIc are not consistent in the literature, with significant associations in some studies (Miller et al. 1998) but not in others (Folsom et al. 1992).

Smoking and Inflammation

Current concepts of the pathogenesis of atherosclerosis increasingly emphasize the central role of inflammation (Ross 1999). As discussed elsewhere in this report, smoking induces a localized inflammatory response in the lungs and induces a systemic inflammatory response manifested by elevations in inflammatory markers such as the leukocyte count in circulating blood, which is a risk marker (and potentially a risk factor) of CVD (Friedman et al. 1973). Both cross-sectional and longitudinal studies have consistently demonstrated that, compared with persons with lower counts, those with moderately elevated leukocyte counts have an increased risk of CHD, stroke, and sudden death (Friedman et al. 1974, 1975; Prentice et al. 1982; Grimm et al. 1985; Ernst et al. 1987). In a recent meta-analysis, a difference of 2,800 leukocytes/mm³ within the normal range of the leukocyte count (e.g., comparing persons with 8,400 leukocytes/mm³ with persons with 5,600 leukocytes/mm³) was

associated with a relative risk (RR) of CHD of 1.4 (Danesh et al. 1998).

The association between cigarette smoking and the leukocyte count is strong and well described in epidemiologic studies (Friedman et al. 1973). There are consistent dose-response relationships with amount smoked, degree of inhalation, duration of smoking, and amount of time since quitting (Petitti and Kipp 1986; Nieto et al. 1992) (see Chapter 2, "Cancer"). Moreover, studies demonstrate that these acute increases in leukocyte counts caused by cigarette smoking are probably due, at least in part, to local inflammatory effects in the bronchial tree (Lehr 1993). However, the effects of cigarette smoking on the activation and adhesion of leukocytes, which initiate the atherosclerotic process when combined with endothelial dysfunction, are perhaps more significant for arterial wall injury. Laboratory studies have demonstrated that both animal and human leukocytes exposed to cigarette smoke express increased chemotactic responses, increased aggregability, and increased expressions of adhesion receptors in response to a variety of stimuli (Anderson 1991; Lehr 1993).

Smoking is also associated with an elevation of the C-reactive protein level, an acute phase protein that provides a measure of inflammatory activity (Das 1985; Tracy et al. 1997; Ridker et al. 2000). Epidemiologic evidence indicates that the C-reactive protein level is positively associated with risks of CHD, stroke, and peripheral arterial disease (Kuller et al. 1996; Ridker et al. 1997; Ridker 2001; Di Napoli et al. 2001).

Smoking, Lipids, and Lipid Metabolism

The evidence supporting an association between smoking and adverse lipid profiles has been reviewed in previous reports (USDHHS 1990), and summarized in a 1989 meta-analysis of 54 studies (Craig et al. 1989). This evidence reveals higher concentrations of total LDL and very low-density lipoprotein (VLDL) cholesterol in smokers compared with nonsmokers, although the most consistent evidence indicates decreased levels of high-density lipoprotein (HDL) cholesterol in smokers compared with nonsmokers (Krupski 1991). The plausibility of a causal association of smoking with decreased HDL is supported by evidence from a population-based, prospective cohort study within the Stanford Five-City Project showing decreasing HDL levels in persons starting to smoke and, conversely, increasing HDL levels in persons who had stopped smoking (Fortmann et al. 1986). These findings have been replicated in other studies (USDHHS 1990).

Smoking may also seriously affect lipid metabolism and LDL modification. Smokers have higher levels of serum malondialdehyde (USDHHS 1990), which may modify LDL cholesterol to promote uptake by macrophages and decrease cholesterol transport from cell membranes to plasma. Malondialdehyde may be a marker of oxidation, and evidence indicates that smoking may promote lipid peroxidation, which is hypothesized to be one key element in the causal pathway of atherogenesis (Steinberg et al. 1989). Furthermore, evidence from an uncontrolled intervention trial demonstrates a significant increase in the HDL/LDL cholesterol ratio in adult smokers without disease following an eight-week period of smoking reduction. The increase was even more pronounced after a further eight-week period of abstinence from smoking (Eliasson et al. 2001). How cigarette smoking could cause changes in serum lipid levels is not entirely understood, but the mechanisms may involve metabolic changes affecting the transport of cholesterol between cells and plasma (de Parscau and Fielding 1986). In laboratory studies, cigarette smoke stimulated the generation of oxidized LDL cholesterol in human plasma (Frei et al. 1991).

Smokers also have elevated levels of plasma and urine F_2-isoprostanes (by-products of lipid peroxidation) compared with nonsmokers (Morrow et al. 1995; Patrono and FitzGerald 1997). Even though no acute effects of smoking were observed, experimental data demonstrated that stopping smoking resulted in a significant reduction in F_2-isoprostane levels within days or just a few weeks. This finding suggests that the in vivo oxidation injury associated with cigarette smoking almost completely disappears within a few weeks of smoking cessation (Morrow et al. 1995; Oguogho et al. 2000).

Smoking and Cardiovascular Function

In addition to the atherogenic effects of smoking, components of cigarette smoke may have adverse effects on the cardiovascular system with regard to oxygen supply and demand, thereby increasing the risk of ischemia. These effects may ultimately precipitate clinical events in persons with compromised coronary circulation that stems from underlying atherosclerosis.

Smoking and Increased Oxygen Demand

Cigarette smoking induces the release of catecholamines (epinephrine and norepinephrine) (Cryer et al. 1976; Hung et al. 1995), which are associated with an increased baseline heart rate and contractility and an increase in vascular tone (Benowitz 1988). In smokers, however, cigarette smoking is associated with a lower than expected heart rate in response to physical exercise (Srivastava et al. 2000), a characteristic that has been associated with increased risks of mortality, arrhythmias, and MI (Lauer et al. 1999).

Even though there is no evidence that smoking is associated with chronic hypertension, there is compelling evidence that smoking acutely increases peripheral vascular resistance and increases blood pressure (Cryer et al. 1976; Koch et al. 1980). These effects seem to be attributable to the pharmacologic properties of nicotine (Benowitz and Gourlay 1997). In carefully controlled experiments in healthy humans, cigarette smoking increased blood pressure and the sympathetic nervous system stimulation to both the blood vessels and the heart (Narkiewicz et al. 1998). Acute and episodic increases in blood pressure, coupled with an increased heart rate, increase the oxygen demands of the myocardium. However, in population studies, cigarette smokers tend to have on average lower blood pressures than do nonsmokers (USDHEW 1979; Friedman et al. 1982).

Smoking, Decreased Oxygen Supply, and Increased Blood Rheology

Studies have long indicated that smoking is associated with a decrease in coronary blood flow (Martin et al. 1984). More recent studies using intracoronary Doppler measurements have demonstrated that smoking causes an immediate constriction of both proximal and distal coronary arteries as well as an increase in coronary vessel tone and hence resistance (Quillen et al. 1993). These effects seem to be mediated by increases in catecholamine levels associated with smoking, suggested by the finding that pharmacologically blocking alpha-adrenergic receptors can reverse the smoking-induced decrease in coronary blood flow in CHD patients (Winniford et al. 1986; Quillen et al. 1993). The decreased vasodilatory response to certain stimuli resulting from the endothelial dysfunction associated with smoking also can limit blood perfusion to the myocardial tissue in certain situations.

The effects of smoking in compromising the oxygen supply to tissues, particularly to the myocardium, are not limited to vasomotor effects but also can be due to smoking-related changes in key physiologic blood components. Carbon monoxide in cigarette smoke diffuses from the pulmonary alveoli to the bloodstream, binds to hemoglobin in the erythrocyte, and forms carboxyhemoglobin, which has a

diminished oxygen-carrying capacity. Compensatory erythrocytosis may result (Rampling 1993). Both hematocrit and hemoconcentration increase with the number of cigarettes smoked. These increases, combined with the hyperfibrinogenemia associated with smoking (see the section on "Smoking and Thrombosis/Fibrinolysis" earlier in this chapter), contribute to the increased blood viscosity associated with smoking, which increases the risk of thrombosis and physically compromises microcirculation (Rampling 1993).

The low-grade inflammatory response associated with smoking not only results in increased plasma fibrinogen levels, but also seems to be responsible for the consistently demonstrated dose-response association between smoking and leukocyte counts (see the section on "Smoking and Inflammation" earlier in this chapter). The level of C-reactive protein, a marker for chronic inflammation and a strong predictor of clinical CHD events (Ridker and Haughie 1998), was associated with pack-years of smoking among persons more than 65 years old in the Cardiovascular Health Study (CHS) cohort (Tracy et al. 1997). This association was present even among persons who had stopped smoking for 30 years or more, suggesting that some of the deleterious effects of smoking on inflammation may persist. These data are consistent with the hypothesis that smoking causes a chronic, increased inflammatory response, especially in the absence of other mitigating factors (Tracy et al. 1997).

The net result of all of these mechanisms (reduced oxygen-carrying capacity of hemoglobin and compromised microcirculation from increased blood viscosity and leukocytosis) is a reduction in the oxygen-delivery capacity of blood both to the heart and to the peripheral tissues. When oxygen demand is increased, the resulting tissue hypoxemia may create a critical imbalance of oxygen need with supply in a person with underlying coronary or peripheral atherosclerosis. Smoking is associated with significant myocardial perfusion abnormalities (Deanfield et al. 1986), thus explaining the increased risk for MI events, unstable angina, and sudden deaths observed in smokers with CHD (Quillen et al. 1993).

Despite abundant laboratory and epidemiologic data linking smoking and a variety of pathophysiologic mechanisms in arterial wall and blood interactions, specific components of smoking responsible for each of these effects are not entirely clear (Pittilo 1990). Both nicotine and carbon monoxide may be involved in inducing endothelial dysfunction and atherosclerosis, although the evidence (animal experiments and laboratory studies of tissue cultures) is not consistent in singling out a specific component as uniquely responsible (Pittilo 1990). Some studies show that nicotine administration to animals results in endothelial abnormalities—increases in the number of endothelial cell carcasses in the blood and decreases in the synthesis of prostacyclin (an inhibitor of platelet aggregation) by endothelial cells (Pittilo 1990). In addition, nicotine seems to be responsible for the platelet activation induced by smoking (Lassila et al. 1988). However, a recent study compared a number of hematologic and coagulation indices in smokers before quitting, after quitting but using nicotine gum or patches, and subsequently when no longer using any nicotine products (Blann et al. 1997). There were significant declines in most outcomes measured after smoking cessation but few changes after stopping the nicotine gum and/or patches. A similar pattern was found in a study of atherogenic and thrombogenic factors in persons attending a smoking cessation program who received either a nicotine nasal spray or a placebo (Ludviksdottir et al. 1999).

Epidemiologic studies have addressed the potential role of nicotine by investigating the risks of heart disease from different forms of tobacco use. Cigar smoking has been associated with an elevated risk for heart disease, but cigar smokers have high intakes of both nicotine and carbon monoxide (Goldman 1977; Pechacek et al. 1985; Iribarren et al. 1999). Of greater interest is the risk for heart disease associated with the use of smokeless oral tobacco, which delivers nicotine rapidly into the bloodstream (Fant et al. 1999). Because of prolonged absorption of nicotine through the buccal mucosa, smokeless tobacco delivers a larger overall exposure to nicotine than cigarette smoking does (Gritz et al. 1981). Smokeless tobacco users are reportedly at an increased risk for high blood pressure (Bolinder et al. 1992) but not for elevated levels of fibrinogen (Eliasson et al. 1995).

One study of Swedish men followed approximately 6,000 smokeless tobacco users for 12 years and compared their cause-specific mortality with that of tobacco smokers and nonsmokers. Although the RR for all CVD was lower than that for tobacco smokers (1.8 [95 percent confidence interval (CI), 1.6–2.0] for smokers of <15 cigarettes per day and 1.9 [95 percent CI, 1.7–2.2] for smokers of 15 cigarettes per day), smokeless tobacco users had a statistically increased RR for all CVD of 1.4 (95 percent CI, 1.2–1.6) compared with those who used no tobacco products (Bolinder et al. 1994). The RRs were high for those aged 35 through 54 years at entry into the study. Adjusting for age, body mass index (BMI), blood pressure, diabetes, and a history of heart symptoms or blood pressure medication at the time of entry did not alter the results. In

contrast, two case-control studies from Sweden have not found that smokeless tobacco is a risk factor for MI (Huhtasaari et al. 1992, 1999). However, in one of these studies (Huhtasaari et al. 1999), restricting the analysis to fatal cases of MI (including sudden death) showed a tendency toward an increased risk for snuff dippers.

Carbon monoxide also compromises the oxygen-carrying and oxygen-delivering capacity of the blood, thus promoting the complications of atherosclerosis. Free radicals present in cigarette smoke may also be involved in atherogenesis by promoting oxidative changes in LDL (Church and Pryor 1985). Oxidized LDL is more readily taken up by macrophages to form foam cells in the atherosclerotic plaque and can be directly involved in promoting endothelial and vasomotor dysfunction (Kaufmann et al. 2000). Furthermore, toxic and reactive glycation products found in aqueous extracts of tobacco can modify certain lipoproteins (Apo B), prevent the normal tissue uptake of LDL, and increase levels of circulating LDL (Zieske et al. 1999). These effects explain the epidemiologic findings of higher concentrations of total, LDL, and VLDL cholesterol in smokers than in nonsmokers (Craig et al. 1989).

Summary

A substantial body of laboratory and experimental evidence now demonstrates that cigarette smoking in general and some specific components of cigarette smoke affect a number of basic pathophysiologic processes at the critical interface between circulating blood components and the inner arterial wall. Smoking leads to endothelial injury and cell dysfunction. The effects of cigarette smoking on circulation produce a substantial shift in the hemostatic balance at the endothelium, leading to atherosclerosis and its thrombotic complications. Furthermore, components of cigarette smoke diminish the ability of the blood to carry oxygen and increase the physiologic demands of the myocardium. The overall result of this constellation of toxic effects is to profoundly and adversely affect the homeostatic balance in the cardiovascular system, thus explaining the well-documented relationship between smoking and both subclinical and clinical manifestations of atherosclerosis that are reviewed in the next sections.

Smoking and Subclinical Atherosclerosis

Epidemiologic Evidence

Atherosclerosis is the most common cause of obstruction within the blood vessels supplying the lower extremities. When the obstruction reduces the blood flow sufficiently, a variety of symptoms may occur. The symptoms usually originate in areas distal to the obstruction, but flow from the collateral vessels can alter the pattern. The most common symptom is intermittent claudication, which can cause persons to feel pain in their legs when exercising, but the pain typically resolves within several minutes after the exercise has stopped. The pain is usually localized to the calf, because the most commonly affected vessels are the superficial femoral and popliteal arteries. Epidemiologic studies indicate that about 5 percent of men and 2.5 percent of women over 60 years of age experience intermittent claudication (Jelnes et al. 1986). Noninvasive studies of the peripheral arteries find a prevalence of peripheral arterial disease at least three times higher than the self-reported prevalence of intermittent claudication. One poor outcome of peripheral arterial disease is leg amputation. In 1995, the above- and below-knee amputation rate for legs was 25 per 100,000 adult Americans (Feinglass et al. 1999).

Studies investigating clinical cardiovascular events among adults middle-aged or older are limited in that they only address the factors related to the late phases of the natural history of atherosclerosis. It is widely recognized that this disease has a long natural history, with early pathologic changes (fatty streaks) developing in the teens or early twenties in many persons (Strong and McGill 1969; Strong et al. 1999). Thus, research addressing only associations between risk factors and clinical events that are late outcomes may overlook or underestimate the effects of risk factors in the early stages of atherogenesis and may miss possible opportunities for prevention. Moreover, inferences from studies of clinical events can be limited because of changes in behavior resulting from

symptoms, which in turn could distort the temporal relationship (reverse causality) between suspected risk factors and outcomes. The distortion of this temporal relationship can be particularly problematic in cross-sectional data, as symptoms or disease diagnosis may influence smokers to quit or to reduce the number of cigarettes smoked. Such changes in smoking are documented in a study that compared cross-sectional and longitudinal associations between cigarette smoking and other risk factors with both clinical and subclinical CVD (Nieto et al. 1999).

Studying subclinical markers for atherosclerosis offers an informative complement to disease outcomes for examining the association between risk factors and earlier phases of atherosclerosis (Table 3.2). Subclinical outcomes are less susceptible to temporal biases, and their use makes it possible to study the pathogenesis of the disease at an earlier stage. When researchers study healthy persons in an epidemiologic setting, measures of subclinical disease need to be noninvasive, imposing no risk and minimizing the burden on study participants (Sharrett 1993).

Table 3.3 describes results of studies reported since 1990 that examined the association between cigarette smoking and the presence of atherosclerosis, using carotid intimal-medial thickness (IMT) as the marker for subclinical disease because of its strong association with incident CHD (Chambless et al. 1997) and with stroke events (Chambless et al. 2000). Conducted with adult populations from different countries, these studies showed a remarkably consistent positive association between smoking and carotid IMT. Furthermore, studies that examined trends of IMT with the amount smoked found evidence of a dose-response relationship. Smoking also was associated with changes in carotid IMT in three prospective cohort studies (Salonen and Salonen 1990; Belcaro et al. 1995; Howard et al. 1998a). In a study of participants in the Atherosclerosis Risk in Communities (ARIC) Study who were free of CVD at baseline, cigarette smoking was a strong risk factor for both the presence of greater baseline carotid IMT and the incidence of CHD events during the three-year follow-up period (Sharrett et al. 1999). Results from pooled analyses using ARIC Study and CHS data indicated that smoking seemed to be strongly related to carotid atherosclerosis, regardless of age. These data show a stronger association in older than in middle-aged white adults in the studies (Howard et al. 1997).

The association between clinical manifestations of peripheral arterial disease and smoking is well established (USDHEW 1979; USDHHS 1990; Krupski 1991). Furthermore, recent studies have added new insights into the critical role of smoking in the natural history, severity, and progression of peripheral arterial disease. In a six-year follow-up study of patients with intermittent claudication, current smokers had a higher incidence of severe ischemic leg symptoms ranging from rest pain to gangrene (Smith et al. 1998). More subtle changes also have been documented in prospective studies. Among 415 peripheral arterial disease patients with intermittent claudication (aged 42 through 88 years), smoking was strongly related to a six-minute walk performance (Cahan et al. 1999). Patients with intermittent claudication who were current smokers (but had been asked to refrain from smoking on the day of the experiment) had significantly decreased time to claudication and more severe pain than patients who had quit smoking an average of seven years earlier (Gardner 1996). In this study the effect of smoking remained significant even after controlling for baseline ankle-arm index (AAI), also known as ankle-branchial index, an index of the degree of underlying peripheral arterial disease (Janzon et al. 1981). Experimental data also demonstrate acute effects of smoking on the peripheral circulation among persons with peripheral arterial disease. In a cross-over study of chronic smokers with peripheral arterial disease,

Table 3.2   Markers of subclinical atherosclerosis used in epidemiologic studies

Disease	Marker	Study technique
Generalized atherosclerosis	Ankle-arm index	Blood pressure measured with Doppler
	Carotid intimal-medial thickness	B-mode ultrasound
Coronary atherosclerosis	Coronary calcium	Computerized tomography
Cerebrovascular disease	Lacunar infarcts	Magnetic resonance imaging

smoking two cigarettes significantly decreased the AAI compared with the AAI on comparison days when the participants refrained from smoking (Yataco and Gardner 1999). These recent experiments, including findings from studies using an objective measure of the underlying peripheral arterial disease (the AAI), call into question earlier claims that smoking did not have an effect on exercise performance in this population (Waller et al. 1989).

Table 3.4 summarizes results from studies on smoking and the AAI. The AAI is the systolic blood pressure of the ankle divided by the systolic blood pressure of the arm, and was proposed as an index of subclinical peripheral arterial disease in the early 1980s (Janzon et al. 1981), with lower values indicating disease. It is a consistently strong predictor not only of peripheral arterial disease outcomes but also of coronary and cerebrovascular disease events among adults middle-aged (Zheng et al. 1997) and older (Criqui et al. 1992; Newman et al. 1999). Most of the results in Table 3.4 also show a consistent association between cigarette smoking and the AAI in diverse study populations and in both older and younger adults. These results are also consistent with the association between smoking and clinical peripheral arterial disease (USDHHS 1989, 1990).

The presence of subclinical CVD can be assessed by the presence of cerebral white matter disease or lacunar infarcts in magnetic resonance imaging (MRI) of the brain in asymptomatic persons. Results from studies reporting on the association between smoking status and MRI findings are not consistent for either abnormality, as shown in Table 3.5. Whereas some studies showed an increased prevalence of white matter disease and brain infarcts in smokers compared with nonsmokers (Longstreth et al. 1996, 1998; Liao et al. 1997; Howard et al. 1998b), other studies did not show statistically significant differences (Breteler et al. 1994; Yamashita et al. 1996; Shintani et al. 1998). The studies with the largest samples did find positive trends, but only a few reached conventional levels of statistical significance.

All of the studies of white matter disease are cross-sectional, however, and thus subject to methodologic limitations (e.g., prevalence-incidence bias). For example, even if smoking is truly associated with an increased risk (incidence) of the underlying disease (e.g., subclinical atherosclerosis) and if smoking also affects disease prognosis, the prevalence ratio obtained in a cross-sectional study will be a biased estimate of the RR. If smoking increases the risk of clinical events and mortality in those with atherosclerosis (e.g., by promoting thrombosis [see the section on "Smoking

and Thrombosis/Fibrinolysis" earlier in this chapter]), survival of smokers with atherosclerosis will be shorter than that of nonsmokers, and thus the prevalence ratio will underestimate the RR. Because this limitation may have different effects in different settings and populations, it is a possible explanation for some of the inconsistent results across different studies.

A combined index of subclinical atherosclerosis in participants aged 65 years or older in the CHS was constructed using the electrocardiogram, echocardiogram, carotid IMT, AAI, and responses to a questionnaire that asked about symptoms of angina and intermittent claudication (Kuller et al. 1994). Current smokers in this study, excluding persons with a clinical disease, were more than twice as likely to have evidence of a subclinical disease in multivariate analyses that adjusted for other major risk factors. The age-adjusted proportions of current smokers without evidence of CVD were 8 percent in men and 6 percent in women; 16 percent and 14 percent, respectively, had evidence of subclinical disease; and 13 percent and 9 percent, respectively, manifested a clinical disease (these numbers reflect the fact that persons with a clinical disease tend to quit smoking). In the CHS, after excluding those with evidence of clinical CVD, the adjusted odds ratios (ORs) for a subclinical disease comparing smokers with nonsmokers were 2.0 (95 percent CI, 1.5–2.7) in women and 2.4 (95 percent CI, 1.6–3.6) in men (Kuller et al. 1994).

All of the evidence discussed so far in this section pertains to studies of smoking and subclinical atherosclerosis in vascular beds other than coronary arteries. Until recently, direct assessment of subclinical coronary atherosclerosis in epidemiologic studies was not feasible because there were no noninvasive measurements suitable for studies in asymptomatic persons. And although studies using coronary angiography have documented an association between smoking and the presence and degree of coronary artery narrowing (Pearson 1984; Chen et al. 1995), inferences from these studies are limited because of the possibility of selection biases stemming from characteristics of the study participants; even the comparison group (those without angiographic evidence of disease) had some clinical indications on the diagnostic angiography (Pearson 1984).

Evidence from pathology studies on a series of autopsies of adults regardless of the cause of death demonstrated clear and strong associations between smoking histories and the presence of aortic and coronary atherosclerosis (Strong and Richards 1976). These early findings have been strengthened by additional pathology studies of young trauma victims

Table 3.3   Studies on the association between smoking and atherosclerosis using the carotid B-mode ultrasound findings

Study	Design/population	Age/gender
Salonen and Salonen 1990	Community-based Cohort Finland n = 100	42–60 years Men
Bonithon-Kopp et al. 1991	Community-based Cross-sectional France n = 517	45–54 years Women
Heiss et al. 1991	ARIC[†] Study Community-based Case-control United States n = 386 case-control pairs	45–54 years Both genders
Salonen and Salonen 1991	Population-based Cohort Finland n = 1,224	42, 48, 54, or 60 years Men
Bots et al. 1992	Rotterdam Elderly Study Community-based Cross-sectional Netherlands n = 954	55 years Both genders
O'Leary et al. 1992	Cardiovascular Health Study Community-based Cross-sectional United States n = 5,201	65 years Both genders
Fine-Edelstein et al. 1994	Framingham Heart Study Community-based Cross-sectional United States n = 1,116	66–93 years Both genders

*IMT = Intimal-medial thickness.
[†]ARIC = Atherosclerosis Risk in Communities.
[‡]OR = Odds ratio.
[§]CI = Confidence interval.
  Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.
[¶]Maximum common carotid artery wall thickness.
**Maximum internal carotid artery wall thickness.

Main results	Comments
Progression of IMT* over 2 years: Smokers 0.21 mm increase Nonsmokers 0.09 mm increase	Differences remained significant after adjusting for age, lipids, leukocyte count, and platelet aggregability

	Percentage with carotid thickening	Percentage with plaque	The association was significant after adjusting for age, blood pressure, and lipids
Smokers	35	10	
Nonsmokers	28	8	

Main results	Comments
Multivariate-adjusted OR‡ of carotid atherosclerosis (high IMT) (95% CI§) Ever vs. never smokers 3.1 (2.1–4.6) Current vs. never smokers 3.9 (2.9–5.9)	Cases and controls were matched for age, gender, race, and center, with additional adjustments for all other major risk factors
Cigarette-years were strongly associated with the maximal IMT (= 0.125, p <0.0001)	Adjusted for age, ambulatory blood pressure, serum low-density lipoprotein cholesterol, history of ischemic heart disease, pre-exercise systolic blood pressure, and diabetes

Percentage of internal carotid artery stenosis	Percentage of current smokers	The increasing percentage of current smoking with higher levels of stenosis remained statistically significant after adjusting for main risk factors
0	23	
1–15	26	
16	32	

Carotid IMT (mm)	Smoking status			All differences were statistically significant even after adjusting for all main risk factors
	Never	Former	Current	
Maximum common¶	0.98	1.03	1.03	
Maximum internal**	1.39	1.59	1.71	
Maximum stenosis (%)	16	20	24	

Main results	Comments
Multivariate-adjusted OR for carotid stenosis comparing current with never smokers Men 2.81 (p = 0.002) Women 3.07 (p = 0.0001)	There was a statistically significant linear dose-response relationship with the amount smoked

Table 3.3   Continued

Study	Design/population	Age/gender
Howard et al. 1994	ARIC[†] Study Community-based Cross-sectional United States n = 12,953	45–64 years Both genders
Salonen et al. 1994	Cohort (from Seven Countries Study) Finland n = 182	70–89 years Men
Belcaro et al. 1995	Community-based sample Cohort Italy n = 472	40–60 years Both genders
Diez-Roux et al. 1995	ARIC Study (Washington County) Community-based Historical cohort United States n = 2,073	45–64 years Both genders
Bonithon-Kopp et al. 1996	European Vascular Aging Study Community-based Cross-sectional France n = 1,384	59–71 years Both genders
Wei et al. 1996	Community-based Cohort San Antonio, Texas (United States), and Mexico City, Mexico n = 867	35–64 years Both genders
Howard et al. 1998a	ARIC Study Community-based Cohort United States n = 10,914	45–64 years Both genders

*IMT = Intimal-medial thickness.
[†]ARIC = Atherosclerosis Risk in Communities.
[††]ETS = Environmental tobacco smoke.
[‡‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Main results	Comments
Mean IMT* (mm)	Among former and current smokers, more pack-years[‡‡] of exposure were associated with an increased IMT
Never smokers	
No ETS[††] exposure 0.693	
With ETS exposure 0.705	
Former smokers 0.756	
Current smokers 0.761	
In 1989 relative risk for current smoking = 2.46 (95% CI, 0.94–6.45) with nonmineralized atheroma and 1.21 (95% CI, 0.22–6.58) with any mineralization; former smoking = 1.99 (95% CI, 0.99–4.00) with nonmineralized atheroma and 1.15 (95% CI, 0.37–3.62) with any mineralization	Adjusted for age (continuous), cholesterol (mmol/L), and pulse pressure (mm Hg)
The progression of carotid atherosclerosis (change in IMT) was slightly higher in smokers than in nonsmokers, but differences were not statistically significant	Only controlled for age
Carotid IMT was associated with both current smoking and smoking status 15 years before the ultrasound measurement	ETS exposure, either concurrent with or 15 years before the ultrasound measurement, was also associated with carotid IMT

Common carotid IMT tertile	Current smokers (%) No plaque	Current smokers (%) Plaque	Differences were statistically significant
Lower (<0.58 mm)	6.4	12.5	
Medium (0.58–0.68 mm)	8.7	15.0	
Higher (>0.68 mm)	11.1	11.4	

Main results	Comments
Among current smokers, = 0.0028 mm (p = 0.84) for IMT for common carotid arteries, and = 0.0508 mm (p = 0.02) for internal carotid arteries	Adjusted for age, gender, city, diabetes, total and high-density lipoprotein cholesterol, systolic blood pressure, and triglycerides
Adjusted IMT progression (µm/3 years)	The association between smoking and IMT was strongest among persons with diabetes and persons with hypertension
Never smokers	
No ETS exposure 25.9	
With ETS exposure 31.6	
Former smokers	
No ETS exposure 32.8	
With ETS exposure 38.8	
Current smokers 43.0	

Table 3.3   Continued

Study	Design/population	Age/gender
Davis et al. 1999	Community-based Cohort United States n = 182 men and 136 women	33–42 years Both genders
Espeland et al. 1999	Case-control Population-based United States n = 280 (141 cases with 50% stenosis of 1 vessel, 139 controls with no lumen irregularities)	45 years Both genders

*IMT = Intimal-medial thickness.

documenting an increased prevalence of advanced lesions and a decreased prevalence of intermediate lesions in young smokers compared with nonsmokers. Data from the Bogalusa Heart Study (Berenson et al. 1998) and from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study (Strong et al. 1999) show that cigarette smoking by young people remains associated with atherosclerosis. Both studies involved careful assessments of the extent of atherosclerotic lesions found in young victims of trauma. Berenson and colleagues (1998) described the association between atherosclerosis and smoking among 93 participants in the Bogalusa Heart Study who had died and were autopsied. Antemortem risk factor information was available from study records; most died from trauma at a mean age of 21 years. Smoking was associated with fibrous plaques in the aorta and fatty streaks in the coronary vessels even at this young age.

The PDAY Study is a multicenter autopsy study of atherosclerosis in trauma victims aged 15 through 34 years. Even among the youngest persons in the study, atherosclerotic lesions were found in the aortas of nearly all persons and in the coronary arteries of the majority (Strong et al. 1999). The extent of atherosclerosis increased with age. Several analyses of the PDAY specimen data have shown that active smoking was associated with the extent of atherosclerosis (PDAY Research Group 1990; Zieske et al. 1999; McGill et al. 2001). McGill and colleagues (2001) reported on the findings in 629 men and 227 women, and they found that smoking was associated with atherosclerosis in the aortas but not in the coronary arteries. Zieske and colleagues (1999) carefully examined coronary arteries from 50 smokers and 50 nonsmokers in the study. They found that smokers were twice as likely to have advanced lesions as nonsmokers, suggesting that lesions progress more rapidly in smokers.

New imaging techniques are now being used to noninvasively assess markers of early coronary artery disease. With recent technological advances, it is now possible to conduct epidemiologic studies of the presence of coronary calcium as a surrogate for the presence of atherosclerosis in coronary arteries of healthy asymptomatic persons. The presence of calcium in plaques is an indicator of atherosclerosis. Using computed tomography (CT) techniques (i.e., helical CT or electron-beam CT [EBCT]), researchers can directly study subclinical atherosclerosis in coronary arteries. Studies measuring coronary calcium in epidemiologic settings (i.e., in population-based samples of asymptomatic persons) are in progress, but only a few studies with selected samples have been published. In two studies with samples that included adults selected because of the presence of cardiovascular risk factors but not necessarily a history of a clinical event (Goel et al. 1992; Wong et al. 1994), a history of smoking was significantly associated with the presence of coronary calcium in multivariate analyses.

In contrast to these results, studies of clinical populations (i.e., patients with acute coronary syndromes) show an inverse association between smoking and the presence of coronary calcium measured by EBCT (Schmermund et al. 1998). Furthermore, another study from an employee screening program of French men (Simon et al. 1995) found no association between current smoking and coronary calcium

Main results	Comments
Pack-years of smoking were significant risk factors for carotid IMT* in men (= 0.0018, standard error = 0.0009 [p <0.05])	Adjusted for age, systolic blood pressure, and low-density lipoprotein cholesterol
For all participants, smoking (μm/pack-years) was associated with a 2.25 mm ± 0.49 (p <0.0001) IMT increase, and for cases only a 1.91 mm + 1.04 (p <0.0001) increase for all sites measured	Adjusted for age, blood pressure, glucose, lipids, and body mass index; IMT sites included common segments, bifurcation segments, internal segments, near walls, and far walls

measured with ultrafast CT. In this same group the degree of extracoronary plaque found in carotid, aortic, and femoral arteries based on ultrasound measurements was strongly associated with smoking. The authors interpreted the contrast between the results for coronary calcium and extracoronary plaque in this study as a reflection of the fact that coronary calcification represents a more advanced lesion than uncalcified plaque, and may be influenced by the cumulative, long-term effects of smoking rather than by a current exposure to tobacco smoke (Simon et al. 1995).

Evidence Synthesis

Recently developed techniques can measure markers of subclinical atherosclerosis in healthy persons in community settings. These techniques have now been applied in a number of cohort and cross-sectional studies with repeated findings of a higher frequency of abnormalities in smokers. Consistently, both cross-sectional and cohort studies measuring carotid artery wall thickness or the AAI have demonstrated strong, dose-response associations between smoking and the presence and progression of subclinical atherosclerosis. Results from earlier autopsy studies and the PDAY and Bogalusa studies also suggest that smoking affects the progression of intermediate to advanced atherosclerotic lesions at early ages. Knowledge of the underlying mechanisms by which smoking causes atherosclerosis adds plausibility to these observations. Smoking has immediate adverse effects on the homeostatic balance of the cardiovascular system.

Studies using other markers, such as the presence of silent brain infarcts or white matter disease detected by an MRI or coronary calcium measured with CT, have been less consistent in their findings, possibly because of the limitations imposed by their cross-sectional nature. Longitudinal studies in progress will provide further data for examining the association between smoking and the development and progression of these subclinical markers.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis.

Implications

Cigarette smoking has a causal relationship with the full natural history of atherosclerosis from the time that it can be detected by sensitive, subclinical markers to its late and often fatal stages. The new findings on subclinical disease indicate the potential for preventing more advanced and clinically symptomatic disease through quitting smoking and maintained cessation.

Table 3.4 **Studies on the association between smoking and clinical peripheral arterial disease using the ankle-arm index (AAI)**

Study	Design/population	Age/gender
Newman et al. 1993	Cardiovascular Health Study Community-based Cross-sectional United States n = 5,201	65 years Both genders
Kornitzer et al. 1995	Occupational cohort Cross-sectional Belgium n = 2,023	40–55 years Men
Curb et al. 1996	Honolulu Heart Program Retrospective cohort United States n = 3,450	71–93 years Both genders
Hooi et al. 1998	Limburg Peripheral Arterial Occlusive Disease (PAOD) Study Community-based Cross-sectional Netherlands n = 3,650	40–78 years Both genders
Shinozaki et al. 1998	Occupational cohort Cross-sectional Japan n = 446	43 years (mean) Men
Fabsitz et al. 1999	Strong Heart Study Community-based American Indians Cross-sectional United States n = 4,549	45–74 years Both genders

*OR = Odds ratio.

†CI = Confidence interval.

‡ABI = Ankle/brachial blood pressure index.

§Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

 No age range was provided.

Main results	Comments
Adjusted OR* for the AAI <1.0 associated with smoking was 2.55	All differences were statistically significant even after adjusting for all main risk factors (history of diabetes, increasing age, nonwhite race)
AAI 0.90 was significantly associated with smoking	In multivariate analyses, the association with smoking was not significant (p = 0.09)

Adjusted OR (95% CI[†]) for the ABI[‡] <0.9 measured in 1991–1993 was associated with current smoking:
  Cross-sectionally (smoking in 1991–1993): 4.32 (2.92–6.39)
  Longitudinally (smoking in 1965–1968): 2.82 (2.15–3.69)
	Pack-years[§] were also associated with AAI in a dose-response fashion

Among persons without intermittent claudication, ABI <0.95 was significantly associated with smoking status	Smoking was more strongly associated with symptomatic than with asymptomatic PAOD
Adjusted OR for AAI <1.0 associated with smoking was 1.74 (95% CI, 1.31–2.99)	None
A low AAI (<0.9) was significantly associated with current cigarette smoking and with pack-years	Associations persisted in multivariate analyses with age, systolic blood pressure, current cigarette smoking, pack-years of smoking, albuminuria (micro and macro), low-density lipoprotein cholesterol level, and fibrinogin level

Table 3.5 **Studies on the association between smoking and the presence of subclinical cardiovascular disease using brain magnetic resonance imaging**

Study	Design/population	Age/gender
Breteler et al. 1994	Rotterdam Elderly Study Community-based Cross-sectional Netherlands n = 111	65–84 years Both genders
Longstreth et al. 1996	CHS[†] Community-based Cross-sectional United States n = 3,301	65 years Both genders
Yamashita et al. 1996	Cross-sectional Japan n = 246	50–75 years Men
Liao et al. 1997	ARIC[§] Study Cross-sectional Community-based United States n = 1,920	51–70 years Both genders
Howard et al. 1998b	ARIC Study Community-based Cross-sectional United States n = 1,737	55–72 years Both genders
Longstreth et al. 1998	CHS Community-based Cross-sectional United States n = 3,660	65 years Both genders

*WML = White matter lesion.
[†]CHS = Cardiovascular Health Study.
[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[§]ARIC = Atherosclerosis risk in communities.
 HDL = High-density lipoprotein.
[¶]BMI = Body mass index.

Main results	Comments
No association was observed between the presence of WMLs* and current or former smoking after adjusting for age and gender	No substantial change in the results was found after further adjustments for a previous stroke and myocardial infarction
In analyses adjusted for age and gender, ever smoking cigarettes (p <0.001) and more pack-years‡ of smoking (p <0.05) were associated with WML grade	None
Cigarette smoking was not related to silent brain infarctions	No adjustments were mentioned

Age, race, and gender were adjusted proportionally by WML grade

	WML grade			
	Normal	Mild	Moderate	Severe
	0	1	2	3–9
Smoking status				
Current smokers	12.3	45.0	24.5	18.2
Former smokers	13.4	52.5	22.9	11.3
Never smoked	16.5	49.8	22.7	10.9

Linear trend was statistically significant (p = 0.004)

Odds ratios (OR) for silent cerebral infarctions:

	OR	OR when adjusted for other risk factors
Smoking status		
Nonsmokers	1	1
Smokers exposed to environmental tobacco smoke	1.03	1.06
Former smokers	1.32	1.16
Current smokers	2.13	1.88

Cigarette smoking had a significant ordinal association (p = 0.029); other risk factors included demographics, cerebrovascular disease risk factors (HDL , triglycerides, hypertension, and diabetes), and lifestyle factors (fat and alcohol intake, BMI¶, and physical activity)

In analyses adjusted for age and gender, pack-years were associated with silent lacunar infarcts (p <0.05)	None

Table 3.5   Continued

Study	Design/population	Age/gender
Shintani et al. 1998	Hospital-based Cross-sectional Japan n = 270	40–87 years Both genders

Smoking, Coronary Heart Disease, and Sudden Death

Epidemiologic Evidence

Coronary Heart Disease

CHD results from atherosclerosis of the coronary arteries. Atherosclerosis is evident in persons as young as 20 years of age but becomes more severe with clinically evident manifestations in middle to older adulthood. The category of CHD includes MI, ischemic heart disease, and angina pectoris. MI results from an interruption of blood flow through the coronary arteries to the myocardium, with acute injury and then scarring and permanent damage to the heart muscles. Ninety percent of those who die from sudden cardiac death have at least two coronary arteries with about 90 percent occlusion. Angina pectoris refers to the chest pain a person experiences resulting from a lack of blood flow to the heart muscle.

The United States has experienced an epidemic of CHD for the past 50 years, and CHD remains the leading cause of death for Americans. In 2003, an estimated 1.1 million Americans had a new or recurrent coronary attack (AHA 2002). In spite of treatment advances, the prognosis after a coronary event is still poor, as 25 percent of men and 38 percent of women die within one year after a recognized MI. Due to primary and secondary prevention interventions and better quality of care for CHD, age-specific death rates from CHD have been substantially declining during the last four decades (Gillum 1994). However, compared with a decline of approximately 25 percent in rates between 1978 and 1997 in the United States, the actual number of deaths has only declined by approximately 9 percent over the same period because the American population is aging. Although 85 percent of those who die of CHD are 65 years or older, CHD also affects younger adults. In Americans younger than 65 years of age, approximately 80 percent of CHD mortality occurs during the first coronary event (AHA 2002).

Previous Surgeon General's reports have reviewed the evidence firmly establishing that smoking is a major cause of CHD (USDHHS 1990). Since these reports, there have been several additions to the large body of evidence previously considered. First, the new data support a causal association between smoking and MI across various racial and ethnic groups (USDHHS 1998). Second, smoking has been identified as a strong risk factor for MI in women younger than 50 years of age (Rosenberg et al. 1985; Croft and Hannaford 1989), even though the incidence of MI is very low in this population. A case-control study of women younger than 44 years of age (mean age 41 years) found that the OR for MI showed a strong dose-response relationship, with a risk of 2.47 (95 percent CI, 1.12–5.45) for those smoking 1 to 5 cigarettes per day and rising to 74.6 (95 percent CI, 33–169) for those smoking more than 40 cigarettes per day compared with nonsmokers (Dunn et al. 1999). The reported population attributable risk for tobacco use and MI in this group was 73 percent. Third, in data on female

Main results	Comments
There was no association between silent lacunar infarctions and smoking habits with or without adjusting for other main risk factors (serum levels or total cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), hemoglobin A1c, age, gender, systolic blood pressure, diastolic blood pressure, duration of hypertension, family history, alcohol intake, obesity [BMI], and atrial fibrillation)	None

smokers from the study by Prescott and colleagues (1998), the highest risk (6.8) for MI was in women younger than 55 years of age. Fourth, prospective cohort results based on approximately 1,100 coronary disease events observed in a 14-year follow-up of about 86,000 women from the Nurses Health Study (Stampfer et al. 2000) showed strong dose-response relationships between the number of cigarettes smoked per day and the risk of CHD. The adjusted RRs of CHD for former smokers, for women smoking 1 to 14 cigarettes per day, and for those smoking 15 or more cigarettes per day were 1.55, 3.12, and 5.48, respectively, compared with lifetime nonsmokers. A further analysis of the Nurses Health Study suggests that the reduction in smoking observed in this cohort from 1980–1994 explains about 13 percent of the concurrent decline in CHD incidence (Hu et al. 2000). Finally, whereas most of the earlier evidence has come from studies in populations of predominantly European origin, recent studies have also demonstrated that the association between smoking and CHD is of a similar magnitude in other ethnic groups, such as African Americans (Liao et al. 1999; Rosenberg et al. 1999).

A recent meta-analysis summarized the cohort studies that measured the effect of smoking cessation on mortality after having an MI (Wilson et al. 2000). Thirteen studies meeting the analysis criteria were reviewed. The combined OR in former smokers compared with current smokers, based on a random effects model for death after MI, was 0.54 (95 percent CI, 0.46–0.62), with no significant heterogeneity among the studies. There was no difference in the OR for studies published before and after 1980. The results did not vary by gender, age, country in which the study took place, or the quality of the study.

The beneficial impact of smoking cessation on survival after acute MI is well established. Several recent studies show that cessation is beneficial at the time of and after percutaneous coronary artery vascularization for CHD. At the time of revascularization, substantial differences between risk factor profiles in smokers and nonsmokers have been observed. About one-third of those who receive percutaneous coronary artery vascularization are current smokers, and 50 to 60 percent continue to smoke after the procedure. Probably because of the thrombogenic properties of tobacco smoking, smokers are usually younger, have had angina for a shorter period of time, and have more favorable profiles for other traditional cardiac risk factors, such as hypertension and hypercholesterolemia, than their nonsmoking counterparts. This more favorable risk factor profile may explain the better outcomes for smokers found in several studies (Barbash et al. 1995).

For studies of outcomes after percutaneous coronary artery vascularization, careful consideration needs to be given as to which measure to use. Because cigarette smoking may increase the rate of restenosis, using repeat percutaneous coronary artery vascularization procedures or coronary artery bypass surgery as the outcome is problematic. However, many physicians are reluctant to recommend invasive procedures for patients who continue to smoke, even if their symptoms return (Underwood and Bailey 1993). One of the largest studies with a broad assessment of outcomes is based on 5,437 patients who had a successful percutaneous coronary artery revascularization and were followed for a mean of 4.5 years (Hasdai et al. 1997). Persistent smokers were at significantly greater risks for electrocardiographically confirmed infarctions

and death than were nonsmokers, and this trend was evident when compared with those who quit smoking after the vascularization. Persistent smokers were less likely to have a repeated percutaneous procedure or coronary bypass surgery than were nonsmokers, but this difference could be due to a reluctance by clinicians to recommend invasive procedures for those who are still at a higher risk for atherogenesis as a consequence of smoking (Hasdai et al. 1997).

Dose-response relationships between tobacco smoking and CVD have been readily established for the highest levels of cigarette smoking, but most studies have not had a sufficient sample size to assess the level of risk for those smoking only a few cigarettes per day. A recent report assessed 25-year mortality rates for the 12,763 men in the Seven Countries Study. Compared with nonsmokers, those smoking one to nine cigarettes per day had a hazard ratio of 1.2 (95 percent CI, 0.99–1.44) for CHD, 1.3 (95 percent CI, 0.51–3.28) for other arterial diseases (Jacobs et al. 1999), and 1.3 (95 percent CI, 1.17–1.43) for total deaths. All of these results were adjusted for baseline cohort of residence, age, BMI, serum cholesterol, systolic blood pressure, and the presence of clinical CVD.

During the past 40 years, there have been numerous changes in cigarette design and manufacturing, with sharp declines in tar and nicotine yields according to measurements based on the Federal Trade Commission protocol (National Cancer Institute [NCI] 1996). During this same interval, a number of case-control studies have assessed cigarette type or tar and nicotine yields and the risk for CVD including MI, CHD mortality, and stroke. The possibility that lower-yield products might be associated with lower risks for CHD draws plausibility from the postulated roles of both nicotine and carbon monoxide in increasing the risks for MI.

However, studies conducted since the 1960s have not consistently found lower risks for CHD in smokers of lower-yield cigarettes (Table 3.6). For acute MI, large case-control studies show that risk does not vary with measures of tar, nicotine, or carbon monoxide yields. Several cohort studies do show lower mortality rates from CHD among users of lower-yield products, but the effects are small. The American Cancer Society Cancer Prevention Study I (CPS-I) found that smokers of lower-tar cigarettes had slightly lower mortality rates from heart disease compared with smokers of high-tar cigarettes (Hammond et al. 1976). In contrast, neither a case-control study of men (Kaufman et al. 1983) nor that of women (Palmer et al. 1989) found any association between cigarette tar yields and the risk of nonfatal MI, and a case-control

study from Italy conducted in the late 1980s also failed to identify a clear trend between cigarette tar yields and risks of acute MI (Negri et al. 1993).

Several more recent studies have found that low-tar cigarettes appear to slightly lower the risks of CHD associated with tobacco smoking (Tang et al. 1995). Four cohorts of British men (n = 56,255) first enrolled in 1967 and followed for an average of 13 years were assessed for all-cause and CHD mortality. An estimated 18 percent of the cohort who smoked manufactured cigarettes reported smoking primarily plain (unfiltered) cigarettes. The RR for CHD (0.76 [95 percent CI, 0.56–1.03]) was lower among filter-tipped cigarette smokers compared with smokers of plain cigarettes. Point estimates for mortality from each smoking-related disease were consistently lower for filter-tipped cigarette smokers than for plain cigarette smokers, but only the relative mortality for all smoking-related diseases was significantly different (RR = 0.83 [95 percent CI, 0.68–1.00]). Another major study investigating the impact of low-tar cigarettes on CHD was based on 13,926 cases and 32,389 controls in the United Kingdom sample of the International Studies of Infarct Survival clinical trial (Parish et al. 1995). Tar yield was classified based on self-reports of the brand of cigarettes usually smoked. For this cohort, almost all smoked filter-tipped cigarettes, and 25 percent used low-tar brands. Because a reduction in tar yields had already occurred by the time of the study, no participants were classified in the high-tar category. With standardization for age, gender, and the daily number of cigarettes smoked, the incidence of MI was 10.4 percent higher in medium-tar compared with low-tar cigarette smokers (p = 0.06). Among persons aged 30 through 59 years, the incidence was 16.6 percent higher (p = 0.02).

There has been a continued suggestion that the association of smoking with CVD risk and with CHD risk specifically could reflect an inadequate control of confounding by lifestyle-related risk factors. Countering this argument are the findings of many studies showing that carefully controlling for these other risk factors does not substantially change the strength of the smoking-CVD association. A recent analysis from the Cancer Prevention Study II (CPS-II) of more than 900,000 adults examined the changes in relative and attributable risks for CHD associated with smoking, comparing models that only adjusted for age with models that also adjusted for other risk factors (Thun et al. 2000). The risk estimates for CHD outcomes were unchanged with multivariate adjustments for potential confounders in both men and women and younger and older persons. The total number of annual CHD

deaths in the United States attributable to smoking changed from an estimated 91,500 in the age-adjusted only model to an estimated 94,200 in the multivariate model that controlled for aspirin use, alcohol consumption, BMI, physical activity, and dietary fat consumption. Thus, controlling for major risk factors had little consequence, and it is doubtful that there would be substantial residual confounding by other factors, whether known or still unknown. In fact, it seems unlikely that there are still unknown risk factors that have both sufficiently strong associations with cigarette smoking and sufficiently strong effects on CHD risk to be important confounders of the smoking-CHD association.

Sudden Death

Sudden death is the sudden, abrupt loss of heart function in a person who may or may not have a diagnosed heart disease, for whom the time and mode of death are unexpected, and for whom death occurs instantly or shortly after the onset of symptoms (AHA 2002). Sudden cardiac death is usually due to cardiac arrest from untreated cardiac arrhythmias, and it may have been the first manifestation of CHD.

Cigarette smoking might increase the risk of sudden cardiac death by increasing platelet adhesiveness, releasing catecholamines, causing acute thrombosis, and promoting ventricular ectopy (arrhythmias). The morphology of cardiac vessels is different in smokers than in nonsmokers who die suddenly from coronary disease. Smokers are more likely to have acute thrombosis than stable plaques at the time of death, but the frequency of plaque rupture and eroded plaque that cause thrombosis is the same in smokers and nonsmokers (Burke et al. 1997). Evidence also indicates that nicotine affects the conductance of myocardial cell channels, providing a plausible mechanism for the putative association of cigarette smoking (and smokeless tobacco use) with arrhythmias and sudden death (Wang et al. 2000).

Cigarette smoking has been associated with sudden cardiac death of all types. During 26 years of follow-up in the Framingham Heart Study, there were 177 sudden deaths in men and 50 in women. One-half of the deaths in men and 75 percent of those in women occurred without evidence of prior CHD. Smokers had a RR of 2.5 compared with nonsmokers (p <0.001), and men had a higher RR for smoking than women (Kannel et al. 1975). In the Nurses Health Study, women who smoked more than 25 cigarettes per day died of CHD at a much higher rate than nonsmokers (RR = 5.4 [95 percent CI, 3.0–10.4]), but the risk was similar for nonfatal MI (RR = 5.8 [95 percent CI, 4.2–8.0]) (Willett et al. 1987). A case-control study of Tasmanian men found a threefold increase in the risk of sudden, unexpected cardiac death from current smoking (Sexton et al. 1997). In a study based on the National Mortality Followback Survey, current smoking was associated with an adjusted OR of 1.8 (95 percent CI, 1.2–2.7) for sudden death in those without a history of CHD (Escobedo and Caspersen 1997). Although many studies document the relationship between tobacco smoking and sudden cardiac death, the association does not seem to be stronger than the relationship between tobacco smoking and MI or CHD in general.

Nicotine has well-characterized effects on the cardiovascular system and increases heart rate through activiation of the sympathetic nervous system (USDHHS 1988). Smoking is associated with increased risk for sudden cardiac death in men and women (USDHHS 1983; Albert et al. 2003). This association might reflect underlying artherosclerosis caused by smoking and possibly an effect of nicotine itself.

Congestive Heart Failure

Smoking-caused CHD may contribute to CHF. In contrast to CHD and stroke, the incidence of CHF is increasing. An estimated 4.6 million Americans have CHF, and 43,000 persons die from CHF every year. In the third National Health and Nutrition Examination Survey (NHANES), the prevalence of CHF ranged from 6.2 percent for men between 55 and 64 years of age to 9.8 percent for men over 75 years of age. The corresponding figures are 3.4 percent and 9.7 percent, respectively, for women (AHA 2002).

Since tobacco smoking has been causally linked to MI and CHD, it is reasonable to consider the extent to which smoking may contribute to causing CHF. Within six years of a recognized MI, 22 percent of men and 46 percent of women will be disabled with heart failure (Ho et al. 1993). Survival after the onset of CHF is poor. According to Framingham Study data collected between 1948 and 1988, five-year survival rates are 25 percent for men and 38 percent for women with CHF (Ho et al. 1993). In the first NHANES Epidemiologic Follow-up Study, cigarette smoking was an independent risk factor (RR = 1.59 [95 percent CI, 1.39–1.83]) for the development of CHF over the 19-year follow-up (He et al. 2001). The estimated population attributable risk for tobacco smoking was 17.1 percent, higher than any other risk factor with the exception of pre-existing CHD. This estimate may be low because the contribution of tobacco smoking to pre-existing CHD was not included in this estimate. Since CHD is

Table 3.6   Studies on the association between smoking low-yield cigarettes and the risk of cardiovascular disease (CVD)

Study	Design/population	Variable analyzed
Hammond et al. 1976	Cohort study of 1 million volunteers in the American Cancer Society Cancer Prevention Study followed from 1960–1972	Tar content (high: 25.8–35.7 mg/cigarette, medium: 17.6–25.7 mg/cigarette, low: <17.6 mg/cigarette)
Hawthorne and Fry 1978	Prospective follow-up study of 18,786 persons attending a multiphasic screening examination from 1965–1977; Scotland	Filter-tipped vs. plain cigarettes
Todd et al. 1978	Prospective cohort study of 10,063 persons aged 35–69 years in a 12.4 year follow-up period from 1965–1977, from a random sample in Great Britain	Filter-tipped vs. plain cigarettes
Lee and Garfinkel 1981	Prospective mortality study of >1 million men and women in a 12-year follow-up period from 1960–1972; United States	Tar yield: low/high
Higenbottam et al. 1982	Cohort study of 17,475 male civil servants aged 40–64 years, and a sample of 8,089 male British residents aged 35–69 years	Current cigarette smoking habits
Borland et al. 1983	Prospective cohort of the Whitehall Study of 4,910 men who smoked cigarettes with known carbon monoxide (CO) yields, followed from 1976–1979; Great Britain	CO yields
Kaufman et al. 1983	Case-control study of 1,337 men aged 30–54 years; northeastern United States	Nicotine and CO yields

*CHD = Coronary heart disease.
†RR = Relative risk.
‡CI = Confidence interval.
§MI = Myocardial infarction.

Outcome	Results
CHD* mortality	Compared with high-tar smokers: CHD standardized mortality ratio = 1.03 for medium-tar smokers and 0.82 for low-tar smokers
CVD mortality	RR[†] of CVD mortality = 1.05 for smokers of filter-tipped cigarettes compared with smokers of plain cigarettes
CHD mortality	RR for men = 0.75 for smokers of filter-tipped cigarettes compared with smokers of plain cigarettes; and 1.03 for women who smoked filter-tipped cigarettes compared with women who smoked plain cigarettes
CHD mortality	RR for men = 0.90 for smokers of low-tar yield cigarettes compared with smokers of high-tar yield cigarettes; and 0.81 for women smokers of low-tar yield cigarettes compared with women smokers of high-tar yield cigarettes
CHD mortality	Ten-year CHD mortality rates per 100 deaths standardized for age; employment grade among inhalers = 4.29 for consuming 1–9 cigarettes/day, 5.98 for 10–19 cigarettes/day, 6.56 for 20 cigarettes/day; among noninhalers, 3.48 for 1–9 cigarettes/day, 5.73 for 10–19 cigarettes/day, and 5.18 for 20 cigarettes/day; coronary deaths were more common among inhalers; effects of tar/nicotine yields were confined to inhalers
CHD mortality	RR = 1.47 in those smoking cigarettes with <18 mg CO yield compared with smokers of cigarettes with 20 mg CO yield, adjusted for age, grade of employment, cigarettes/day, and tar yield; persons smoking high CO-yield cigarettes (>20 mg) smoked fewer cigarettes/day
MI[§]	RR = 2.8 (95% CI[‡], 2.0–4.0) for current smokers compared with nonsmokers; risk varied with number of cigarettes smoked (up to 7.5 [95% CI, 3.7–15.3] for men aged 30–44 years who smoked 45 cigarettes/day); little or no significance was found comparing lower with higher nicotine yields: 3.0 (95% CI, 1.9–4.9) for <0.8 mg/cigarette to 2.6 (95% CI, 1.5–4.4) for 1.5 mg/cigarette; or in CO levels: 2.7 (95% CI, 1.5–4.8) for <10 mg/cigarette to 2.8 (95% CI, 1.5–5.1) for 19 mg/cigarette

Table 3.6   Continued

Study	Design/population	Variable analyzed
Alderson et al. 1985	Case-control study of 12,693 in-patients from 1977–1982; Great Britain	Always filter-tipped vs. plain cigarettes
Petitti and Friedman 1985	Prospective cohort study of 16,270 current regular cigarette smokers and 42,113 persons who never used any form of tobacco, from 1979–1983; United States	Low-yield cigarette use
Palmer et al. 1989	Case-control study of 910 women <65 years of age with incident MI, and 2,375 hospital controls; United States	Low-yield cigarette use
Kuller et al. 1991	Prospective cohort study of a 10-year follow-up of the Multiple Risk Factor Intervention Trial of men from 1972–1985; United States	Tar and nicotine levels
Negri et al. 1993	Multicenter case-control study, 916 patients with acute MI without a history of IHD[¶] and 1,106 controls admitted to the hospital for acute conditions unrelated to risk factors for IHD, between September 1988 and June 1989, from over 80 coronary care units in various regions of Italy	Cigarette tar and nicotine yields
Parish et al. 1995	Hospital-based, case-control study of 4,923 recently discharged MI cases and 6,880 controls, all current smokers of cigarettes with known tar yields, early 1990s, United Kingdom	Tar yields of manufactured cigarettes were assessed at the beginning of the study

OR = Odds ratio.
[§]IHD = Ischemic heart disease.

Outcome	Results
CHD mortality	Aged 35–54 years: OR = 1.78 for men who always smoked filter-tipped cigarettes compared with men who always smoked plain cigarettes; 0.24 for women who always smoked filter-tipped cigarettes compared with women who always smoked plain cigarettes; aged 55–74 years: OR = 2.67 for men who always smoked filter-tipped cigarettes compared with men who always smoked plain cigarettes; 1.32 for women who always smoked filter-tipped cigarettes compared with women who always smoked plain cigarettes; all ORs were adjusted for the number of cigarettes/day
CVD and MI[§]	RR = 1.15 (95% CI, 1.05–1.27) for CVD per 5.0 mg increase in tar among current cigarette smokers compared with nonsmokers, adjusted for age, gender, and race; RR = 1.22 (95% CI, 1.00–1.50) for acute MI per 5.0 mg increase in tar among current cigarette smokers compared with nonsmokers, adjusted for age, gender, and race; CVD risk was consistently higher in smokers of higher-yield cigarettes compared with smokers of lower-yield cigarettes (small differences in magnitude)
Nonfatal MI risk	RR = 4.7 (95% CI, 2.8–8.0) for current smokers who smoked brands with the lowest nicotine levels (<0.40 mg/cigarette) compared with lifetime nonsmokers; 4.2 (95% CI, 2.4–7.2) for smokers of higher-yield brands (>1.30 mg)
CHD mortality	Compared with men who smoked cigarettes with nicotine levels 1 mg, RR = 1.04 (95% CI, 0.8–1.35) for men who smoked cigarettes with 1.1–1.4 mg and 1.27 (95% CI, 0.92–1.77) for men who smoked cigarettes with 1.5 mg; compared with men who smoked cigarettes with tar levels 15 mg, RR = 1.08 (95% CI, 0.8–1.45) for men who smoked cigarettes with 16–19 mg and 1.19 (95% CI, 0.86–1.65) for men who smoked cigarettes with 20 mg; estimates were adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes/day; low-tar and low-nicotine cigarette smokers smoked more cigarettes/day
MI risk	Compared with nonsmokers, RR = 3.8, 4.3, 3.2, and 3.7 for the four categories of tar yield (<10, 10–15, 16–20, and >20 mg/cigarette, respectively); there was no trend in risk across yields when the analysis was restricted to smokers; RR = 1.2, 0.8, and 1.0 for higher-yield categories, respectively, compared with the lowest-yield category; RR = 9.3–12.6 for persons aged <50 years but no trend was observed with increasing yields; thus, lower-tar yields were not effective for reducing MI morbidity
Incident nonfatal MI	After standardization for age, gender, and amount smoked, the rate was 10.4% higher (standard deviation = 5.4) in medium-tar (10 mg/cigarette) than in low-tar (<10 mg/cigarette) cigarette smokers (p = 0.06)

Table 3.6   Continued

Study	Design/population	Variable analyzed
Tang et al. 1995	Four cohort studies of 56,255 men between 1967 and 1982 from the British United Provident Association Study (London), Whitehall Study (London), Paisley-Renfrew Study (Scotland), and United Kingdom Heart Disease Prevention Project	Tar yields of manufactured plain and filter-tipped cigarettes were assessed at the beginning of the study
Powell et al. 1997	Case-control study, 291 smokers with newly referred peripheral arterial disease, 828 controls without the disease, from outpatient clinics, 1988–1992, London, United Kingdom	Tar and nicotine yields and carboxyhemoglobin levels

the underlying cause for roughly 65 percent of CHF cases, the risk of CHF from smoking is probably mediated through CHD.

Evidence Synthesis

These new data reaffirm the already well-documented causal association of smoking with the risk for CHD. Compared with lifetime nonsmokers, the RR in smokers rises with the number of cigarettes smoked and falls after cessation. The type of cigarette smoked has little influence on CHD risk. The association cannot be explained by confounding.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease.

2. The evidence suggests only a weak relationship between the type of cigarette smoked and coronary heart disease risk.

Implications

Because of its prevalence, smoking is a major cause of CHD, particularly among younger smokers. While CHD mortality rates have continued to fall, a substantial proportion of the population's burden of CHD could be avoided with smoking prevention and cessation. Products with lower yields of tar and nicotine, as measured by a smoking machine, have not been found to reduce CHD risk substantially and they are not a lower-risk alternative for smokers who cannot quit. By causing CHD and MI, smoking may also contribute to the development of CHF, an increasingly frequent disease that is disabling and has a poor prognosis.

Outcome	Results
Mortality from CHD and stroke	Compared with lifetime nonsmokers, RR for CHD = 1.21 (95% CI, 1.06–1.38) for former smokers, 2.05 (95% CI, 1.73–2.42) for current smokers of plain cigarettes, and 1.94 (95% CI, 1.70–2.21) for current smokers of filter-tipped cigarettes; RR for stroke = 1.0 (95% CI, 0.73–1.36) for former smokers, 1.98 (95% CI, 1.36–2.88) for current smokers of plain cigarettes, and 1.62 (95% CI, 1.19–2.21) for current smokers of filter-tipped cigarettes; risk of IHD and stroke showed an interaction with age; relative mortality in cigarette smokers of a 15 mg decrease in tar yield/cigarette was 0.77 (95% CI, 0.61–0.97) for CHD and 0.86 (95% CI, 0.50–1.50) for stroke
Peripheral arterial disease	OR = 1.75 for smokers of cigarettes with ≥14 mg tar compared with smokers of cigarettes with <9 mg; 1.54 for smokers of cigarettes with ≥1.2 mg nicotine compared with smokers of cigarettes with <0.8 mg; 1.62 for whole blood carboxyhemoglobin ≥4.5% among cases compared with whole blood carboxyhemoglobin <2.7% among controls; all ORs were adjusted for age, gender, and depth of inhalation

Smoking and Cerebrovascular Disease

Cerebrovascular disease is a syndrome of neurologic deficits resulting from interruptions in the arterial blood flow to the brain. Deficits range from mild to severe, depending on the zone of the brain that is affected, and can be transitory (transient ischemic attack) or permanent (stroke). In the United States, the incidence of stroke is an estimated 600,000 cases per year. The one-year, case-fatality rate is about 30 percent, and strokes caused an estimated 160,000 deaths in the United States in 1996 (the third leading cause of death after CHD and malignant neoplasms). According to estimates from the AHA (2002), there are approximately 4.6 million stroke survivors in the United States, with cases equally distributed between women and men.

The causes of strokes are either ischemic (brain infarction stemming from a reduction of blood flow because of local atherothrombosis or emboli from the heart or extracranial arteries) or hemorrhagic (either subarachnoid or parenchymal). Many of the pathophysiologic mechanisms discussed in preceding sections for atherosclerosis and CHD also apply to cerebrovascular disease, particularly for ischemic stroke.

The epidemiologic association between cigarette smoking and stroke is well established. The 1964 Surgeon General's report summarized studies conducted in the 1950s describing the increase in mortality from strokes in smokers compared with nonsmokers (USDHEW 1964). Subsequent Surgeon General's reports reviewed further evidence indicating that (1) smoking is clearly associated with an increase in both the incidence of and mortality from cerebrovascular disease; (2) smoking is associated with the risk of both ischemic stroke and subarachnoid hemorrhage; (3) the smoking-associated risk of stroke is particularly elevated in younger persons, and the smoking-associated risk of subarachnoid hemorrhage is elevated in women (USDHHS 1990); and (4) as with many other smoking-related diseases, later studies (e.g., CPS-II 1982–1986) tend to show a higher RR of stroke in relation to smoking than did earlier studies (e.g., CPS-I 1959–1965). These more recent findings may be explained by cohort effects related to smoking duration and earlier smoking initiation in birth cohorts who reached middle to older ages (Garfinkel and Stellman 1988).

A meta-analysis reviewed 32 case-control and cohort studies and documented that cigarette smoking increased the risk of stroke by an estimated 50 percent, although the effect differs according to stroke subtype: the RR for ischemic stroke was 1.9, and 2.9 for subarachnoid hemorrhage, but no elevation in risk was found for cerebral hemorrhage (Shinton and Beevers 1989).

Based on the wealth of epidemiologic, biologic, and laboratory evidence available at the time, the 1989 Surgeon General's report concluded that there was a causal association between smoking and cerebrovascular disease (USDHHS 1989). Using estimates of prevalence and RR from the large CPS-II study, the report estimated that among persons younger than 65 years of age, smoking was responsible for 51 percent of cerebrovascular disease deaths in men and 55 percent in women.

The 1990 Surgeon General's report on smoking cessation examined all previously published studies comparing the risk of stroke for lifetime nonsmokers with both current and former smokers (USDHHS 1990). The report confirmed previous conclusions of a twofold to fourfold increase in risk associated with current smoking and concluded that the risk decreases steadily after smoking cessation, becoming indistinguishable in former smokers from that of lifetime nonsmokers after 5 to 15 years, depending on the study.

Epidemiologic Evidence

Both case-control and cohort studies published since the 1990 Surgeon General's report have confirmed the epidemiologic association of cigarette smoking with the main subtypes of stroke (i.e., ischemic stroke and subarachnoid hemorrhage). One of the most important publications provides results from the British Doctors Study, reporting an association between smoking and stroke (among other disease outcomes) in more than 30,000 male British physicians followed for over 40 years, from 1951–1991 (Doll et al. 1994). These findings confirmed previous reports of a strong and consistent epidemiologic association between smoking and mortality from stroke subtypes. Compared with lifetime nonsmokers, current smokers at baseline had RRs of 1.31 for thrombotic stroke, 1.37 for hemorrhagic stroke, and 2.14 for subarachnoid hemorrhage. Dose-response relationships with an increasing number of cigarettes smoked per day were reported for both thrombotic and hemorrhagic subtypes, and were particularly strong for subarachnoid hemorrhage (RR = 1.43, 1.71, and 3.43 for smokers of

1–14, 15–24, and >24 cigarettes per day, respectively; p for trend <0.001).

Another report addressed the association between smoking and stroke mortality in the Multiple Risk Factor Intervention Trial (MRFIT) (Kuller et al. 1991). Among the more than 360,000 people initially screened, current smokers had a RR for overall stroke mortality of 2.5 (p <0.001) during a 10-year follow-up, with a clear dose-response relationship between an increased risk and an increase in the average number of cigarettes smoked per day.

In addition to the risk for stroke mortality, other studies have reported on the effects of smoking on stroke incidence. Data from a 10-year follow-up of more than 22,000 participants in the United States Physicians Study showed that, compared with lifetime nonsmokers, current smokers of 1 to 19 cigarettes per day had an age-adjusted RR for stroke incidence of 2.02 (95 percent CI, 1.23–3.31), and smokers of 20 or more cigarettes per day had an adjusted RR of 2.52 (95 percent CI, 1.75–3.61; p for trend <0.0001) (Robbins et al. 1994). Similar dose-response associations between the amount smoked and stroke incidence were reported in the British Regional Heart Study, a population-based cohort study of about 7,700 middle-aged men (Shaper et al. 1991). In subsequent analyses of this study (Wannamethee et al. 1995), stroke risks for former smokers fell to the lowest levels around five years after smoking cessation; the remaining risk levels depended on the amount smoked: former heavy smokers fell to a level similar to that of light smokers, and former light smokers fell to a level similar to that of lifetime nonsmokers. Switching to a pipe or cigar had little effect on risk. Benefits from smoking cessation were observed after controlling for all possible relevant confounders and were present in both normotensive and hypertensive persons, although the benefit seemed to be more marked in the latter group. This study also confirmed the conclusions of the 1990 Surgeon General's report on the benefits of smoking cessation on stroke risk (Wannamethee et al. 1995).

The above studies were all conducted on men of mostly European origin. However, there is a wealth of evidence demonstrating that smoking is also associated with strokes in women and in all ethnic groups and countries where the hypothesis has been tested. In contrast to some earlier studies that suggested that the RR for stroke (especially subarachnoid hemorrhage) was more elevated in female smokers than in male smokers, recent cohort studies of a variety of population samples tend to show similar RRs in both men and women. In a large cohort study of more than

42,000 participants in a health survey in Finland, RRs for the incidence of subarachnoid hemorrhage were 2.4 (95 percent CI, 1.6–3.7) in men and 2.5 (95 percent CI, 1.5–4.1) in women, independent of other known stroke risk factors (i.e., age, hypertension, and body weight) (Knekt et al. 1991). Another issue of particular concern to women is the possible synergism between oral contraceptives and smoking on the risks of stroke. Whereas earlier studies suggested that possibility (Kannel 1987), it was recently argued that low-dose oral contraceptive combinations may not interact with smoking to substantially increase these risks (Mishell 1999). However, a report based on a large cohort of reproductive-aged women in the Kaiser Permanente study (Petitti et al. 1996), where 408 strokes were observed among 1.1 million women (>3.6 million person-years of observation), found that the RRs for ischemic stroke and for hemorrhagic stroke among current smokers compared with nonsmokers were 2.66 (95 percent CI, 1.65–4.30) and 2.70 (95 percent CI, 1.71–4.27), respectively. The combination of smoking and low-dose oral contraceptives was associated with an overall stroke RR of 3.64 (95 percent CI, 0.95–13.87).

Even though few studies have published ethnic- or minority-specific data on the relationship between smoking and stroke risks, there is consistent evidence of an association in African Americans, a group with a particularly high risk for cerebrovascular disease (Gillum 1999). Furthermore, in ecologic analyses conducted with data from the World Health Organization's MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project, smoking and hypertension were the main factors explaining the variability of stroke mortality rates across populations (Stegmayr et al. 1997). Similar conclusions were reached in analyses based on persons from the multinational Seven Countries Study (Jacobs et al. 1999).

In a cohort study of a Korean population with low cholesterol levels, the risk for stroke was linearly associated with increasing amounts of cigarette smoking (Jee et al. 1999). Another large cohort study in an Asian population was conducted in a cohort of approximately 265,000 Japanese men and women (Hirayama 1990). The RRs for nonhemorrhagic strokes were only slightly elevated in current smokers compared with lifetime nonsmokers (1.08 in men and 1.18 in women), whereas for subarachnoid hemorrhage the corresponding RRs were 1.82 and 1.71.

The higher RRs for a subarachnoid hemorrhage compared with other stroke subtypes are consistent with the observations summarized in previous Surgeon General's reports as well as in most recent studies. Among those screened for the MRFIT, the smoking-related RR for a nonhemorrhagic stroke was 2.1, whereas the RR for a subarachnoid hemorrhage was 3.0 (Neaton et al. 1993). Teunissen and colleagues (1996) reviewed the data and consistently found smoking to be an independent risk factor for subarachnoid hemorrhage. The mechanisms for this increased risk are likely due to damage to the cerebral artery wall associated with one or more components of cigarette smoke (Weir et al. 1998). Cumulative damage to the arterial elastica layer can result in an aneurysmal dilatation, and the presence of this dilatation with the additional impact of smoking on vasoactivity, especially in the presence of hypertension, may create high risks for a hemorrhagic event.

Most of the recent studies described in this section adjusted for risk factors that could possibly confound the association between smoking and stroke. From the epidemiologic standpoint, only hypertension appears as consistently related to stroke risks as smoking does. However, controlling for blood pressure or hypertension status has very little effect on the observed strength of the smoking-stroke association seen in most studies. This finding would be expected, given the weak and inverse relationship of smoking with hypertension. In the analysis by Thun and colleagues (2000) of the CPS-II cohort, the estimate of stroke deaths for the United States based on the age-adjusted risk estimate was 21,400. With adjustment for several potential confounding factors there was a slight drop to about 17,800.

Evidence Synthesis

The more recent evidence remains fully consistent with a causal effect of smoking on risk for cerebrovascular disease. The recent evidence extends the range of populations in which an association with smoking has been demonstrated and shows consistent associations of smoking with all major types of stroke.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and stroke.

Implication

Cigarette smoking remains a major cause of stroke in the United States.

Smoking and Abdominal Aortic Aneurysm

Aortic aneurysm refers to the dilatation or expansion of the aorta between the arch and the division into the iliac arteries, while AAA occurs in the abdominal portion of the aorta. The aorta has a high pressure across its wall and rupture can quickly lead to death. Most AAAs are the result of atherosclerosis, although other conditions can cause them (Davies 1998). Evidence of pathogenesis includes atherosclerosis, degradation of elastin in the aorta's wall, and inflammation (Blanchard 1999). In the young trauma victims in the PDAY study, smoking was associated with the extent of atherosclerosis in the abdominal aorta (McGill et al. 2001). In the smaller sample from the Bogalusa Heart Study, the findings were similar (Berenson et al. 1998). The natural progression of AAAs is to grow increasingly larger, and when they become greater than 4 cm in diameter there is a substantial risk for rupture. Most persons do not have any symptoms until the aneurysm ruptures; at that point, sudden death can occur. Surgical repair is much less successful once the aneurysm begins to leak. Estimates for 2003 were that AAAs caused more than 15,000 deaths and 60,000 hospitalizations in the United States (AHA 2002).

Epidemiologic Evidence

Evidence linking tobacco smoking and aortic atherosclerosis has been available for several decades (Table 3.7). In 1983, the Surgeon General's report suggested that cigarette smoking aggravates or accelerates aortic atherosclerosis (USDHHS 1983), and several epidemiologic studies indicated that smokers had elevated death rates from ruptured abdominal aneurysms compared with nonsmokers. A literature review published in 1999 found a positive, strong, and independent association between smoking and AAA in 10 studies of cohort, case-control, and cross-sectional designs (Blanchard 1999).

The findings of the long-term cohort studies provide clear evidence for an association of smoking with AAA. During the 40 years of follow-up of the British physicians cohort, the risk for death from AAA was increased more than fourfold in current smokers compared with lifetime nonsmokers and was increased twofold in former smokers (Doll et al. 1994). In the

U.S. veterans cohort, there was a fivefold increase for current smokers and a more than doubling of mortality for this cause of death in former smokers (Rogot and Murray 1980). In CPS-I, the increased risk for current smokers was of a similar magnitude (Burns et al. 1997).

Recent studies not included in the 1999 review also confirm this association. For example, in a case-control study using state-of-the-art clinical and epidemiologic methods (Blanchard et al. 2000), smoking was strongly associated with AAA with adjustment for all known risk factors. A dose-response relationship was evident. Compared with lifetime nonsmokers, the adjusted OR was 2.75 (95 percent CI, 0.85–8.91) for 1 to 19 pack-years, 7.31 (95 percent CI, 2.44–21.9) for 20 to 34 pack-years, 7.35 (95 percent CI, 2.40–22.5) for 35 to 49 pack-years, and 9.55 (95 percent CI, 2.81–32.5) for 50 or more pack-years. Other recent case-control studies have also found dose-response relationships (Wilmink et al. 1999), as have earlier cohort studies.

As in other cohort studies published in recent years, the Edinburgh Artery Study, a population-based cohort study of men and women 55 through 74 years of age, found that current (or recent) smoking also was strongly associated with AAA (OR = 3.1 [95 percent CI, 1.5–6.2]) (Lee et al. 1997). This association can be partially explained by atherosclerosis (Reed et al. 1992), although cohort data from the Edinburgh Artery Study suggest an increased risk for aortic aneurysm associated with smoking beyond that from underlying atherosclerosis (Lee et al. 1997). Lee and colleagues (1997) found that smoking remained associated with a risk for incident aneurysm after adjusting for CVD and the AAI at baseline. In a cohort of Finnish males, risk for AAA was positively associated with the number of years of smoking (Törnwall et al. 2001) and with the number of cigarettes smoked in a 33-year cohort study in Sweden (Nilsson et al. 2001).

The CHS is a multicenter prospective cohort study of cardiovascular disease in older Americans (Alcorn et al. 1996). In the fifth year of follow-up, ultrasound was used to evaluate the abdominal aortas of all participants. The prevalence rates for aneurysm by smoking were 6.8 percent, 11.5 percent, and 14.4 percent for never, former, and current smokers, respectively.

Evidence Synthesis

Smoking causes atherosclerosis in arteries, including the abdominal aorta. Autopsy studies show that even young adults who smoke have more plaque in their aortas than do lifetime nonsmokers. Other mechanisms by which smoking might injure the abdominal aorta include inflammation and damage to elastin.

The epidemiologic evidence, coming from multiple studies of differing design and location, shows a strong association of smoking with risk for AAA. Dose-response relationships with the amount and duration of smoking have been reported and risks are lower in former than in current smokers. Uncontrolled confounding cannot explain the findings.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm.

Implication

Smoking is one of the few currently avoidable causes of this frequently fatal disease.

Summary

Research during the past decade has produced further evidence that tobacco smoking is causally related to all of the major clinical cardiovascular diseases. A large body of evidence coming from multiple populations, age groups, and both genders outlined in previous Surgeon General's reports indicates that tobacco smoking causes atherosclerosis and associated clinical syndromes. A dose-response relationship has been repeatedly demonstrated with higher levels of cigarette smoking and a longer duration of smoking. Evidence now suggests that light smokers (fewer than 10 cigarettes per day) have moderate but measurable increases in the risks for CVD, and passive smoking has been causally associated with CHD (California Environmental Protection Agency 1997; Scientific Committee on Tobacco and Health 1998). New evidence also documents that tobacco smoking is associated with subclinical or very early atherosclerosis. Multiple potential confounding factors have been considered, and none account for the association between tobacco smoking and CVD. Most large prospective studies of the association between smoking and cardiovascular outcomes conducted in recent years controlled for other known cardiovascular risk factors that could be proposed as possible confounders (e.g., diet, physical exercise, BMI, and other lifestyle habits).

The temporal relationship between tobacco smoking and CVD has never been in doubt due to the extensive data from carefully conducted prospective cohort studies. A large body of research documents the impact of tobacco smoke on a wide range of biologic processes related to atherosclerosis, establishing biologic plausibility. New evidence also documents that tobacco smoking is associated with subclinical atherosclerosis (i.e., with the presence of atherosclerosis) earlier in its natural history, before it manifests clinically. The cross-sectional and prospective evidence summarized in this chapter consistently demonstrates that tobacco smoking is related to the thickness of the intimal-medial layers of the carotid and popliteal arteries as well as to the presence of coronary atherosclerosis (by angiographic and pathology studies) and subclinical markers of cerebrovascular disease (white matter disease and subclinical infarcts). This conclusion is entirely consistent with the strong evidence linking tobacco smoking and clinical cardiovascular disease manifestations as reviewed in this and in previous Surgeon General's reports. Atherosclerosis is a complex disease process that progresses slowly across different vascular beds and involves multiple metabolic, inflammatory, and homeostatic pathways.

Table 3.7   Studies on the association between smoking and the risk of abdominal aortic aneurysm (AAA)

Study	Design/population	Tobacco exposure	Outcome
Kahn 1966	U.S. veterans cohort study 293,658 persons aged 31–84 years (mainly white male World War I [WWI] veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 8.5 years of follow-up United States (nationwide)	• Cigarettes/day • Pipes and cigars only	Death from nonsyphilitic aneurysm of the aorta
Weir and Dunn 1970	Cohort study 68,153 men aged 35–64 years 482,658 person-years of observation California Began in 1954	• Nonsmokers/all smokers • Packs/day	Death from aortic aneurysm
Rogot and Murray 1980	U.S. veterans cohort study (update) 293,658 persons aged 31–84 years (mainly white male WWI veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 16 years of follow-up United States (nationwide)	• Never smoked • Former cigarette smokers • Current cigarette smokers • Cigarettes/day • Cigars only • Pipes only	Death from aortic aneurysm
Strachan 1991	Whitehall Cohort Study of 18,403 male civil servants examined at the ages of 40–64 years 18-year follow-up England	• Nonsmokers • Manufactured cigarettes • Hand-rolled cigarettes • Pipes or cigars only	Death from aortic aneurysm

*CI = Confidence interval.
†RR = Relative risk.

Findings	Risk estimates (95% CI*)		Comments
• Significant mortality rate for current and former cigarette smokers (greater than expected) • Dose-response relationship was observed	Mortality ratios Total current smokers 10–20 cigarettes/day 21–30 cigarettes/day Current pipe and cigar smokers only Former cigarette smokers	 5.15 (significant) 5.58 (significant) 6.55 (significant) 1.76 2.75 (significant)	Never smokers were the comparison group; age distributions were standard-ized using the 1960 distribu-tion of the U.S. male popula-tion by single years; p values and 95% CIs were not provided
• Increased risk was associated with cigarette smoking	RR[†] Nonsmokers All smokers About 1/2 pack or less About 1 pack About 1 1/2 or more packs	 1.0 (referent) 2.64 2.44 2.88 2.54	Nonsmokers included pipe and cigar smokers; p values and 95% CIs were not provided
• Dose-response rela-tionship was observed with more cigarettes/day	Mortality ratios Former cigarette smokers All current cigarette smokers <10 cigarettes/day 10–20 cigarettes/day 21–39 cigarettes/day 40 cigarettes/day Cigars only Pipes only	 2.58 5.23 2.29 5.46 6.36 7.18 2.04 2.07	Never smokers were the comparison group; p values and 95% CIs were not provided
• 99 outcome events • All forms of tobacco use in this study were associated with increased mortality rates	Mortality ratios Manufactured cigarettes Hand-rolled cigarettes Pipes or cigars only	 5.3 (3.1–9.1) 20.1 (9.2–43.8) 5.4 (1.9–15.3)	Mortality ratios were calcu-lated against nonsmokers at entry; mortality ratios were adjusted for diastolic blood pressure, and were adjusted by analysis of matched sets using conditional logistic regression

Table 3.7   Continued

Study	Design/population	Tobacco exposure	Outcome
Doll et al. 1994	Cohort study 34,439 British male doctors who replied to a postal questionnaire in 1951 United Kingdom 1951–1991	• Nonsmokers • Former smokers • Current smokers • Cigarettes/day	Death from aortic aneurysm
Alcorn et al. 1996	Cross-sectional study 656 persons aged 65–90 years from a Pittsburgh subgroup of the Cardiovascular Health Study Pittsburgh 1990–1992	• Never smoked • Former smokers • Current smokers	AAA was defined as an infrarenal aortic diameter 3 cm, an infrarenal to suprarenal diameter ratio 1.2, or a history of AAA repair
Powell et al. 1996	Screening cross-sectional study of patients with peripheral arterial disease 44 AAA patients 244 hospital controls matched for age and gender London 1989–1992	• Pack-years[‡] • Cigarettes/day	NR[§]

[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[§]NR = Data were not reported.
OR = Odds ratio.

Findings	Risk estimates (95% CI)		Comments
• Significant association; p <0.001 for trend	**Annual mortality per 100,000 men**		Mortality rates were standardized for age and calendar period
	Nonsmokers	15	
	Former smokers	33	
	Current smokers	62	
	1–14 cigarettes/day	38	
	15–24 cigarettes/day	74	
	25 cigarettes/day	81	
• AAAs were more prevalent among smokers	**Prevalence among those with AAA**		p values were calculated using logistic regression and were adjusted for age, gender, height, and weight
	Never smoked	6.8%	
	Former smokers	11.5%	
	Current smokers	14.4%	
	p value for trend <0.0001		
• Pack-years p value for trend = 0.174	**OR**		Matched analyses were carried out using conditional logistic regression
	<35 pack-years	1.0 (referent)	
• Cigarettes/day p value for trend = 0.008	35–55 pack-years	2.07 (0.95–4.52)	
	>55 pack-years	1.84 (0.61–3.42)	
• No association was found between AAA risk and type of tobacco used	0–10 cigarettes/day	1.0 (referent)	
	11–20 cigarettes/day	3.03 (1.29–7.22)	
	21 cigarettes/day	1.99 (0.97–3.73)	

Table 3.7   Continued

Study	Design/population	Tobacco exposure	Outcome
Burns et al. 1997	Cohort study Cancer Prevention Study I Approximately 68,000 American Cancer Society volunteers Questionnaires administered: 1959–1960, 1961, 1963, 1965, and 1972 United States (nationwide) 1959–1972	• Cigarettes/day stratified by age	Death from aortic aneurysm
Hrubec and McLaughlin 1997	U.S. veterans cohort study 293,658 persons aged 31–84 years (mainly white male WWI veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 26-year follow-up (1954–1980) United States (nationwide)	• Former regular cigarette smokers	Death from aortic aneurysm

Findings	Risk estimates (95% CI)		Comments
• For men, there was a dose-response relationship in every age category	Mortality risk ratios		None
	Men		
	Aged 50–64 years		
	1–19 cigarettes/day	3.1	
	20 cigarettes/day	4.2	
	21 cigarettes/day	5.3	
	Aged 65–79 years		
	1–19 cigarettes/day	4.4	
	20 cigarettes/day	6.1	
	21 cigarettes/day	8.2	
	Aged 80 years		
	1–19 cigarettes/day	3.0	
	20 cigarettes/day	3.9	
	21 cigarettes/day	4.5	
	Women		
	Aged 35–49 years		
	1–19 cigarettes/day	6.2	
	20 cigarettes/day	6.1	
	21 cigarettes/day	NR	
	Aged 50–64 years		
	1–19 cigarettes/day	3.4	
	20 cigarettes/day	7.5	
	21 cigarettes/day	12.4	
	Aged 65–79 years		
	1–19 cigarettes/day	2.4	
	20 cigarettes/day	4.4	
	21 cigarettes/day	1.4	
	Aged 80 years		
	1–19 cigarettes/day	4.5	
	20 cigarettes/day	4.2	
	21 cigarettes/day	NR	
• Significant risk was associated with former regular smoking	RR		RR was calculated using Poisson regressions
	Never regular smokers	1.0 (referent)	
	Former regular smokers	2.6 (2.2–3.1)	

Table 3.7   Continued

Study	Design/population	Tobacco exposure	Outcome
Wilmink et al. 1999	Nested case-control study From a population-based screening program for AAA Men aged >50 years 210 cases (infrarenal aortic diameter >29 mm) 237 controls Huntington, United Kingdom	• Duration of smoking • Cigarettes/day	NR
Blanchard et al. 2000	Case-control study 98 incident diagnoses of AAA 102 hospital controls Winnipeg, Manitoba (Canada) 1992–1995	• Pack-years	NR
Nilsson et al. 2001	Cohort study Questionnaire replies from 16,458 men and 25,086 women aged 18–69 years, chosen from the 1960 census population Analysis was done in 1996 Sweden 1963	• Never smoked • Former smokers • Current smokers	Death from aortic aneurysm

Findings	Risk estimates (95% CI)		Comments
• When cigarettes/day ORs were adjusted for duration of smoking, associations became insignificant	Duration of smoking 0 years 20 years 21–40 years >40 years Cigarettes/day 0 cigarettes/day 1–5 cigarettes/day 6–10 cigarettes/day 11–15 cigarettes/day 16–20 cigarettes/day >20 cigarettes/day	OR 1.0 (referent) 1.4 (0.6–3.4) 3.6 (1.6–8.2) 5.8 (2.6–13.0) OR 1.0 (referent) 2.1 (0.7–6.1) 5.1 (2.0–13.0) 3.4 (1.3–8.8) 4.2 (1.7–10.5) 7.0 (2.7–18.0)	ORs were calculated using multivariate unconditional regression and were adjusted for age, family history of AAA, history of ischemic heart disease and treated hypertension, and the presence of peripheral arterial occlusive disease

• Smoking was significantly associated with AAA in women but not in men	Men
	 1–19 pack-years
	 20–34 pack-years
	 35–49 pack-years
	  50 pack-years
	
	Women
	 1–19 pack-years
	 20–34 pack-years
	 35–49 pack-years
	  50 pack-years
		OR
		1.21 (0.22–6.66)
		2.45 (0.51–11.7)
		2.96 (0.63–14.0)
		3.83 (0.84–17.5)
		
		OR
		 5.81 (0.95–35.5)
		21.7 (3.87–121.5)
		18.2 (3.01–110.5)
		28.9 (2.30–362.1)
			ORs were calculated using unconditional logistic regression; risk estimates were adjusted for age, diastolic blood pressure, diabetes mellitus status, and family history of AAA

• Risk associated with current smoking was significant for both men and women	Men Never smoked Former smokers Current smokers Women Never smoked Former smokers Current smokers	RR 1.00 (referent) 1.57 (0.94–2.63) 3.30 (2.08–5.23) RR 1.00 (referent) 0.42 (0.06–3.02) 3.43 (2.11–5.59)	RRs were calculated using Cox proportional hazards regression model; risk estimates were adjusted for age and place of residence

Table 3.7   Continued

Study	Design/population	Tobacco exposure	Outcome
Törnwall et al. 2001	Cohort study 29,133 male smokers aged 50–69 years Participants in an alpha-tocopherol, beta-carotene cancer prevention study Enrollment: 1985–1993 Ended: spring 1993 Finland	• Cigarettes/day • Duration of smoking	AAA, ruptured or unruptured
American Cancer Society, unpublished data, 2002	Cohort study Cancer Prevention Study II (CPS-II) Approximately 77,000 American Cancer Society volunteers Initial questionnaire: 1982 United States (nationwide and Puerto Rico)	• Nonsmokers • Former cigarette smokers • Current cigarette smokers	Death from aortic aneurysm

As reviewed above, there is very strong evidence from animal and laboratory experiments documenting the potential for tobacco products to have multiple detrimental effects at different stages of the natural history of atherosclerosis, both in its subclinical evolution and in the precipitation of its clinical manifestations.

The new conclusion regarding tobacco smoking and heart disease in this report relates to subclinical disease.

Findings	Risk estimates (95% CI)		Comments

• 181 outcome events
• Duration of smoking was a stronger risk factor than cigarettes/day
	Cigarettes/day
	    14 cigarettes/day
	    15–24 cigarettes/day
	    25 cigarettes/day
	
	Duration of smoking
	    32 years
	    33–40 years
	    >40 years
		RR
		1.00 (referent)
		1.01 (0.70–1.46)
		0.81 (0.52–1.27)
		
		RR
		1.00 (referent)
		1.45 (0.88–2.39)
		2.25 (1.33–3.81)
			RRs were calculated using Cox proportional hazards model; comparisons were limited to smokers only; risk estimates were adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, serum alpha-tocopherol, serum beta-carotene, total energy intake, alcohol consumption, history of diabetes mellitus, education, and exercise performed in leisure time

• 1,275 outcome events in men
• 413 outcome events in women
• Significantly increased mortality among both men and women who were current cigarette smokers
	Death rate ratios
	Men
	  Nonsmokers
	  Former smokers
	  Current smokers
	
	Women
	  Nonsmokers
	  Former smokers
	  Current smokers
		
		1.00 (referent)
		2.42 (2.03–2.88)
		5.97 (5.03–7.09)
		
		1.00 (referent)
		1.81 (1.41–2.32)
		6.82 (5.66–8.22)
			Death rates were standardized to the CPS-II population

Conclusions

Smoking and Subclinical Atherosclerosis

1. The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis.

Smoking and Coronary Heart Disease

2. The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease.

3. The evidence suggests only a weak relationship between the type of cigarette smoked and coronary heart disease risk.

Smoking and Cerebrovascular Disease

4. The evidence is sufficient to infer a causal relationship between smoking and stroke.

Smoking and Abdominal Aortic Aneurysm

5. The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm.

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Chapter 4
Respiratory Diseases

Introduction

Smoking has adverse health effects on the entire lung—affecting every aspect of lung structure and function—including impairing lung defenses against infection and causing the sustained lung injury that leads to chronic obstructive pulmonary disease (COPD). In fact, among the postulated causes of COPD are acute respiratory infections, for which smokers are at an increased risk. This chapter addresses smoking and acute and chronic respiratory diseases other than lung cancer (see Chapter 2, "Cancer"), and discusses the relevant evidence of the underlying mechanisms. COPD was the focus of the 1984 Surgeon General's report (U.S. Department of Health and Human Services [USDHHS] 1984), and a number of previous reports have addressed acute respiratory infections, which can range in severity from minor to fatal. This chapter emphasizes acute respiratory illnesses and COPD, which are leading causes of morbidity and mortality in the United States and worldwide.

Acute Respiratory Illnesses

Acute respiratory illnesses are presumed to have an infection as the predominant underlying cause. Smoking might act to increase the frequency or severity of infections. In this section, acute respiratory infections are examined separately for persons with and without smoking-related chronic obstructive lung diseases (COLDs), because patients with smoking-related diseases have frequent exacerbations of their underlying diseases. Whenever possible, effects of smoking that increase the incidence of disease are distinguished from effects that relate to the severity of the disease.

A MEDLINE search was conducted to identify relevant studies published between 1966 and 2000. To identify studies focusing on the biologic basis of and the evidence linking smoking and acute respiratory infections in persons without COPD, the following Medical Subject Headings (MeSH) terms were searched: "respiratory tract infections" and "smoking," "respiratory tract infections" and "immunology," "smoking" and "immunology," "nicotine" and "immunology," and "smoking" and "respiratory tract infections" and "epidemiology." To identify studies focusing on smoking and acute respiratory infections accompanied by COPD and asthma, the MeSH term "lung diseases, obstructive" was searched in combination with multiple key words: "antibiotic(s)," "respiratory infection(s)," "respiratory tract infection(s)," "infection(s)," "Tecumseh," "immunization," and "immunotherapy." The MeSH terms "bronchitis" and "asthma" were also searched in conjunction with the above key words. The searches were then repeated substituting the key words "COPD," "chronic obstructive pulmonary disease," "asthma," "chronic bronchitis," and "acute bronchitis." The Cochrane database was also searched. All searches included a hand search of bibliographies and authors' files.

Acute respiratory illnesses are usually divided into those that include the upper respiratory tract (nose and pharynx) and larynx, and those that include the lower respiratory tract (below the larynx). In people with normal immune systems, viruses account for most cases of upper respiratory syndromes (Gwaltney 1995c): acute bronchitis (Gwaltney 1995a), bronchiolitis (Hall and Hall 1995), and a majority of pneumonia cases (Marrie et al. 1989). Bacteria can cause pharyngitis (Gwaltney 1995b) and some pneumonias (Marrie et al. 1989). Cigarette smoke combustion products reportedly increase morbidity and mortality in acute respiratory infections by impairing physical defenses in the respiratory tract, and by impairing cellular and humoral immune responses to microbes (Donowitz and Mandell 1995). Moreover, the effects of smoking can be expected to differ in respiratory infections caused by viruses and in infections caused by bacteria, because each class of microbes stimulates different immune responses specific to the infection (Mandell et al. 1995).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports on smoking and health have noted possible adverse effects of cigarette smoking on acute respiratory infections. The 1979 report (U.S. Department of Health, Education, and Welfare [USDHEW] 1979) cited data from the 1964–1965 Health Interview Survey, which found a higher age-adjusted incidence of self-reported influenza in male and female smokers when compared with nonsmokers, and more upper respiratory illnesses (URIs) in female smokers than in female nonsmokers. The 1989 report (USDHHS 1989a) identified a number of studies that reported higher mortality ratios for smokers than for nonsmokers suffering from respiratory tuberculosis (the range of ratios was 1.27–5.0 in three studies), and from influenza and pneumonia as one combined category (the range of ratios was 1.4–2.6 in seven studies). The 1990 report focused on the health benefits of smoking cessation, and it comprehensively reviewed evidence suggesting that smoking increased the risk of acute respiratory illnesses (USDHHS 1990).

Providing a more detailed analysis of the smoking-related mortality data presented in the 1989 report, the 1990 report identified exposure-response relationships between mortality from pneumonia and influenza and the number of cigarettes currently smoked, and identified reductions in mortality rates of former smokers in relation to years of not smoking (USDHHS 1990). A review of possible mechanisms related to acute respiratory illnesses documented a variety of effects on host defenses: increases in peripheral blood total leukocyte counts, increases in polymorphonuclear leukocyte and monocyte counts, decreases in monocyte intracellular killing, decreases in the CD4/CD8 ratio in heavy smokers, decreases in concentrations of serum immunoglobulins (other than IgE), an increase in alveolar macrophage release of superoxide anions, a decrease in microbicidal activity of the macrophages, and a blunted immune response to an influenza vaccination. Although the 1990 report noted that smoking cessation restored many of these impaired defenses, it also found that few epidemiologic studies directly addressed the effects of smoking on acute respiratory morbidity. Conflicting data were observed for nonspecific acute lower respiratory illnesses (LRIs), but findings for increased morbidity from influenza virus infections in smokers were more consistent. The 1994 report (USDHHS 1994), which focused on young people, added little new information.

Biologic Basis

Animal Studies

More than 25 years ago, in vitro exposure of rabbit alveolar macrophages to a water soluble fraction of tobacco smoke was shown to impair the ability of macrophages to kill bacteria (Green and Carolin 1967). An extensive body of data has since accumulated on the effects of exposure to tobacco smoke on immune and cellular function in animal models. However, differences in responses among species to different experimental exposures of tobacco smoke and its products make it difficult to provide a simple, unifying summary of the animal data. Impaired immunoglobulin responses to immunization (Roszman and Rogers 1973) and dose-dependent decreases in responses to T cell and B cell mitogens have been reported for both short-term in vitro (Roszman et al. 1975) and in vivo (Johnson et al. 1990) exposures to tobacco smoke. Johnson and colleagues (1990) provide a comprehensive review of in vivo subchronic exposures in animals (Table 4.1) and of the voluminous relevant animal toxicology literature through 1990. In addition to the general immunologic effects summarized in Table 4.1, direct effects of tobacco smoke exposure on lung defenses include suppressed functioning of bronchial-associated lymphoid tissue, increased numbers of alveolar macrophages that have a higher than normal metabolic rate, and increased generation of reactive oxygen species precursors during phagocytosis, but without changes in bactericidal capacity (rat alveolar macrophages [summarized in Johnson et al. 1990]).

Studies of the effects of nicotine on the immune function of rodents provide some relevant insights into the effects of tobacco smoke on host responses. Exposing rats to a four-week continuous infusion of nicotine inhibited the increase of intracellular calcium that usually happens when the T cell antigen receptor is blocked (Sopori et al. 1998). The calcium ion plays a role in the early receptor-mediated activation of cells in general (Sopori and Kozak 1998), and this effect of nicotine on calcium fluxes could explain a number of observed nicotine effects on host defenses: (1) suppressed febrile response to turpentine-induced abscesses in mice (Sopori and Kozak 1998), (2) decreased inflammatory response to influenza infections with an increased proliferation of virus in mice (Sopori and Kozak 1998), (3) decreased responses to T cell mitogens in mice (McAllister-Sistilli et al. 1998) (T cell anergy [Sopori and Kozak 1998]), and (4) decreased

Table 4.1   Summary of subchronic exposure to cigarette smoke on immune function in animals*

Animal species	Findings
Mice	• Increased followed by decreased mitogenic response of spleen cells • Decreased hemagglutinating and hemolytic antibody titers • Decreased primary and secondary antibody responses in cells from lungs, spleen, and lymph nodes (this finding was not uniform across studies) • Decreased lymphocyte adherence and cytotoxicity • Enhanced primary and secondary antibody responses
Monkeys	• Decreased lymphocyte response to concanavalin A (a T cell mitogen) • No effect on phytohemagglutinin and lipopolysaccharide (a B cell mitogen) responses • Decreased natural killer cell cytotoxicity

*Exposures ranged from 15–416 weeks (adapted from Table 2 in Johnson et al. 1990).

induction of antibody-forming cells and proliferative response to anti-CD3 antibody in rats (McAllister-Sistilli et al. 1998).

Human Studies

Studies of the effects of tobacco smoke on immune function and host defenses can be broadly grouped as those focusing on markers in peripheral blood, serologic responses to specific antigens, and markers in specimens obtained by bronchoalveolar lavage.

Studies of immune response markers in peripheral blood to acute respiratory infections are summarized in Table 4.2. However, the interpretive value of many of these studies is limited by insufficient information on the sources and health status of the participants. Of the studies noted in Table 4.2, only those by Gulsvik and Fagerhol (1979), Tollerud and colleagues (1989a,b), Mili and colleagues (1991), Kurtti and colleagues (1997), and Sankilampi and colleagues (1997) are based on population samples with clearly defined criteria for classifying the health status of smokers and nonsmokers. Torres and colleagues (1996) also examined population samples in an effort to assess clinical characteristics of COPD patients with community-acquired pneumonia. The remaining studies have small samples, and the sources of the participants are not always clear. Although innumerable studies have observed increased peripheral white blood cell counts in smokers when compared with nonsmokers, the consequences of this increase remain unclear, especially because few data exist on the effects of smoking on peripheral phagocytic and immune-competent cells.

Inconsistent findings in studies observing exposure-response relationships based on the amount of smoking may reflect varying definitions of smoking and the small numbers of persons in some of the studies. Even among those studies that were population-based or those that were larger, exposure-response relationships have not been consistently demonstrated (Gulsvik and Fagerhol 1979; Petitti and Kipp 1986; Tollerud et al. 1989b).

Nasal mucociliary clearance is probably important in the clearing of microorganisms from the nasopharynx. A study of the rate of nasociliary clearance found the rate of clearance to be delayed in smokers (20.8 [standard deviation = 9.3] minutes versus 11.1 [standard deviation = 3.8] minutes in nonsmokers). In this study the beat frequency of the cilia was not affected in smokers, and this finding suggests that the slower clearance is due either to a loss of cilia and/or changes in the viscoelastic properties of nasal mucus caused by cigarette smoke (Stanley et al. 1986). A study of bacterial adherence to buccal cells found that *Streptococcus pneumoniae* (*S. pneumoniae*) but not *Hemophilus influenzae* (*H. influenzae*) had an increased adherence in cigarette smokers. Since bacterial adherence to the cell is the first step in the colonization of bacteria, this finding may indicate an important mechanism for enhancing bacterial colonization and infection in smokers (Piatti et al. 1997).

Although smoking generally seems to suppress immune function, the evidence does not suggest particular mechanisms by which smoking might act to increase the risk of an acute infection (Table 4.2). One possible mechanism relates to the effect of cigarette

Table 4.2 Studies on the effects of smoking on markers of human immune function and host defenses, derived from analyses of peripheral blood

Marker	Findings in smokers compared with nonsmokers
White blood cell counts (WBCs)	Higher total WBC (Silverman et al. 1975; Miller et al. 1982; Tollerud et al. 1989a) • differential count may not be altered (Tollerud et al. 1989a) • questionable relationship to the amount smoked (Tollerud et al. 1989b) • in African Americans, lymphocyte increases were greater than increases in PMNs* (Tollerud et al. 1991) • overall increase was less in African Americans (Petitti and Kipp 1986)
Distribution of specific cell type	Increase in total number of T lymphocytes (Silverman et al. 1975; Miller et al. 1982; Costabel et al. 1986) • no increase in overall percentage (Miller et al. 1982) • some studies documented lower CD4 and higher CD8 rates (Miller et al. 1982; Tollerud et al. 1989b; Tanigawa et al. 1998) but other studies did not (Costabel et al. 1986; Mili et al. 1991) • higher CD4/CD8 ratio (Tollerud et al. 1989b; Mili et al. 1991) except in African Americans (Tollerud et al. 1991) Decrease in NK[†] cells (Ginns et al. 1985; Tollerud et al. 1989a; Meliska et al. 1995) except in African Americans (Tollerud et al. 1991) Higher B cell counts in some studies (Mili et al. 1991; Tanigawa et al. 1998) but not in one study (Tollerud et al. 1989b)
Cellular function	Phagocytosis, Chemotaxis • no effect on the PMN phagocytic index or on myeloperoxidase levels; minimal effect on redox activation after an acute exposure (Corberand et al. 1979) • decreased activity in the chemotactic factor inactivator in vitro (Robbins et al. 1990) • decreased leukocyte migration (Johnson et al. 1990) Lymphocyte function • effects on mitogenic responses to phytohemagglutinin/concanavalin A were variable (Daniele et al. 1977; Petersen et al. 1983; Meliska et al. 1995) • reversible decreases in NK function (Johnson et al. 1990; Meliska et al. 1995) • in vitro nicotine inhibition of NK function (Nair et al. 1990)
Immunoglobulin (Ig)	• Lower serum IgG, IgA, and IgM concentrations (Gulsvik and Fagerhol 1979; Mili et al. 1991; McMillan et al. 1997) • Higher serum IgE concentrations (Burrows et al. 1981)

*PMNs = Polymorphonuclear neutrophil leukocytes.
[†]NK = Natural killer.

Table 4.2 Continued

Marker	Findings in smokers compared with nonsmokers
Serologic responses to specific antigens	<u>Bacterial antigens</u> • no association of IgG titers with pneumococci in the elderly, but titers to *Hemophilus influenzae* (*H. influenzae*) **and** *Moraxella catarrhalis* **were higher (Kurtti et al. 1997)** • reversible increases in antibody concentrations to the common cell-wall polysaccharide of pneumococcal types 6A and 8 (Sankilampi et al. 1997) <u>Viral antigens</u> • a higher *H. influenzae* titer response to natural influenza infection but a lower response to vaccination (Finklea et al. 1971a) • no effect on *H. influenzae* and single radial diffusion titers from 2 strains of influenza (Mancini et al. 1998) • no evidence for a decreased efficacy of influenza vaccination in persons aged 65 years (Cruijff et al. 1999)
Other	• An increased risk of carriage and acquisition of *Neisseria meningitidis* in military recruits (Riordan et al. 1998)

smoke on the enhancement of IgE immunoglobulin responses through effects on interleukin-4 (IL-4) production by CD4 lymphocytes (Byron et al. 1994). IgE levels tend to be higher in smokers than in nonsmokers, and the age-related decline in serum IgE levels is not seen in smokers (Burrows et al. 1981). Exposure to cigarette smoke also skews immune responses away from a T-helper (Th) 1 type response, characterized by the production of interferon , IL-2, tumor necrosis factor alpha, and IL-12 that lead to phagocytosis and the destruction of microbial pathogens (Fearon and Locksley 1996; Locksley et al. 1998). As a result, smoking may enhance the ability of common respiratory microbial pathogens (e.g., viruses) both to infect the host and decrease the host's ability to control the infection.

Studies of markers in bronchoalveolar lavage specimens provide additional insights into how exposure to tobacco smoke could alter host defenses and increase morbidity from acute infections (Table 4.3). Moreover, the differences in marker profiles (e.g., distribution of CD4 and CD8 T lymphocytes) between peripheral blood and bronchoalveolar lavage data suggest that both systemic and pulmonary responses need to be evaluated to assess the effects of smoking on host defenses against respiratory pathogens. New data from bronchoalveolar lavage studies also suggest that

smoking can alter regulation of the cytokine network. The lower production in smokers of the cytokine IL-1 by alveolar macrophages may be responsible for decreased levels of serum immunoglobulins and decreased antibody responses to vaccines because of IL-1's role in the production of light chains in B cells (Yamaguchi et al. 1989). The suppression of regulatory cytokines IL-1 receptor antagonist and IL-6 (Mikuniya et al. 1999), the inhibition of the chemotactic factor inactivator by tobacco smoke, and the increase in numbers of neutrophils in the lung (Robbins et al. 1990; Costabel et al. 1992; Repine et al. 1997) could contribute to a heightened inflammatory response that increases morbidity and/or mortality from a respiratory infection.

In summary, since the last Surgeon General's reports to address the topic (USDHHS 1989a, 1990), new evidence has emerged buttressing the biologic basis of how cigarette smoking could increase the risk of and morbidity from acute respiratory infections: (1) animal data on the inhibitory effects of nicotine on T cell receptor stimulation indicate a plausible basis for the decreased mitogenic responses observed in smokers; (2) bronchoalveolar lavage fluid in smokers shows a more pro-inflammatory cytokine profile than in nonsmokers, suggesting that dysregulation of the cytokine network and inhibition of inflammation

Table 4.3 Studies on the effects of smoking on markers of human immune function and host defenses, derived from analyses of bronchoalveolar lavage fluid

Marker	Findings in smokers compared with nonsmokers
Distribution of cell types (other than macrophages)	• Lower CD4, higher CD8, and lower CD4/CD8 counts not found in blood (Costabel et al. 1986; Yamaguchi et al. 1989; Mikuniya et al. 1999) • Higher numbers of alveolar macrophages (Holt 1987; Yamaguchi et al. 1989; Mikuniya et al. 1999) • Higher numbers of neutrophils (Costabel et al. 1992)

Cellular function	• Increase in activation of alveolar macrophages (Razma et al. 1984; Holt 1987)
	  – conflicting data on the expression of activation marker Human Leukocyte Antigen (Clerici et al. 1984; Razma et al. 1984)
	  – conflicting data on antigen presentation and T cell activation by alveolar macrophages (Holt 1987)
	• Conflicting data on the uptake of opsonized bacteria and complement-mediated phagocytosis (Holt 1987)
	• A decreased response to phytohemagglutinin/concanavalin A in lung lymphocytes was reversed 6 weeks after cessation (Daniele et al. 1977)
	• Decreased production of interleukin-1 (IL-1) by alveolar macrophages after endotoxin stimulation (Yamaguchi et al. 1989); unstimulated production of IL-1 did not increase (Mikuniya et al. 1999)
	• No effects on tumor necrosis factor or IL-8 in unstimulated cells (Mikuniya et al. 1999)
	• Decreased IL-1 receptor antagonist in stimulated and unstimulated cells, and decreased IL-6 only in stimulated cells; no effects on granulocyte macrophage colony stimulating factor (Mikuniya et al. 1999)
	• Increase in IL-16 (lymphocyte chemoattraction factor) (Laan et al. 1999)

regulators provide a basis for more severe inflammation in smokers with respiratory infections; and (3) the emergent understanding of the role of Th-1 and Th-2 lymphocyte phenotypes on immune responses to foreign antigens indicates that the capacity of cigarette smoke to skew immune responses to a Th-2 phenotype could play a role in host responses to an infection. These immunologic alterations can be expected to increase the risk of acute infections through various effects on pulmonary airways, including decreased ciliary function and impaired mucociliary clearance (Janoff et al. 1987), and metaplasic changes in the airway epithelium (Sherman 1992) that diminish the capacity of physical clearance mechanisms.

Acute Respiratory Infections in Persons Without Chronic Obstructive Pulmonary Disease

Epidemiologic Evidence

Influenza Infections

Some of the earliest studies of the effects of cigarette smoking on acute respiratory infections focused on the influenza virus (Table 4.4). Studies have shown an increased incidence of clinical influenza illness and infection in young, healthy smokers when compared with young, healthy nonsmokers (Finklea et al. 1969,

Table 4.4   **Studies on the association between smoking and the occurrence of influenza virus illness and infection**

Study/method	Findings	Comments
Finklea et al. 1969 Surveillance of 1,900 male cadets after the 1968 Hong Kong A$_2$ influenza epidemic at a South Carolina military academy included – standardized questionnaire – serology and virus isolation – outcomes based on influenza symptoms and bed rest – smoking by category and number of cigarettes/day (never smokers; former cigarette, pipe, or cigar smokers; or current smokers of 1–20 cigarettes/day or >20 cigarettes/day)	• Compared with nonsmokers – heavy smokers (20 cigarettes/day) had 21% more illnesses and 20% more bed rest – light smokers (<20 cigarettes/day) had 10% more illnesses and 7% more bed rest • Smoking had no effect on severity as measured by ratio of illness to bed rest • The number of cadets with hemagglutination inhibition (HI) titers >40 increased – never smokers = 39% heavy smokers = 50% – clinically well smokers were more likely to have titers >40 than clinically well never smokers (36 vs. 20%)	Findings were adjusted for important confounders (e.g., socioeconomic class, vaccination status); population was homogeneous by age, gender, and race; OR* for heavy vs. never smokers for illness was 1.52 and for bed rest 1.33 (based on percentages given in the text—actual numbers were difficult to determine); overall conclusion is that clinical and subclinical illnesses increased but severity did not
Finklea et al. 1971a Serologic survey of 289 cadets at the same South Carolina military academy as above, who were blood donors after the 1968 Hong Kong A$_2$ influenza epidemic	• Ill smokers had a lower HI antibody titer response than ill never smokers to influenza A$_2$ – well smokers had higher titers compared with never smokers • Smokers had a lower antibody persistence 1 year after natural infection or vaccination, compared with never smokers – there were no differences based on the amount smoked • Ill smokers had higher titers to influenza B than ill never smokers – smokers had lower responses to vaccination with B antigen and lower prevaccination titers	Findings were adjusted for important confounders (e.g., socioeconomic class, vaccination status); findings were not consistent for influenza A$_2$ and B for ill smokers compared with ill never smokers; when these results were combined with those from the above study, A$_2$ data were consistent with impaired immune responses leading to an increased susceptibility in smokers to epidemic influenza and other acute respiratory illnesses

*OR = Odds ratio.

Table 4.4   Continued

Study/method	Findings	Comments

Kark and Lebiush 1981
Surveillance of a 1979 out-break at a military base for women in Israel (n = 176)
– retrospective assessment of illness with standard-ized questionnaire
– ill persons were identified as nonsmokers (never and former smokers) or current smokers (occasional and regular smokers)
	• Risk of influenza-like illness among current smokers compared with nonsmokers
	  – OR = 1.44 (95% CI[†], 1.03–2.01)
	  – 60.0% in current smokers vs. 41.6% in nonsmokers
	• Current smokers sought medical attention more frequently than nonsmokers (38.9 vs. 14.9%) but had no differences in severity of illness[‡]
	• Population attributable risk (PAR) estimate was 13% (95% CI, 9.9–31.5)
		Study group selection was based on high morbidity in the unit: unknown biases were associated with the selection process; PAR estimates have limited utility and suggest a small effect; retrospective assessments of illness were not verified; PAR estimate did not specifically account for smoking prevalence (34.6%)

Kark et al. 1982
Outbreak of influenza A_1 among 336 male military recruits in the winter of 1978 in Israel
– limited virus isolation
– postinfection serology
– clinic records were used to assess morbidity
– smoking status was determined with a ques-tionnaire 8–10 weeks after an epidemic, checked against induction data
– ill persons were classified as nonsmokers or current smokers
	• 18 of the 22 recruits tested seroconverted to the epidemic strain
	• Influenza-like illness in current smokers compared with non-smokers
	  – 68.5 vs. 47.2%
	  – adjusted OR = 2.49 (95% CI, 1.56–3.96)
	• Severity of illness in current smokers compared with non-smokers: adjusted OR = 2.56 (95% CI, 1.60–4.12)
	• Suggestion of exposure-response relationship with ordinal classifi-cation of current smoking was not significant
	• Seroconversion in smokers vs. nonsmokers: OR = 1.46 (95% CI, 0.96–2.28)
	• Attributable risk estimate among current smokers was 31.2% (95% CI, 16.5–43.1)
	• PAR estimate for smoking for all illnesses was 18.6% (95% CI, 8.5–27.5) (47% for current smokers)
	  – for severe illness: 25.7% (95% CI, 11.2–37.9)
	  – estimates explicitly accounted for the prevalence of smoking
		Not clear if the medical evaluation was standardized; adjusted for confounding effects of education and ethnicity

[†]CI = Confidence interval.
[‡]Severity of illness was defined as mild (returned to duty after visiting the clinic) or severe (hospitalized at the base or released from duty but not bedridden).

Table 4.4   Continued

Study/method	Findings	Comments

Petitti and Friedman 1985b
    Stratified random sample of smokers and simple random sample of never smokers from current larger study based on a U.S. health maintenance organization database; 4,610 current smokers and 2,035 never smokers (6,645) enrolled between July 1979 and December 1983
  – standardized questionnaire for tobacco tar yield was based on the 1978 Federal Trade Commission report
  – medical record reviews
  – outcomes were based on acute respiratory diseases, pneumonia/influenza, and chronic obstructive pulmonary disease (COPD)
	• Smokers of low-tar vs. high-tar yield cigarettes had no underlying COPD; other findings included
	  – OR (pneumonia/influenza) = 0.9/5 mg decrease in tar (95% CI, 0.7–1.0)
	  – effects were not seen in smokers of a single brand
	• Smokers of low-tar yield cigarettes vs. never smokers
	  – OR (pneumonia/influenza) = 1.7 (95% CI, 1.0–3.0)
	  – no control for underlying COPD
		No effects were seen for the broad category of acute respiratory infections (*International Classification of Diseases* **460–466**); analyses were adjusted for age, gender, race, and number of cigarettes/day; the use of nonstandardized medical records is a serious limitation; age distribution was not provided

Cruijff et al. 1999
    Double-blind, placebo control trial of influenza vaccinations in persons aged 60 years from 31 general medical practices in the Netherlands during the 1991–1992 influenza season
  – a questionnaire was used to obtain smoking history and occurrence of influenza
  – 321 smokers and 1,152 nonsmokers were categorized as none, light (1–9 cigarettes/day), moderate (10–19 cigarettes/day), or heavy (20 cigarettes/day)
  – serology
	• No significant differences in rates of infection with the influenza virus between smokers and nonsmokers
	  – trend toward increased rates of infection in smokers who received placebo
	  – when classified by the amount smoked, increased smoking was associated with a decreased serologic infection rate in the vaccine group, with an opposite trend for the placebo group
	    – infection rates for the vaccine group by smoking level: none, 6%; light, 3%; moderate, 3%; heavy, 0%
	    – infection rates for the placebo group by smoking level: none, 9%; light, 11%; moderate, 13%; heavy, 15%
	  – no trends for clinical influenza
	  – no evidence of decreased vaccine efficacy in smokers
	  – placebo data indicate that smokers are at a greater risk for serologic infections than nonsmokers (adjusted OR = 1.61)
		Poor definition of clinical influenza; vaccine efficacy evaluation was complicated by the fact that the highest rate of disease was in smokers who received a placebo

1971a; Kark and Lebiush 1981; Kark et al. 1982). An attributable risk of 31.2 percent (95 percent confidence interval [CI], 16.5–43.1) was reported for clinical influenza in U.S. male military recruits in a closed outbreak environment (Kark et al. 1982). The data for the severity of an illness are less clear, with studies of young, healthy persons providing conflicting results (Table 4.4) (Finklea et al. 1969; Kark et al. 1982). The evidence on smoking and influenza-like illnesses in older populations is even more limited. A randomized, placebo-controlled Dutch trial of influenza vaccines in persons aged 60 years and older (Cruijff et al. 1999) did not show an increase in clinical disease among smokers, but did show an increase in asymptomatic (by serology) infections in smokers in the placebo arm of the trial (the odds ratio [OR] adjusted for age, gender, and an underlying risk group = 1.61 [95 percent CI, 0.91–2.83]). A study of adults (age distribution not given) from a health maintenance organization in the United States found an increased OR for a physician/nurse practitioner visit for pneumonia/influenza (no distinction made) among smokers of high-tar cigarettes compared with low-tar cigarette smokers (Table 4.4) (Petitti and Friedman 1985b). Unfortunately, the study depended on a medical record review of practitioner diagnoses, with no criteria in the report as to how the "pneumonia/influenza" diagnosis was assigned. Without these criteria, it is difficult to interpret the OR of 1.7 (95 percent CI, 1.0–3.0) for the occurrence of illness in smokers of low-tar cigarettes compared with nonsmokers, since this analysis was not adjusted for the presence of COPD in the smokers.

Whether smokers have an increased risk of infection with influenza viruses in contrast to more often having a clinically recognizable illness remains clouded. A study of healthy U.S. military cadets found evidence of increased asymptomatic infections among smokers in addition to a larger percentage of smokers with high hemagglutination inhibition (HI) titers (>1:40) to influenza A (Finklea et al. 1969, 1971a). As a group, however, ill smokers tended to have lower HI titers to influenza A_2 than ill lifetime nonsmokers, after adjusting for the effects of illness and vaccination status. Ill smokers also had higher titers to influenza B but poorer responses to vaccination with influenza B antigen. Overall responses to vaccination with influenza A and B antigens did not differ among various smoking groups and lifetime nonsmokers. However, smokers had a decreased persistence of antibody at a one-year follow-up evaluation. In the Dutch study of persons aged 60 years or older (Cruijff et al. 1999), smoking status was inversely related to the likelihood of a serologic infection among those who were

vaccinated—possibly because smokers develop a better immunologic protection after vaccination than nonsmokers—but showed a direct relationship in those who received a placebo (Table 4.4). These findings do not suggest that smokers are less responsive to the beneficial effects of influenza vaccination, at least in the elderly.

Pneumonia and Infections with Pathogens that Infect the Lower Respiratory Tract

Several well-designed and well-executed U.S. population-based studies have provided evidence of a link between cigarette smoking and acute lower respiratory tract infections (Table 4.5). A population-based, case-control study of 205 cases of community-acquired pneumonia (Almirall et al. 1999a,b) reported an attributable risk of 23.0 percent (95 percent CI, 3.3–42.7) for a history of ever smoking. An exposure-response relationship based on the number of cigarettes smoked per day was observed in former smokers, who had an adjusted OR close to that of current smokers of 10 to 20 cigarettes per day (Table 4.5). The Centers for Disease Control and Prevention sponsored a case-control study of invasive pneumococcal disease based on a population surveillance system (Nuorti et al. 2000). Although the number of cases for which pneumonia was the underlying source of the invasive disease was not given, pneumonia is likely to have been the main diagnosis in the 216 (out of a total sample of 228) cases in patients with bacteremia. The population attributable risk estimate for smoking was 51 percent (no CIs were given), compared with 14 percent for chronic illnesses. The authors estimated that reducing the prevalence of smoking to 15 percent among persons aged 18 through 64 years would prevent 4,000 cases per year of invasive pneumococcal disease in the United States. Of particular interest in this study was the observation that after 10 years of smoking cessation, the risk of invasive pneumococcal disease reached that of nonsmokers.

Serologic evidence of infection with *Chlamydia pneumoniae* (*C. pneumoniae*) was evaluated in a sample from the European Respiratory Health Survey (Table 4.5) (Ferrari et al. 2000). The adjusted OR as evidence of recent infection (IgG titer >512 or IgM titer >16) with *C. pneumoniae* in smokers compared with nonsmokers was 3.51 (95 percent CI, 1.26–9.67). Finally, a matched, case-control study of community-acquired infections with *Legionella pneumophila* was carried out with cases derived from a prospective pneumonia surveillance system in the United States (Table 4.5) (Straus et al. 1996). The univariate OR for infection in current

smokers compared with nonsmokers was 3.75 (95 percent CI, 2.27–6.17). However, in a multivariable logistic regression model, an effect from current smoking was observed only in those patients with no evidence of an underlying disease (OR = 7.49 [95 percent CI, 3.27–17.17]).

A study of Finnish twins (all zygosities) discordant for smoking reported that male current and former smokers were more likely to have evidence of ongoing infections with *C. pneumoniae* (IgA titer >40) than their male twins who had never smoked (Table 4.5) (von Hertzen et al. 1998a,b). Antigen-specific lymphocyte responses to *C. pneumoniae*, but not to other

Chlamydia antigens, also were decreased in the male smokers (von Hertzen et al. 1998b). No effects were observed in female twins. The authors interpreted the lymphocyte data as being consistent with Th-2 skewing of the immune response in males. The gender differences in these responses are not explained.

Data from several different types of studies have suggested a link between smoking and infection with *Mycobacterium tuberculosis* (Table 4.5). A study of one million deaths from 1988–1990 in 98 urban and rural areas of China estimated that 11.3 percent of deaths from tuberculosis could be attributed to smoking (Table 4.5) (Liu et al. 1998). Exposure-response

Table 4.5   Studies on the association between smoking and the occurrence of pneumonia and infection with pathogens that infect the lower respiratory tract

Study/method	Findings	Comments
Population-based samples		
Straus et al. 1996 Cases (n = 146) of community-acquired *Legionella* identified as part of a prospective pneumonia surveillance from 15 hospitals in 2 Ohio counties from December 1990–October 1992 – cases were matched to 2 hospital controls (by gender, age, and underlying disease) – standardized questionnaire – standardized home survey	• Univariate OR* for current smoking = 3.75 (95% CI†, 2.27–6.17) compared with nonsmokers – OR = 2.21 (95% CI, 1.51–3.21)/packs/day • In multivariable models, smoking had an effect only in cases without an underlying disease – adjusted OR = 7.49 (95% CI, 3.27–17.17)	None
Woo et al. 1996 Random sample of 62 nursing homes in the catchment area of a tuberculosis referral hospital in Hong Kong during November and December 1993 – cluster samples within each home – total n = 587 – questionnaire for smoking – skin testing performed by trained medical students	• After adjusting for age, gender, previous hospitalization, and association with other patients, smoking was not associated with a positive skin test	No information was provided on the definition of "clusters" used for sampling; no estimates were provided for smoking prevalence; metrics used were not stated

*OR = Odds ratio.
†CI = Confidence interval.

Table 4.5   Continued

Study/method	Findings	Comments
Population-based samples		

Liu et al. 1998
    Study of smoking histories for 1 million persons who died between 1986 and 1988, in 98 urban and rural areas in China
    – smoking histories were obtained from next of kin and friends (rural only)
    – smoking histories were available only up to 1980
    – deaths were identified from death certificates and medical record reviews
	• 11.3% of tuberculosis deaths in men were attributed to smoking; 2.8% in women (smoking prevalence was very low in women)
	• Exposure-response relationship, based on the number of cigarettes/day in both urban and rural environments for urban male smokers vs. nonsmokers
	    – risk ratios for 1–19, 20, >20 cigarettes/day = 1.24, 1.48, and 2.03, respectively
	• Exposure-response relationship based on age when smoking began
	    – risk ratios for urban male smokers (began at age <20 years, 20–24 years, 25 years) vs. nonsmokers were 1.86, 1.42, and 1.22, respectively
		Small subsample to validate smoking histories by spouses (major source of data)

Almirall et al. 1999a,b
    Population-based matched (gender and age) case-control study of persons aged >14 years in Barcelona, Spain, between 1993 and 1995
    – 205 cases of community-acquired pneumonia
    – 475 community controls
    – standardized questionnaire with test-retest on a sample
	• OR for pneumonia compared with nonsmokers
	    – former: 1.77 (95% CI, 1.05–3.00)
	    – current: 1.68 (95% CI, 1.02–2.80)
	• EF[‡]: 23.0% (95% CI, 3.3–42.7)
	• Effects of the number of cigarettes/day (adjusted OR) compared with never smokers
	    – 1–9: 0.80 (95% CI, 0.32–2.05)
	    – 10–20: 1.40 (95% CI, 0.69–2.81)
	    – >20: 2.77 (95% CI, 1.14–6.70)
	    – former smokers: 1.58 (95% CI, 0.86–2.91)
		The analysis was restricted to persons without COPD[§]; persons whose illness met the case definition of pneumonia, which included those who received therapy but had no clinical findings, had findings confirmed using x-ray; PAR estimates were based on Miettinen's EF[¶], which used exposures from the case series; results were sensitive to control for many factors (e.g., past history of a variety of respiratory and chronic disease conditions and medication use)

[‡]EF = Etiologic fraction—proportion of disease attributable to a given factor.
[§]COPD = Chronic obstructive pulmonary disease.
 PAR = Population attributable risk.
[¶]Miettinen's EF = CF_1 multiplied by EF, where CF_1 = case fraction in the higher risk category.

Table 4.5 Continued

Study/method	Findings	Comments
	Population-based samples	
Ferrari et al. 2000 Participants were adults aged 20–44 years from the European Respiratory Health Study (n = 369) living in Verona, Italy, from December 1992–June 1993 – standardized questionnaire with a clear definition of smoking – serologic evidence of IgG antibodies to *Chlamydia* (*C.*) *pneumoniae* – *C. psittaci* **and** *C. trachomatis* antigens were used as controls	• OR for recent infections in smokers of 20 cigarettes/day = 3.51 (95% CI, 1.26–9.67) compared with nonsmokers – 25.7% of all smokers compared with 9.0% of nonsmokers had evidence of recent infections	Analyses were controlled for gender, occupation, socio-economic class, education, and family size; IgG antibody >512 or IgM >16 was interpreted as evidence of a recent infection

Nuorti et al. 2000
Population-based, active surveillance system in Atlanta (Georgia), Baltimore (Maryland), and Toronto (Canada)
– 25% sample (n = 228) of invasive pneumococcal infections in nonimmuno-compromised persons aged 18–64 years, studied between January 1995 and May 1996
– standardized interviews
– 301 controls obtained by random-digit telephone dialing
	• Adjusted OR for current smokers overall compared with nonsmokers: 4.1 (95% CI, 2.4–7.3)
	• Adjusted OR for current smokers based on cigarettes/day
	 – 1–14: 2.3 (95% CI, 1.3–4.3)
	 – 15–24: 3.7 (95% CI, 1.8–7.8)
	 – 25: 5.5 (95% CI, 2.5–12.9)
	• Exposure-response relationship based on pack-years**
	 – OR among former smokers according to years since quitting compared with nonsmokers
	  – <5 years: 3.5 (95% CI, 1.3–9.8)
	  – 5–9 years: 3.7 (95% CI, 1.1–13.2)
	  – 10 years: 0.6 (95% CI, 0.2–1.3)
	• PAR estimate for smoking was 51% compared with 14% for chronic illness (no CIs were given)
		Only 2% of eligible cases died before being interviewed; authors estimated that if smoking prevalence decreased to 15% among persons aged 18–64 years, 4,000 cases of invasive pneumococcal disease per year would be prevented in the United States; the percentage of the 216 persons with bacteremia cases who had pneumonia was not given; pneumonia would be expected to be a major underlying source of bacteremia; controlled for age, gender, COPD, other chronic conditions, socioeconomic class, race, vaccination status, and children in the home

PAR = Population attributable risk.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 4.5   Continued

Study/method	Findings	Comments
	Case-control studies	

Buskin et al. 1994
    Case-control study at a
    tuberculosis clinic in Seattle,
    Washington, 1988–1990
    – newly diagnosed cases of
        tuberculosis (n = 151)
    – controls (n = 545) from the
        same clinic
    – standardized question-
        naire
    – smoking status and
        cigarettes/day
	• No exposure-response relation-
	    ship with the number of ciga-
	    rettes/day
	• Adjusted OR (for age and
	    alcohol use) for smoking
	    duration compared with
	    controls
	    – 20–29 years: 1.8 (95% CI,
	        0.7–4.6)
	    – 30 years: 2.6 (95% CI,
	        1.1–5.9)
		69% of eligible cases partici-
		pated; 63% of eligible controls
		participated; alcohol use and
		smoking were correlated but no
		data were given; numbers were
		too small to evaluate smoking
		effects in nondrinkers

Alcaide et al. 1996
    Cases (n = 46) of newly
    diagnosed tuberculosis in
    patients aged 15–24 years in
    Spain in 1992
    – 46 controls with a positive
        purified protein derivative
        skin test but no clinical
        evidence of disease
    – standardized question-
        naire and cotinine testing
        were used to determine
        smoking status
	• Adjusted OR for smoking = 3.6
	    (95% CI, 1.5–2.2)
	    – results were not sensitive to
	        classification
	    – passive exposure had addi-
	        tive effects
	• Exposure-response relationship
	    with the number of cigarettes/
	    day
	    – 0: referent
	    – 1–20: adjusted OR: 3.0
	        (95% CI, 1.3–7.9)
	    – >20: adjusted OR: 13.0
	        (95% CI, 2.3–73.8)
	• Miettinen's EF[¶]: 48% (95% CI,
	    13–69)
		Source or method of ascertaining
		the controls was not stated;
		sample size was based on a
		smoking prevalence of 0.38,
		OR = 4 with power 0.90; con-
		trolled for age, gender, occupa-
		tion, social class, and passive
		smoking; marked differences in
		social class between cases (13%
		in the highest income group) and
		controls (88% in the highest)

[¶]Miettinen's EF = CF_1 multiplied by EF, where CF_1 = case fraction in the higher risk category.

Table 4.5   Continued

Study/method	Findings	Comments

<center>**Case-control studies**</center>

Study/method	Findings	Comments
Anderson et al. 1997 Inmates in South Carolina prisons who had data on tuberculosis status at intake and who were re-evaluated in a 1990 survey – endpoint: skin test conversion – case (converter, n = 116/141) – control frequency matched by race (n = 127/182) – medical records – computerized data reviewed from computerized inmate records – questionnaire on smoking habits	• Adjusted OR (race, age, gender, and prison living conditions) for conversion among smokers compared with nonsmokers – number of cigarettes/day since incarceration – 1–10: 1.88 (95% CI, 0.96–3.69) – >10: 1.87 (95% CI, 0.92–3.78) – cigarettes/day before incarceration – 1–20: 1.32 (95% CI, 0.76–2.31) – >20: 1.75 (95% CI, 0.83–3.71) – duration of smoking (referent: never/former) – 1–15 years: 1.60 (95% CI, 0.81–3.16) – >15 years: 2.12 (95% CI, 1.03–4.36)	82% participation by cases; 70% participation by controls; prisoners who smoked before incarceration decreased their smoking in prison, but the authors could not explain this decrease; the authors suggest that an association between long duration of smoking and decreased mucociliary clearance can explain the effects of duration and the current amount of smoking

<center>**Twin studies**</center>

Study/method	Findings	Comments
von Hertzen et al. 1998a,b Twin pairs (n = 111 out of 210 eligible pairs) from a registry of twins born before 1958 in Finland who were most discordant for smoking (all zygosities) – aged 38–64 years – standardized questionnaire – *Chlamydia pneumoniae* serology – lymphocyte proliferation to *Chlamydia* antigens in a small subset	• Male current and former smokers with IgA titers 40 were compared with their never smoking brothers – OR conditional logistic 5.0 (95% CI, 1.45–17.3) • Female current and former smokers with IgG titers 128 were compared with their never smoking sisters – OR conditional logistic 3.0 (95% CI, 0.97–9.30) • There was no exposure-response relationship with the number of cigarettes/day • Antigen-specific lymphocyte response – no effects of smoking in female pairs – decreased responses in male smokers compared with their never smoking brothers	The presence of IgA was interpreted as evidence of a chronic, active infection; elevated IgG titers indicated a past infection; unknown bias, since data were provided for only 53% of the eligible pairs; an even smaller subset had lymphocyte proliferation data (13 men and 33 women)

relationships with the number of cigarettes smoked per day and time since onset of smoking were observed in both urban and rural environments. However, a survey of the occurrence of positive tuberculin skin tests in a large nursing home population in Hong Kong (Woo et al. 1996) failed to find an association with smoking (Table 4.5). In contrast, three case-control studies provided evidence of an association. A nonpopulation-based, case-control study in Spain evaluated smoking as a risk factor for newly diagnosed tuberculosis (Table 4.5) (Alcaide et al. 1996), and found an estimated attributable risk of 48 percent (95 percent CI, 13–69). Moreover, the authors observed a strong exposure-response relationship with the number of cigarettes smoked per day and an additive effect from passive exposure to tobacco smoke. Two other case-control studies in the United States (both in Washington state) demonstrated associations between the duration of smoking and risk for newly diagnosed tuberculosis (Buskin et al. 1994) and skin test conversion (Anderson et al. 1997), but no

association with the current number of cigarettes smoked per day (Table 4.5).

Acute Upper and Lower Respiratory Illnesses with and Without Identification of Specific Pathogens

A large number of studies on the incidence of URI and LRI in relation to cigarette smoking were reviewed in the 1990 Surgeon General's report on smoking and health (USDHHS 1990), some of which are summarized in Table 4.6. Although not provided in the text of the papers, attributable risk estimates for the effects of smoking (Rockhill et al. 1998) can be calculated for several of the previously reviewed studies (Table 4.6) (Parnell et al. 1966; Finklea et al. 1971b; Monto et al. 1975; Blake et al. 1988). Attributable risk estimates of URI for smokers were similar in studies from divergent populations: 31 percent (95 percent CI, 23–39) in student nurses (Parnell et al. 1966) and 22 percent (95 percent CI, 12–30) and 29 percent (95 percent CI, 10–44) in two military trainee populations (Finklea et

Table 4.6 Studies on the association between smoking and the occurrence of acute upper respiratory illness (URI) and lower respiratory illness (LRI), with and without identification of specific pathogens

Study/method	Findings	Comments

Boake 1958
• 101 participants from 59 families who were part of a Western Reserve University family longitudinal study in Cleveland, Ohio
  – smoking groups were divided into never; 1–10, 11–20, or >20 cigarettes/day; and pipe and cigar smokers
• Analysis of incidence from 1949–1954 and symptoms of
  – common respiratory diseases (cold, rhinitis, laryngitis, bronchitis, or pharyngitis)
  – specific respiratory diseases (streptococcal tonsillitis and pharyngitis, pneumonia, and influenza)
	• Frequency of illness was not related to the amount smoked	The common respiratory diseases group comprised approximately 95% of the total respiratory diseases found in the family study population; overall results do not show a consistent increase in frequency of illness or types of symptoms

Table 4.6   Continued

Study/method	Findings	Comments

Haynes et al. 1966
• 179 males aged 11–19 years from a Princeton, New Jersey, preparatory school
• Smoking histories were recorded on a questionnaire
  – regular: 1 cigarette or pipe/day
  – heavy: >10 cigarettes/day for >1 year
  – occasional: 1 cigarette or pipe/week
• Respiratory illness classifications were based on infirmary record entries (a need for antimicrobial therapy served as the distinguishing criterion between mild and severe respiratory infections)
  – (1) upper mild and (2) upper severe: sinusitis, rhinitis, pharyngitis, and laryngitis
  – (3) lower mild and (4) lower severe: tracheobronchitis, bronchitis, and pneumonia
  – (5) combined (upper and lower) mild
  – (6) combined (upper and lower) severe
• Smoking habit and illness history questionnaire
• 1-year period of observation (incidence)
	• Increase in episodes/10 persons with increased smoking
	  – exposure-response gradient from never to regular but not to heavy when all episodes were considered together
	  – heavy smokers were 6.5 times more likely than nonsmokers (actual data were not given) to have a severe LRI and a LRI combined with URI; these findings were similar to findings comparing smokers and nonsmokers
	• Severe URI freqency was the same for occasional and regular smokers
		Detailed age-adjusted data were not given; cannot compute actual RR* and AR† rates

*RR = Relative risk.
†AR = Attributable risk.

Table 4.6   Continued

Study/method	Findings	Comments
Parnell et al. 1966 • 47 current-smoking and 47 never-smoked student nurses in Vancouver, Canada, matched for time on pediatric duty (greatest probable exposure to upper respiratory tract infections), followed September 1963–August 1964 • Retrospective assessment of respiratory illnesses while working at the health service • 4 categories of illness – pure URI – tracheitis/bronchitis/pneumonia – coryza syndrome (could have LRI) – other	• Incidence (10^{-3}) per 1,000 in smokers vs. nonsmokers – pure URI: 7.52 vs. 5.18 – tracheitis/bronchitis/pneumonia: 3.18 vs. 1.42 – coryza syndrome: 8.14 vs. 5.17 • There were no differences in severity	Selection of the sample and determination of smoking habits were performed independently of the surveillance to avoid bias; usual clinical records were used with no standardized data collection; true incidence rates were counted using proper person-time (for purposes of analysis, each person per unit of time); ARs[†] can be estimated from the data provided (AF[‡] [%] was calculated from incidence rates in Table 3, Parnell et al. 1966): all ARI[§] = 38% (95% CI , 32–44)[¶] URI = 31% (95% CI, 23–39)[¶] LRI = 55% (95% CI, 45–64)[¶]
Finklea et al. 1971b • 1,848 cadets in a military academy in South Carolina • Noninfluenzal illness during 1968–1969 – URI (cold, sinusitis, pharyngitis) – LRI (laryngitis, bronchitis, pneumonia) • Questionnaire for smoking history and habits was completed at the beginning of the school year – never, regular (pipe, cigar, former) – smokers classified as: 1 pack/day; >1 pack/day	• Smokers had a greater frequency of URI – no exposure-response gradient among smoking categories • Smokers had a greater frequency of LRI, but the effect was limited to smokers of >1 pack/day – for inpatient illnesses, an exposure-response relationship was found but was not statistically significant • Severity of the illness had no clear association with smoking	Data provided can be used to compute ARs (AF [%] was calculated from incidence rates in Table 3, Finklea et al. 1971b, of outpatient illnesses for heavy smokers): URI = 22% (95% CI, 12–30)[¶] LRI = 63% (95% CI, 41–78)[¶]

[†]AR = Attributable risk.

[‡]AF = Attributable fraction.

[§]ARI = Acute respiratory illness.

 CI = Confidence interval.

[¶]Confidence intervals were calculated with "Epitab" of STATA 6.0 for incidence density and cumulative incidence data, where appropriate. Confidence intervals for rate fractions are only approximate, since actual person-time data were not available.

Table 4.6 Continued

Study/method	Findings	Comments

Monto et al. 1975
• Family selection in Tecumseh, Michigan, was based on the occurrence of chronic bronchitis (CB) or low FEV_1** in a member, matched with families without CB
• 290 men, 293 women, 266 children
• Studies of health and disease in Tecumseh began in 1957, and 3 series of examinations of the residents took place in 1959–1960, 1962–1965, and 1967–1969
• Families were followed for 1 year (incidence)
• Persons were studied at baseline, 6 months, and 12 months
• Family histories of respiratory infections were recorded on questionnaires
• Serologic blood testing
• Weekly contacts by phone to detect a respiratory illness—if reported within 2 days of onset, specimens for isolation were obtained
	• Annual cumulative incidence of serologically proven infection with influenza A and B; respiratory syncytial virus; parainfluenza 1, 2, and 3; *Mycoplasma pneumoniae*; and coronavirus OC43
	  – higher among smokers in all categories for males and females
	  – 9.9% among male smokers vs. 4.4% among male nonsmokers
	  – 11.1% among female smokers vs. 9.4% among female nonsmokers
		Data and evaluation were restricted to healthy members of control households (i.e., no CB or low FEV_1); no adjustment for age: age range was 16 years and older; data can be used to compute ARs[†] (AF[‡] [%] was calculated for healthy persons from cumulative incidence data in Table 5, Monto et al. 1975, combined across participant groups): males, 54% (95% CI, 6–77)[¶]; females, 15% (95% CI, -55 to 54)[¶]; 2 subsequent publications reported that stratification by CB eliminated differences in male smokers (Monto and Ross 1977, 1978); RR was approximately 1.4 for females in both strata

Pollard et al. 1975 • Naval recruits from February 1971–January 1972 in Orlando, Florida • 10% sample of records from infirmary: final sample of 1,100 from original of 1,554 • Questionnaires assessed smoking at the beginning and end of 9-week training period	• There were no differences in illness frequency between smokers and nonsmokers • Frequency was unrelated to duration of smoking	Unknown biases because almost one-third of the data could not be used; definitions of respiratory illnesses were not provided

[†]AR = Attributable risk.

[‡]AF = Attributable fraction.

[¶]Confidence intervals were calculated with "Epitab" of STATA 6.0 for incidence density and cumulative incidence data, where appropriate. Confidence intervals for rate fractions are only approximate, since actual person-time data were not available.

**FEV$_1$ = Forced expiratory volume in 1 second.

Table 4.6   Continued

Study/method	Findings	Comments

Aronson et al. 1982
• 867 walk-in patients (534 females, 333 males) from 2 health maintenance organizations in Providence, Rhode Island, and Boston, Massachusetts, and 2 hospital-based practices; December 1976–November 1977
  – limited to chief complaints of coughing, chest congestion, head or neck swollen glands, difficulty swallowing, or sore throat
• Classified as URI, LRI, or laryngopharnygeal
	• Female patients had age-adjusted OR[††] = 2.65 (95% CI, 1.97–3.60) for smoking
	• Smokers were more likely than nonsmokers to have LRI (57 vs. 45%)
	  – greater duration of coughing: 8.9 vs. 6.8 days
	  – exposure-response relationship was found between the amount smoked and number of days of coughing (never smoked, 6.8 days; <1 pack/day, 7.7 days; and 1 pack/day, 9.4 days)
	  – no age or gender differences
		Methods for data collection and verification of smoking status were not given; a nonstandard data collection method was probably used

Blake et al. 1988
• 1,230 Army recruits at Ft. Benning, Georgia, from January 1982–April 1982; 862 recruits made up Cohort 1
• Self-reported smoking questionnaires were administered before and after the 13-week basic training period
• Medical record reviews focused on URI and viral syndrome
	• 13-week cumulative incidence of URI in Cohort 1:
	  – 25.3% of continuous smokers (113 of 446)
	  – 36.0% of recruits who quit smoking during training (9 of 25)
	  – 21.4% of recruits who initiated smoking during training (9 of 42)
	  – 16.9% of nonsmokers (59 of 349)
	• No difference in hospitalization rates for febrile variant
	• Logistic regression with age, ethnicity, and geographic region of residence found that only smoking status was significantly associated with ARIs[§]
		No standard data collection for classification; ARs[†] for military population (AF[‡] [%] was calculated from cumulative incidence in Table 1, Blake et al. 1988, for all cohorts): 29% (95% CI, 10–44)[¶]

[†]AR = Attributable risk.
[‡]AF = Attributable fraction.
[§]ARI = Acute respiratory illnesses.
[¶]Confidence intervals were calculated with "Epitab" of STATA 6.0 for incidence density and cumulative incidence data, where appropriate. Confidence intervals for rate fractions are only approximate, since actual person-time data were not available.
[††]OR = Odds ratio.

Table 4.6   Continued

Study/method	Findings	Comments

Cohen et al. 1993
• 154 men, 263 women (volunteers) in Salisbury, England, who received an intranasal challenge with rhinovirus types 2, 9, or 14 respiratory syncytial virus; or coronavirus 229E
  – aged 18–54 years
  – infection was defined as virus isolation or serologic response at 28 days post inoculation
• Smoking only by status: smokers (average cotinine 15 ng/mL) or nonsmokers (<15 ng/mL)
	• Development of colds
	  – nonsmokers: 36%
	  – 1–15 cigarettes/day: 40%
	  – >15 cigarettes/day: 48%
	• Adjusted OR for smokers vs. nonsmokers = 2.03 (95% CI, 1.18–3.70)
	• Negative interaction with alcohol (i.e., smoking reversed the negative association between alcohol and colds)
		Controlled for alcohol use, prior serologic status (serologically positive for rhinoviruses [antibody titer >2]), rooming with an infected person, gender, and allergy history

Jaakkola and Heinonen 1995 • 893 workers (439 men and 454 women) in Finland in a single office building were evaluated to determine the relationship between sharing an office and self-reported common colds in the past year (study period not specified) • Standardized questionnaire was used to obtain information	• Logistic regression: current smoking was not associated with self-reported illnesses after adjusting for sharing an office, having young children, aged <40 years, female gender, and hay fever history (OR = 1.05 [95% CI, 0.76–1.42])	Data on colds were self-reported without any validation

Nicholson et al. 1996
• Prospective weekly follow-up of Leicester, England, community sample of persons during the winters of 1992–1993 and 1993–1994
• 60–90 years of age (n = 533)
• Virus isolation and serology
• Standardized questionnaire was used to obtain information
	• Current, but not former, smokers had an increased risk of complicated LRI compared with never smokers
	  – incapacity, need to see medical doctor, hospitalization
	  – logistic regression: OR for current smoking and complications = 1.47 (95% CI, 1.14–1.90)
		There were data on the overall relationship between smoking and the occurrence of respiratory infections

al. 1971b; Blake et al. 1988). A similar coherence was found for LRI (Table 4.6) (Parnell et al. 1966; Finklea et al. 1971b). In the Tecumseh, Michigan, population-based cohort study (Monto et al. 1975), smokers tended to have a higher incidence of serologically determined infections (Table 4.6).

Of three studies published since the 1990 report, two supported an association between smoking and acute respiratory illnesses (Table 4.6) (Cohen et al. 1993; Nicholson et al. 1996). The third study, which did not support this association (Jaakkola and Heinonen 1995), was based entirely on self-reported illnesses. A study of volunteers who received an intranasal challenge with rhinovirus and coronavirus (Table 4.6) (Cohen et al. 1993) found an adjusted OR for infection in smokers compared with nonsmokers (virus isolation or serologic response at 28 days) of 2.03 (95 percent CI, 1.18–3.70). A prospective study of a community sample of people aged 60 through 90 years (Nicholson et al. 1996) reported an adjusted OR associated with current smoking for complicated LRI of 1.47 (95 percent CI, 1.14–1.90).

Acute Respiratory Infections in Persons with Human Immunodeficiency Virus Infection

Respiratory infections are a main source of morbidity in persons with human immunodeficiency virus (HIV) infection. Several studies have evaluated cigarette smoking and risk for incident lower respiratory infections in persons infected with HIV (Table 4.7).

A large observational cohort study with up to four years of follow-up found a CD4-adjusted relative hazard (RH) for bacterial pneumonia in HIV-infected current smokers of 1.57 (95 percent CI, 1.14–2.15) (Table 4.7) (Burns et al. 1996). No excess risk from tuberculosis or infection with *Pneumocystis carinii* (*P. carinii*) was observed. A second cohort study did not find an excess risk of bacterial pneumonia in HIV-infected patients who smoked when compared with infected patients who did not smoke (Hirschtick et al. 1995). However, among HIV-infected patients with a CD4 count below $200/mm^3$, smokers had an incidence of pneumonia more than three times higher (13.8/100 person-years compared with 4.0 in nonsmokers) (Table 4.7). A cross-sectional study of a variety of infections within the past six months in HIV-positive and HIV-negative women with similar characteristics based on self-reporting documented an OR for pneumonia in smokers of 2.7 (95 percent CI, 1.2–5.9) (Table 4.7) (Flanigan et al. 1999). No other infections were associated with smoking. A study based on a retrospective evaluation of medical records found that the median

time from the onset of HIV infection to a clinical infection with *P. carinii* was significantly shorter in smokers (9 months) than in nonsmokers (16 months) (Nieman et al. 1993). Smoking did not appear to affect the time of onset of acquired immunodeficiency syndrome (AIDS) for non-*Pneumocystis* AIDS-defining conditions.

Evidence Synthesis

Since the publication of the 1990 Surgeon General's report (USDHHS 1990), the biologic basis for evaluating associations between cigarette smoking and acute respiratory infections has been strengthened, adding to the plausibility of an association of smoking with respiratory infection. Animal studies on the effects of nicotine demonstrate a mechanism for immune suppression. The effects of cigarette smoke on the regulation of the cytokine network and in producing a Th-2 bias in lymphocyte responses to antigens imply that smokers will have an increase in inflammation and a decrease in protective host responses to infections with respiratory pathogens.

A review of the evidence across all of the studies indicates that cigarette smokers, particularly current smokers, have an increased risk for an acute URI or LRI. The findings are generally consistent among studies and some provide evidence for dose-response with amount of smoking. When persons are classified as current or former smokers or lifetime nonsmokers, ORs generally have been above 1.5 for acute respiratory infections in smokers without an underlying illness compared with nonsmokers (Tables 4.4 through 4.6). However, ORs as high as seven have been reported in at least one well-conducted study of *Legionella* infection (Straus et al. 1996). The few studies that focused on persons with HIV infection documented a similar range of excess infection rates (Table 4.7). When current smokers are classified by the number of cigarettes smoked per day, exposure-response relationships have been found in some studies. The lack of a standardized measure for current smoking makes the comparison of estimates from various studies difficult. Lower tar content of cigarettes is associated with a decrease in the incidence of acute respiratory illnesses (Petitti and Friedman 1985b), consistent with the exposure-response relationship observed with the amount smoked each day and with population-based studies showing a decreased incidence in former smokers when compared with current smokers (Almirall et al. 1999a,b; Nuorti et al. 2000). A range of potential confounding factors has been considered across the studies.

The evidence is less clear as to whether the risk associated with smoking varies for lower versus upper respiratory infections. In studies reporting an excess incidence of lower respiratory infections, infections tended to be in the heaviest smokers. Studies of military populations have produced conflicting results. A single study of persons aged 60 years or older (Nicholson et al. 1996) indicated that smokers were more likely than nonsmokers to have a complicated LRI.

Finally, the available data do not provide a basis for identifying subgroups particularly susceptible to the smoking-induced risks of acute respiratory illnesses. Studies of HIV-infected persons suggest that the incremental incidence of disease is similar to that in non-HIV-infected people. One study did provide evidence that the effects of smoking on acute respiratory illnesses might be greatest in those most severely immunocompromised (Hirschtick et al. 1995).

Table 4.7   Studies on the association between smoking and the occurrence of acute respiratory infections in persons with human immunodeficiency virus (HIV) infection

Study/method	Findings	Comments

Nieman et al. 1993
  84 cases of HIV infection from a pool of 516 cases in London, England, who were assessed from 1986–1991 before the onset of acquired immuno-deficiency syndrome (AIDS), for progression time to AIDS in relation to smoking habits
  – retrospective assessment of medical records
  – nonstandardized periodic follow-up
	• Median time of progression to AIDS from HIV infection was 8.17 months for smokers vs. 14.5 months for nonsmokers
	  – median time to *Pneumocystis carinii* pneumonia (PCP) onset was 9 months for smokers vs. 16 months for nonsmokers (significant by log rank test)
	  – smoking had no effect on onset time to non-PCP AIDS
	• Distribution of stages at presentation was similar for smokers and nonsmokers
		A major problem is the lack of data on the duration of infection before the first HIV test; results could all be due to longer duration of infection in smokers; no data were given on CD4 counts

Hirschtick et al. 1995
  Cohort of 1,130 HIV-positive and 167 HIV-negative partici-pants from a multicenter study (San Francisco, Los Angeles, Chicago, Detroit, New York, and Newark [New Jersey]) from December 1988–February 1990
  – all had 1 follow-up evalua-tion
  – standard protocols were used for evaluation and follow-up
  – outcome: bacterial pneumonia based on a priori criteria
  – smoking classifications were never, current, and former
	• No overall effect of smoking on the occurrence of pneumonia after adjusting for transmission category (confounding with injection-drug users, CD4 levels, race, and alcohol use)
	• Adjusted rates (person-years) among groups with CD4 levels <200/mm^3 were:
	  – nonsmokers: 4.0 per 100 person-years (95% CI*, 1.7–6.3)
	  – smokers: 13.8 per 100 person-years (95% CI, 9.9–17.7)
		Incidence ratio for smokers vs. never smokers with CD4 levels <200/mm^3 was 3.4 (95% CI, 2.4–4.9)[†]

*CI = Confidence interval.

[†]Calculation is based on data available in the report; 95% CI is only approximate, since actual person-time data (each person[s] per unit of time, in this case years) were not available (Hirschtick et al. 1995).

Table 4.7   Continued

Study/method	Findings	Comments
Burns et al. 1996 Observational cohort of 3,221 HIV-positive persons, from 17 clinics in a community network in 13 U.S. cities, enrolled from September 1990–November 1992 – all with baseline CD4 measurements – standardized data collection was used in all of the clinics – follow-up was twice a year for up to 4 years – outcome: various indices of disease progression – smoking classifications were never, current, and former – number of cigarettes/day was obtained only at baseline	• There was no overall association of smoking with respiratory disease progression or death • Current smokers had an increased risk of bacterial pneumonia compared with never smokers – adjusted relative hazard (RH) of 1.57 (95% CI, 1.14–2.15) – similar risk among persons with CD4 levels above and below 200/mm^3 • Current smokers showed no excess risk for tuberculosis compared with never smokers (RH = 1.17 [95% CI, 0.58–2.36]) • Results were not affected by various stratified analyses used to evaluate both confounding and interaction • No exposure-response relationships with the number of cigarettes/day	A careful attempt was made to identify confounders (CD4 count, other drugs, therapy, previous HIV progression, race, and functional status); the effects of changes in smoking behaviors over the follow-up period were not studied; 25 conditions were evaluated with the RH of smoking above and below 1 (e.g., cryptococcal infections)
Flanigan et al. 1999 Cross-sectional analysis of a multicenter U.S. cohort of HIV-positive (871) and HIV-negative (439) women at risk for HIV infection with similar risk backgrounds (New York City; Providence, Rhode Island; Baltimore, Maryland; and Detroit, Michigan; ongoing) – self-reported history of 5 infections (sepsis, tuberculosis, pneumonia, urinary tract infection, and sinusitis)	• Adjusted odds ratio for self-reported pneumonia in past 6 months for smokers vs. non-smokers = 2.7 (95% CI, 1.2–5.9)	No formal evaluation compared potential non-HIV-related risk factors between HIV-positive and HIV-negative persons; model was adjusted for CD4 counts, injection-drug use, cocaine and alcohol use, all in the past 6 months

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.

Implications

There are numerous studies providing population attributable risk estimates of the effects of smoking on respiratory illness outcomes (Table 4.8). Two of these estimates have limited generalizability because they were based on selected military populations (Kark and Lebiush 1981; Kark et al. 1982). The estimate based on a surveillance system of invasive pneumococcal disease (Nuorti et al. 2000) is indirectly useful, because it has to be assumed that in most of the cases studied the disease originated in the respiratory tract. Although this assumption is reasonable given the particular bacterium, no data on this point were given. Nonetheless, the 51 percent estimate indicates a large contribution to disease burden in the populations studied. The remaining estimates in Table 4.8 are the attributable fractions for smokers. Excluding the estimate with CIs including 1, estimates ranged from 19 to 63 percent. Because the various estimates are based on incidence density data as well as on cumulative incidence data, it is not possible to give a unifying interpretation (etiologic or excess fraction) for all of the estimates (Greenland and Robins 1988). However, considering all of these estimates as "excess" cases (Greenland 1999) of acute respiratory illness provides a maximum estimate of the excess burden that smoking imposes on the occurrence of these illnesses. In most cases, the estimated amount of excess cases is greater than 20 percent.

From a public health standpoint, an argument could be made that additional studies on the broad question of smoking and acute respiratory illnesses are not needed. However, studies to assess the economic and social impacts of this association may still be useful, particularly if they establish common definitions of and criteria for acute respiratory conditions and smoking status. Ideally, these studies should provide data detailing current smoking patterns and smoking patterns for the five years before the study. Using open populations in these studies should make estimates of both population and smoking attributable fractions possible. Such studies must be large enough to provide precise estimates of these fractions and to take into account whatever confounders may be relevant. Small studies are not likely to be useful. National studies, such as the National Health and Nutrition Examination Survey, would be an ideal venue for addressing these components.

Finally, in the context of health care services, health care providers need to make all smokers aware of the implications of these data for their health. The effects of smoking on the incidence of acute respiratory diseases should be included in all health care messages to smokers.

Acute Respiratory Infections in Persons with Chronic Obstructive Pulmonary Disease and Asthma

Epidemiologic Evidence

The population-based Tecumseh study was one of the most extensive epidemiologic investigations examining the effects of cigarette smoking on acute respiratory infections in persons with and without chronic lung disease in the United States (Monto et al. 1975; Monto and Ross 1977, 1978). This multiyear study recruited several stratified random samples of families. During a one-year period, people participated in weekly telephone interviews to identify prospectively the occurrence of an acute respiratory illness. Each participant also underwent serial clinical, spirometric, and serologic examinations. Two definitions of an acute respiratory infection were used: self-reported acute respiratory symptoms and serology (a fourfold rise in serum antibody titer to selected respiratory pathogens).

The observed association between current smoking and self-reported acute respiratory infections was addressed in a series of study reports (Table 4.9). The small sample sizes in subgroups resulted in wide CIs, complicating the interpretation of results. However, smoking has been associated with an increased risk for several indexes of illness: acute respiratory infections in healthy men, based on both self-reported and serologic evidence of infection (Monto et al. 1975); serologic evidence of respiratory infections in women with or without chronic bronchitis (Monto and Ross 1978); and acute, self-reported lower respiratory tract infections in men, especially in those with chronic bronchitis (Monto and Ross 1977). However, not all of the analyses found smoking to be associated with a higher risk of acute respiratory infections in persons with chronic bronchitis (Table 4.9).

In the Tecumseh study, COPD, as indicated by chronic bronchitis or pulmonary function impairment, was itself associated with a greater risk of developing

Table 4.8 **Estimates of attributable risk fractions for smoking and acute respiratory illness (ARI) in persons without chronic obstructive pulmonary disease**

Study Population	Type of risk estimate*	Estimate (95% CI[†])
Parnell et al. 1966 • Incidence data from student nurses	• Attributable fraction – all ARI – upper respiratory illness (URI) – lower respiratory illness (LRI)	38% (95% CI, 32–44) 31% (95% CI, 23–39) 55% (95% CI, 45–64)
Finklea et al. 1971b • Male military academy students • Noninfluenzal illness	• Attributable fraction (smokers >1 pack/day) – URI – LRI	22% (95% CI, 12–30) 63% (95% CI, 41–78)
Monto et al. 1975 • Selected population surveillance • Serologically diagnosed infection	• Attributable fraction – men – women	54% (95% CI, 6–77) 15% (95% CI, -55–54)
Kark and Lebiush 1981 • Female military recruits • Influenza-like illness	Population attributable risk (PAR)	13% (95% CI, -9.9–31.5)
Kark et al. 1982 • Male military recruits • Influenza-like illness	• PAR – all clinical influenza – influenza – attributable risk for smokers (all clinical influenza)	18.6% (95% CI, 8.5–27.5) 25.7% (95% CI, 11.2–37.9) 31.2% (95% CI, 16.5–43.1)
Blake et al. 1988 • Army recruits • URI and viral syndrome	Attributable fraction	29% (95% CI, 10–44)
Alcaide et al. 1996 • Case-control study of newly diagnosed tuberculosis cases	Etiologic fraction	48% (95% CI, 13–69)
Almirall et al. 1999a,b • Population-based case-control study • Pneumonia	Etiologic fraction	23.0% (95% CI, 3.3–42.7)
Nuorti et al. 2000 • Population surveillance • Invasive pneumococcal disease	PAR	51% (no CI given)

*All terms used, except "attributable fraction," are those of the author of the specific study. Estimates labeled "attributable fraction" were calculated only from studies that provided complete data from clearly defined source populations in addition to sufficient primary data.
[†]CI = Confidence interval.

an acute respiratory infection (Table 4.10), although the effects of smoking were stronger and more consistent among men. In men, the risk varied with the number of cigarettes smoked and the presence of chronic bronchitis, with the risk of an acute respiratory illness highest in heavy smokers of more than one pack per day with chronic bronchitis (relative risk [RR] = 1.63), followed by moderate smokers of approximately one and one-half packs per day (RR = 1.45), and nonsmokers (RR = 1.16). (The smoking categories were based on the sum of three reports measuring the number of cigarettes smoked per day: none equals zero packs, category 1 equals less than one pack, category 2 equals one to one and one-half packs, and category 3 equals one and one-half packs or more per day; moderate smokers were in the four to six packs category and heavy smokers were in the seven to nine packs category.) This pattern was not apparent in women.

Many studies have documented a high prevalence of potentially pathogenic bacteria isolated from the sputum of persons with an exacerbation of COPD (Tager and Speizer 1975; Fagon et al. 1990; Murphy and Sethi 1992; Monsó et al. 1995; Murphy et al. 2000; Voelkel and Tuder 2000). In most studies, the specific role of current cigarette smoking in acute infections was not examined. Soler and colleagues (1998) used bronchoscopy with a protected specimen brush to examine bacterial infections in 50 patients with severe COPD exacerbations requiring mechanical ventilation. The prevalence of a positive culture for gram-negative bacilli, including *Pseudomonas* species, was similar in former and current smokers (23 percent versus 32 percent). In contrast, a study of 91 ambulatory patients with an acute exacerbation of COPD demonstrated an association between current smoking and a greater risk for a quantitative sputum culture yielding *H. influenzae* (OR = 8.16 [95 percent CI, 1.9–43]) (Miravitlles et al. 1999).

A population-based, cross-sectional study from Norway examined the association between a clinical diagnosis of obstructive lung disease (COPD or asthma) and serologic evidence of a respiratory viral infection (influenza A and influenza B viruses, parainfluenza virus types 1–3, adenovirus, and respiratory syncytial virus [RSV]) (Omenaas et al. 1996). The prevalence of a positive serology, indicating recent or past infections, was higher among persons with obstructive lung disease (74 percent) than among those with chronic respiratory symptoms (60 percent) or persons who were asymptomatic (48 percent). Compared with persons without evidence of infections, those with positive serology for RSV and influenza B virus had lower standardized forced expiratory volume in one

second (FEV_1) residuals (-0.61 and -0.54, respectively). For these viruses, an exposure-response relationship was observed between viral titers and FEV_1 residuals. The association between a positive RSV serology and FEV_1 residuals was of a greater magnitude in smokers (-0.93) than in former smokers (-0.65) or nonsmokers (-0.48), although the interaction between smoking and RSV infections was not significant. The investigators observed a similar pattern of results for influenza B virus serology (-1.02 among smokers, -0.46 among former smokers, and -0.30 among nonsmokers). Analyses were not carried out to assess the interaction between the joint effect of having obstructive lung disease and smoking, which would directly address the risk posed by smoking for viral infections among persons with COPD. The cross-sectional design precludes determining whether a viral infection reduces lung function or whether decreased lung function increases susceptibility to viral infections.

The impact of smoking on the risk of death from pulmonary infections among persons with COPD was examined in the population-based Copenhagen City Heart Study (Prescott et al. 1995). In the cohort of 13,888 persons followed for 10 to 12 years, 214 persons died from COPD (8 percent of deaths). Of these deaths, 133 occurred in the hospital. Medical records were reviewed for 101 patients to determine whether death was due to a pulmonary infection. Compared with persons who died without pulmonary infections (n = 51), those who died from a pulmonary infection (n = 38) had similar smoking statuses. Both groups also had similar prevalence rates of current smoking (75 percent of those without pulmonary infection versus 82 percent of those with infection) and current heavy smoking (53 percent for both), and a similar mean duration of smoking (36 years versus 40 years). In a Cox proportional hazard model that controlled for age, gender, and FEV_1, daily tobacco use was related to the risk of death from a pulmonary infection (RH = 1.4 per 10 grams of tobacco used; 95 percent CI, 1.04–1.80). When current smokers and lifetime nonsmokers were compared, smoking was not associated with an increased risk. Although a selection bias from examining a subset of COPD deaths cannot be excluded, the data strongly suggest a relationship between current smoking intensity and the risk of death from a pulmonary infection.

A population-based, case-control study demonstrated that cigarette smoking was a strong risk factor for invasive pneumococcal disease (Nuorti et al. 2000). Moreover, both COPD and asthma were associated with a greater risk of pneumococcal infection (OR = 3.4 [95 percent CI, 1.6–7.0] and OR = 2.5 [95 percent

**Table 4.9   Studies on the association between smoking and the risk of acute respiratory illness (ARI)—
Results from the Tecumseh Study**

Study	Population	RR* and 95% CI†
		Men

Monto et al. 1975	• Stratified random sample of families followed during 1967–1969, containing 1 member with chronic lung disease: symptomatic CB‡ or low FEV$_1$§ without symptoms (presumed emphysema)
	• Comparison groups were healthy persons and persons with other chronic illnesses (diabetes and coronary artery disease)
		RR for current smoking vs. never or former smoking
		• Self-reported ARI
		  – persons with CB: 0.84
		  – low FEV$_1$: 1.08
		  – healthy persons: 1.59
		  – other chronic diseases: 1.54
		• Serologic definition¶ of an ARI
		  – persons with CB: 2.17 (95% CI, 0.94–5.02)
		  – low FEV$_1$: 0.43 (95% CI, 0.053–3.55)
		  – healthy persons: 1.57 (95% CI, 0.60–4.08)
		  – other chronic diseases: 0.72 (95% CI, 0.08–6.47)

Monto and Ross 1977	Stratified random sample of families followed during 1966–1971	Self-reported ARI (total)**
		• Heavy smoking vs. none: 0.89
		• Moderate smoking vs. none: 0.61
		• Light smoking vs. none: 0.94
		• Any current smoking vs. none in persons with and without CB
		  – persons with CB: 0.90
		  – persons without CB: 0.71
		Self-reported ARI (lower tract only)
		• Heavy smoking vs. none: 1.67
		• Moderate smoking vs. none: 0.67
		• Light smoking vs. none: 1.5
		• Any current smoking vs. none in persons with and without CB
		  – persons with CB: 1.44
		  – persons without CB: 1.0

*RR = Relative risk.

†CI = Confidence interval.

‡CB = Chronic bronchitis.

§FEV$_1$ = Forced expiratory volume in 1 second.

  Relative risks were calculated using STATA 5.0 "Epitab" function. Confidence intervals were calculated where adequate data in the publication were available.

¶Serologic definition of an acute infection = a 4-fold rise in serum antibody titer to respiratory syncytial virus, parainfluenza virus type 3, influenza A virus, influenza B virus, or *Hemophilus influenzae.*

**Cigarette smoking was assessed 3 times during the study year. No smoking was assigned a score of 0; smoking <1 pack/day = 1; 1 pack but <1.5 packs/day = 2; and 1.5 packs/day = 3. A summary score was created by adding the 3 individual scores. Using the summary score, 0 = nonsmoking, 1–3 = light smoking, 4–6 = moderate smoking, and 7–9 = heavy smoking.

RR and 95% CI

Women

RR for current smoking vs. never or former smoking
- Self-reported ARI
  – persons with CB: 0.72
  – low FEV_1: 1.61
  – healthy persons: 1.07
  – other chronic diseases: 1.46
- Serologic definition of an ARI
  – persons with CB: 1.08 (95% CI, 0.32–3.62)
  – low FEV_1: 0.96 (95% CI, 0.36–2.51)
  – healthy persons: 0.94 (95% CI, 0.41–2.14)
  – other chronic diseases: 0 (CI undefined)

Self-reported ARI (total)
- Heavy smoking vs. none: 0.95
- Moderate smoking vs. none: 1.0
- Light smoking vs. none: 0.86
- Any current smoking vs. none in persons with and without CB
  – persons with CB: 0.81
  – persons without CB: 0.90

Self-reported ARI (lower tract only)
- Heavy smoking vs. none: 1.38
- Moderate smoking vs. none: 1.38
- Light smoking vs. none: 1.13
- Any current smoking vs. none in persons with and without CB
  – persons with CB: 1.0
  – persons without CB: 1.29

CI, 1.4–4.7]), respectively. In a multivariate analysis that included smoking variables and demographic characteristics, neither disease was associated with a greater risk of pneumococcal infection. Other investigators also found that COPD was associated with a greater risk of pneumococcal pneumonia and bronchitis (RR = 1.96 [95 percent CI, 1.51–2.56]) (Simberkoff et al. 1986).

A recent report from the Lung Health Study evaluated the effects of the frequency of self-reported nonspecific LRI that resulted in a visit to a physician on the annual rate of change in FEV_1 levels in participants with mild COPD (Kanner et al. 2001). The number of illness episodes was few in this population, averaging about 0.24 per year for the study population as a whole. Illnesses in the year before the study and female gender were the best predictors of subsequent illnesses, but these two variables explained only 8.4 percent of the total variation. However, during the five-year observation period, participants who were continuous smokers had significantly more illnesses than those who had quit smoking for the entire five-year period (p = 0.0003). Intermittent smokers had illness rates that fell between the continuing smoker and sustained quitter groups. In this study, nonspecific lower respiratory tract illnesses that resulted in a physician visit had an adverse effect on the annual rate of change in lung function only in those who continued to smoke. The illness effect on changes in the FEV_1 was not seen in sustained quitters (Kanner et al. 2001).

Evidence from Antibiotic Trials

The potential etiologic role of smoking in acute respiratory infections among persons with COPD can be assessed indirectly by examining data from clinical trials of the efficacy of antibiotic treatments for acute exacerbations of COPD. If a bacterial infection plays an important causal role in the acute exacerbation of COPD, characterized by increases in coughing, sputum production, wheezing, dyspnea (difficulty breathing and shortness of breath), and/or airflow obstruction, then treatment with appropriate antibiotics should accelerate symptomatic resolution. Current smoking might decrease the efficacy of antibiotic therapy, and past smoking might influence the risk for infections by determining the level of lung function. This section considers the evidence from trials of antibiotics in exacerbations of COPD. These trials are potentially informative as to the role of bacteria in causing these exacerbations and whether current smoking modifies the effects of antibiotics. Furthermore, they offer evidence on the role of bacteria in causing

Table 4.9   Continued

Study	Population	RR* and 95% CI†
		Men
Monto and Ross 1978	Stratified random sample of families followed during 1969–1971	Self-reported ARI • Persons with CB‡ – heavy smoking vs. none: 0.96 – moderate smoking vs. none: 0.91 • Persons without CB – heavy smoking vs. none: 0.73 – moderate smoking vs. none: 0.68 Serologic definition of ARI, current smokers vs. nonsmokers • Persons with CB: 0.37 (95% CI, 0.11–1.24) • Persons without CB: 0.29 (95% CI, 0.15–1.02) • Both groups (total): 0.43 (95% CI, 0.21–0.89)

‡CB = Chronic bronchitis.

the exacerbations and provide insights into a causal pathway that begins with smoking, is followed by the onset of COPD, and finally leads to an increased risk for a bacterial infection. However, these studies do not address the role of viruses, which cause the majority of acute upper respiratory infections in the general population.

Beginning in 1957, randomized placebo-controlled clinical trials have examined the efficacy of antibiotics in acute exacerbations of chronic bronchitis characterized by coughing, sputum production, wheezing, or dyspnea (Table 4.11). Studies have examined patients hospitalized for acute exacerbations of chronic bronchitis (Elmes et al. 1965; Petersen et al. 1967; Pines et al. 1968, 1972; Nicotra et al. 1982) and persons treated as outpatients (Elmes et al. 1957; Berry et al. 1960; Fear and Edwards 1962; Anthonisen et al. 1987; Jørgensen et al. 1992; Sachs et al. 1995). Except for one single-blind study (Petersen et al. 1967), all trials were double-blind. Several trials demonstrated that antibiotic treatments reduced respiratory symptoms (Elmes et al. 1957; Anthonisen et al. 1987), physician-assessed clinical severity (Berry et al. 1960; Pines et al. 1968, 1972), work loss (Elmes et al. 1957), and sputum purulence (Pines et al. 1972). Other trials found that antibiotic treatment improved peak expiratory flow rates (Elmes et al. 1965; Anthonisen et al. 1987). Conversely, other clinical trials showed no effects of antibiotics on respiratory symptoms (Fear and Edwards 1962; Sachs et al. 1995), clinical severity (Elmes et al. 1965; Jørgensen et al. 1992), sputum volume or purulence (Elmes et al. 1965; Petersen et al. 1967; Nicotra et al. 1982), or peak expiratory flow or other pulmonary function testing (Petersen et al. 1967; Pines et al. 1972; Nicotra et al. 1982; Jørgensen et al. 1992; Sachs et al. 1995).

In a randomized controlled trial that has been widely cited, Anthonisen and colleagues (1987) tested three different antibiotic treatments (trimethoprim-sulfamethoxazole, ampicillin, or doxycycline) against a placebo. In contrast to earlier studies, all patients had a clinical diagnosis of COPD and a FEV_1/forced vital capacity (FVC) ratio of less than 70 percent. Nearly all patients had a history of smoking cigarettes (95 percent), with 21 percent indicating current smoking. After two weeks of standard treatments for COPD, patients received an antibiotic or placebo for acute exacerbations characterized by increased dyspnea, sputum volume, and sputum purulence. In the trial, 173 patients had 362 exacerbations. Treatment success, defined as symptom resolution within 21 days, was significantly more apparent in the antibiotic group than in the placebo group (68 percent versus 55 percent of exacerbations). The duration of antibiotic-treated exacerbations was also shorter (averaging 2.2 days less). When the analysis was restricted to first exacerbations, the results were similar. Increases in peak expiratory flow rates were also greater in patients treated with antibiotics.

In the largest clinical trial, Jørgensen and colleagues (1992) randomly assigned 278 general practice patients with acute exacerbations of chronic

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RR and 95% CI

Women

Self-reported ARI
- Persons with CB
  - heavy smoking vs. none: 0.80
  - moderate smoking vs. none: 0.78
- Persons without CB
  - heavy smoking vs. none: 0.81
  - moderate smoking vs. none: 0.92

Serologic definition of ARI, current smokers vs. nonsmokers
- Persons with CB: 1.32 (95% CI, 0.47–3.72)
- Persons without CB: 1.41 (95% CI, 0.78–2.57)
- Both groups (total): 1.42 (95% CI, 0.85–2.36)

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bronchitis to amoxicillin or a placebo. Smoking history was not reported. Based on blinded physician assessments, there were no differences in clinical outcomes between the amoxicillin (63 percent) or placebo (64 percent) groups after eight days. Although peak expiratory flows improved in all patients, there were no differences between the groups.

These studies are limited by a small sample size and low statistical power, which likely reduced the ability to detect antibiotic efficacy. One study of hospitalized patients included patients with radiographic infiltrates, suggesting pneumonia (Elmes et al. 1965); other studies of inpatients did not explicitly exclude persons with pneumonia (Petersen et al. 1967; Pines et al. 1968). Inclusion of patients with pneumonia would likely inflate the apparent efficacy of antibiotics in acute COPD exacerbations. Although most patients with chronic bronchitis have smoked cigarettes, most studies did not report smoking histories (Elmes et al. 1957, 1965; Berry et al. 1960; Fear and Edwards 1962; Petersen et al. 1967; Pines et al. 1972; Nicotra et al. 1982; Anthonisen et al. 1987; Jørgensen et al. 1992). Even if the efficacy of antibiotics were to suggest that smoking plays a causal role in acute bacterial infections, none of the studies separated remote effects from immediate effects of cigarette smoking on the risk of infection. Remote effects of smoking on acute respiratory infections are those mediated through chronic airway obstruction, mucous hyper-secretion, and impaired mucociliary clearance; immediate effects are the alteration of immune and inflammatory functions (USDHHS 1990).

The limitations of low study power were addressed by a meta-analysis that combined 11 of the randomized controlled trials (Elmes et al. 1957, 1965; Berry et al. 1960; Fear and Edwards 1962; Petersen et al. 1967; Pines et al. 1968, 1972; Nicotra et al. 1982; Anthonisen et al. 1987; Jørgensen et al. 1992; Sachs et al. 1995). Because the studies used many different outcome measures, Saint and colleagues (1995) calculated a standardized effect size. The overall summary effect size, which was the difference between mean outcomes in the antibiotic and placebo groups divided by the pooled standard deviation, was 0.22 (95 percent CI, 0.10–0.34), indicating a small benefit from antibiotics. Combining the six trials that measured peak expiratory flow rates yielded a summary improvement of 10.75 liters per minute with antibiotic treatments (95 percent CI, 4.96–16.54 liters per minute).

Observational data also support the efficacy of antibiotics in treating acute exacerbations of COPD. A nonrandomized clinical trial examined the efficacy of cefaclor in 106 outpatients with acute exacerbations of chronic bronchitis (Cazzola et al. 1991). In this trial all patients were current cigarette smokers, and potentially pathogenic bacteria were isolated from the sputum of most participants. On the basis of clinical examinations, the majority of patients were considered to be cured (75.5 percent) or improved (17 percent). There was no significant change in pulmonary function. A major limitation of this trial is the absence of a placebo control group. Taken together with randomized trials, this trial suggests the efficacy of antibiotics for current smokers with acute exacerbations of chronic bronchitis.

A cohort study examined 173 patients who had 362 emergency department visits for acute exacerbations of COPD during an 18-month period (Adams et al. 2000). For patients to be included, the investigators required evidence of airway obstruction verified by pulmonary function testing during the previous three years. Of 1,754 patient visits to the emergency department for an acute COPD exacerbation, 1,392 were excluded. The most common reason for exclusion was no record of recent pulmonary function testing (1,122 visits). Although antibiotics were prescribed preferentially to patients with more severe exacerbations, antibiotic administration was associated with a lower proportion of recurrent emergency department visits during the ensuing 14 days (19 percent versus 32 percent, p <0.001). Active cigarette smoking was associated with a greater risk of relapse (OR = 4.45 [95 percent CI, 2.09–10.13]), which suggests that smoking may increase the severity of an acute exacerbation. Selection bias, introduced by excluding many emergency

Table 4.10   Studies on the association between smoking, chronic obstructive pulmonary disease, and the risk of acute respiratory illness (ARI)—Results from the Tecumseh Study

| Study | Relative risk (RR) and confidence interval (CI)* | |
	Men	Women
Monto and Ross 1977	Total ARI (self-reported) • Chronic bronchitis (CB) vs. none: 1.44 Lower respiratory illness (LRI) (self-reported) • CB vs. none: 2.8	Total ARI (self-reported) • CB vs. none: 1.1 LRI (self-reported) • CB vs. none: 1.5
Monto and Ross 1978	Total ARI (self-reported) • CB vs. none: 1.23 CB vs. none, stratified by smoking intensity[†]: • Heavy smoking: 1.63 • Moderate smoking: 1.45 • None: 1.16 Low FEV_1[‡] vs. normal • Self-reported LRI: 1.5 • Serologic evidence[§] of a respiratory infection: 2.1 (95% CI, 1.02–4.29)	Total ARI (self-reported) • CB vs. none: 1.20 CB vs. none, stratified by smoking intensity: • Heavy smoking: 1.31 • Moderate smoking: 1.12 • None: 1.32 Low FEV_1 vs. normal • Self-reported LRI: 1.1 • Serologic evidence of a respiratory infection: 1.27 (95% CI, 0.75–2.15)

*Relative risks were calculated using STATA 5.0 "Epitab" function. Confidence intervals were calculated where adequate data in the publication were available.

[†]Cigarette smoking was assessed 3 times during the study year. No smoking was assigned a score of 0; smoking <1 pack/ day = 1;   1 pack but <1.5 packs/day = 2; and   1.5 packs/day = 3. A summary score was created by adding the 3 individual scores. Using the summary score, 0 = nonsmoking, 1–3 = light smoking, 4–6 = moderate smoking, and 7–9 = heavy smoking.

[‡]FEV_1 = Forced expiratory volume in 1 second.

[§]Serologic definition of an acute infection = a 4-fold rise in serum antibody titer to respiratory syncytial virus, parainfluenza virus type 3, influenza A virus, influenza B virus, or *Hemophilus influenzae.*

department visits by patients without recent pulmonary function testing, limits any conclusions based on this study.

Prevention of COPD Exacerbation. Randomized trials of antibiotic prophylaxis in patients with COPD, conducted mostly in the 1950s and 1960s, provide evidence on cigarette smoking and the risk of respiratory infections in persons with chronic lung disease. If data indicate that antibiotics could prevent exacerbations of COPD, the indication would be that bacterial infection plays a role in COPD exacerbation. Because smoking is the principal cause of COPD, smoking would then have been shown to act on the causal pathway to acute bacterial respiratory infections in this patient group.

Placebo-controlled, randomized clinical trials have tested a variety of antibiotics, including tetracycline, penicillin, sulfonamides, and combination agents (Table 4.12). Preventive treatment with antibiotics was administered for 2 weeks to 20 months, with treatment in most trials lasting 4 to 6 months during the winter months (McVay and Sprunt 1953; Buchanan et al. 1958; Cherniack et al. 1959; Francis and Spicer 1960; Pirdie et al. 1960; Davis et al. 1961, 1965; Francis et al. 1961; Johnston et al. 1961, 1969; Fear and Edwards 1962; Medical Research Council 1966; Pines 1967; Liippo et al. 1987). Only three trials reported smoking status: 79 to 95 percent ever smoked, and 29 to 79 percent were current smokers (Medical Research Council 1966; Johnston et al. 1969; Liippo et al. 1987).

Of the various study outcomes examined, preventive antibiotics have demonstrated the most consistent efficacy in reducing missed workdays among persons with chronic bronchitis (Table 4.12). In two early large-scale, well-conducted clinical trials, Francis and Spicer (1960) and Francis and colleagues (1961) demonstrated that the prophylactic administration of tetracycline decreased the number of lost workdays by about 50 percent. The benefits of penicillin were less clear. A later clinical trial conducted by the Medical Research Council (1966) of Great Britain also suggested that oxytetracycline reduced the duration of missed workdays (22 percent reduction, 95 percent CI, 55 percent reduction to 4 percent increase, but the CI did not exclude a lack of benefit). Smaller or less well-controlled trials suggested that antibiotic prophylaxis reduced lost workdays (Pirdie et al. 1960; Johnston et al. 1961, 1969).

The salutary impact of prophylactic antibiotics on other clinical outcomes has been less consistent. Some clinical trials demonstrated that preventive antibiotics reduced acute exacerbations of chronic bronchitis (McVay and Sprunt 1953; Buchanan et al. 1958; Cherniack et al. 1959; Davis et al. 1961; Pines 1967), whereas others showed no benefit (Francis and Spicer 1960; Francis et al. 1961; Davis et al. 1965; Medical Research Council 1966; Johnston et al. 1969; Liippo et al. 1987). Despite reducing lost workdays, the two early British trials found that antibiotics did not reduce the incidence of symptomatic exacerbation, suggesting an effect mostly on symptom severity or duration (Francis and Spicer 1960; Francis et al. 1961). Although patients receiving prophylactic antibiotics may experience subjective (McVay and Sprunt 1953) or clinical improvements as determined by physicians (Fear and Edwards 1962), these benefits were not always observed (Davis et al. 1961, 1965; Johnston et al. 1961). In all trials that examined pulmonary function, antibiotics were not associated with any benefit (Francis and Spicer 1960; Pirdie et al. 1960; Davis et al. 1961, 1965; Medical Research Council 1966; Johnston et al. 1969; Liippo et al. 1987). Taken together, the conflicting evidence does not allow for a clear conclusion regarding the efficacy of prophylactic antibiotics in persons with COPD.

Randomized, placebo-controlled clinical trials tested the efficacy of an oral vaccination against formalin-killed *H. influenzae* bacteria in patients with COPD (Clancy et al. 1985, 1990; Lehmann et al. 1991; Tandon and Gebski 1991). The efficacy of vaccinations would support a role for bacterial infections in acute exacerbations of COPD, with smoking acting on the causal pathway. Most persons in these trials reported having ever smoked cigarettes (78 to 91 percent), and

fewer indicated current smoking (10 to 73 percent). In an early trial of 50 patients, Clancy and colleagues (1985) reported a tenfold reduction in the cumulative incidence of acute episodes of bronchitis after oral immunizations (6 percent in the placebo group versus 63 percent in the immunized group, RR = 0.10 [95 percent CI, 0.014–0.64]). The same investigators demonstrated in a subsequent controlled trial (n = 40) a reduction in episodes of acute wheezy bronchitis (30 percent versus 80 percent, RR = 0.38 [95 percent CI, 0.19–0.76]) and a decreased use of antibiotics (25 percent versus 60 percent, RR = 0.42 [95 percent CI, 0.18–0.96]) (Clancy et al. 1990). The study also suggested a reduction in the cumulative incidence of acute bronchitis exacerbations (50 percent versus 80 percent, RR = 0.63 [95 percent CI, 0.38–1.02]). Compared with the placebo group, the group that received oral vaccinations had no reductions in symptom duration or reports of dyspnea, and no improvement in FEV_1. The RRs and CIs for both studies by Clancy and colleagues (1985, 1990) were not published; the calculations were based on data available in the papers. A similar trial conducted in the highlands of Papua, New Guinea, enrolled 62 adults with chronic bronchitis (Lehmann et al. 1991). Oral vaccinations were associated with a reduced risk of acute bronchitis (RR for placebo group = 1.92 [95 percent CI, 1.58–2.26]). There was no impact on the risk of pneumonia (RR = 0.66 [95 percent CI, 0.23–1.09]). In a similar study of 64 persons with chronic bronchitis, an oral vaccination was associated with a reduced risk of acute lower respiratory tract infections (OR = 0.4 [95 percent CI, 0.2–0.9]) and improved general well-being assessed by a visual analog scale (median score 5.0 versus 2.5) (Tandon and Gebski 1991).

Large-scale randomized controlled trials also have examined the efficacy of an oral vaccination with OM-85 BV, an antigenic extract of eight microorganisms commonly found in the respiratory tract that has been subjected to alkaline lysis. These agents are thought to activate lung macrophages and enhance antigen presentation to T lymphocytes (Collet et al. 1997). For the following studies, the RRs and CIs were calculated based on data available in the papers. In a study by Orcel and colleagues (1994), 354 adults aged 65 years or older with chronic bronchitis were randomly selected to receive OM-85 BV or a placebo. Of these patients, 51 percent had ever smoked and 25 percent were current smokers. Among the 290 patients analyzed, the cumulative incidence of acute lower respiratory tract infections was lower in the active treatment group (35 percent versus 52 percent, RR = 0.67 [95 percent CI, 0.51–0.88]). More recently, Collet and

Table 4.11   Studies on the efficacy of antibiotic treatment in acute exacerbations of chronic obstructive pulmonary disease

Study	N*	Smoking status	Antibiotic[†]
Elmes et al. 1957	88	NR[§]	O
Berry et al. 1960	53	NR	O
Fear and Edwards 1962	62	NR	O
Elmes et al. 1965	56	NR	A
Petersen et al. 1967	19	NR	CH
Pines et al. 1968	30	NR	P and S
Pines et al. 1972	259	NR	T or CH
Nicotra et al. 1982	40	75% current smokers	T
Anthonisen et al. 1987	173	95% ever smoked 21% current smokers	TS or A or D
Jørgensen et al. 1992	278	NR	A
Sachs et al. 1995	71	69% ever smoked 41% current smokers	A or C

*N = Total study size.

[†]O = oxytetracycline, A = ampicillin, CH = chloramphenicol, P = penicillin, S = streptomycin, T = tetracycline, TS = trimethaprim-sulfamethoxazole, D = doxycycline, C = co-trimoxazole.

[‡]All p values given are for between-group comparisons (antibiotic vs. placebo).

[§]NR = Data were not reported.

 Reflects both the total number of exacerbations and the duration of each exacerbation.

[¶]NS = Not significant.

**Trial was stopped early because of a high proportion who deteriorated in the placebo group.

[††]FEV$_1$ = Forced expiratory volume in 1 second.

Main outcome measures	Findings (antibiotic vs. placebo)[‡]
• Duration of missed work (total days)	242 vs. 528 (p = 0.1)
Physician-assessed clinical severity score (mean at day 7) • persons with mild exacerbation • persons with moderate to severe exacerbation	0.23 vs. 0.32 (p = NS[¶]) 0.53 vs. 1.36 (p <0.05)
• Duration of exacerbation (mean days) • Clinical symptom improvement score (mean)	13.5 vs. 7.5 days (p = NS) 71 vs. 35 (p >0.30)
• Clinical assessment (by investigators) • Decrease in sputum volume (mean mL) • Duration of hospitalization (mean days) • Increase in peak expiratory flow (at 7 days)	"No difference" 9.6 vs. 4.9 mL/day (p = NS) 18.3 vs. 18.8 days (p = NS) 51.5 vs. 27.9 L/min (p <0.1)
• Change in sputum volume (by >30%) • Change in vital capacity (by >15%) • Change in peak expiratory flow (by >15%)	22 vs. 22% (p = NS) 44 vs. 30% (p = NS) 56 vs. 60% (p = NS)
• Clinical assessment—percentage who deteriorated**	13 vs. 60% (p <0.05)
• Clinical assessment—percentage of success • Resolution of sputum purulence • Improvement in peak expiratory flow (mean)	**T vs. CH vs. placebo** 67 vs. 64 vs. 47% (p <0.05) 64 vs. 59 vs. 34% (p <0.05) 10.7 vs. 12.6 vs. 4.7% (p = NS)
• Change in partial oxygen pressure (mmHg) • Change in FEV_1[††] (L) • Change in peak expiratory flow (L/min) • Reduction in sputum volume	15.8 vs. 7.8 (p = NS) 0.14 vs. 0.16 (p = NS) 38 vs. 27 (p = NS) 32 vs. 21% (p >0.3)
• Treatment success (symptom resolution) • Change in peak expiratory flow	68 vs. 55% (p <0.01) **Increases in peak expiratory flow rates were greater in the antibiotic group (p <0.02)**
• Treatment success (evaluated by physicians) • Change in peak expiratory flow	63 vs. 64% (p >0.5) No difference (p >0.4)
• Increase in peak flow per day (percent predicted) • Reduction in symptom score per day	**A vs. C vs. placebo** 0.58 vs. 0.78 vs. 0.34 (p = NS) 0.05 vs. 0.06 vs. 0.06 (p = NS)

Table 4.12   Studies on the efficacy of antibiotic preventive treatment of persons with chronic obstructive pulmonary disease

Study	N*	Subjects†	Duration of treatment	Smoking	Antibiotic‡
McVay and Sprunt 1953	30	CB, E, B, or A	2 weeks–20 months	NR	C and T
Buchanan et al. 1958	51	CB	12 months	NR	T
Cherniack et al. 1959	67	CB or B	3–18 months	NR	T OL and P P
Francis and Spicer 1960	226	CB	4 months	NR	P T
Pirdie et al. 1960	139	CB	24 weeks	NR	O P and SU
Davis et al. 1961	29	E	11–14 months	NR	T
Francis et al. 1961	533	CB	5 months	NR	Daily T, daily P, intermittent T, or intermittent P
Johnston et al. 1961	36	CB	6 months	NR	PH
Fear and Edwards 1962	132	CB	6 months	NR	Various

*N = Total population size.

†CB = chronic bronchitis, E = emphysema, B = bronchiectasis, A = asthma.

‡C = co-trimoxazole, T = tetracycline, OL = oleandomycin, P = penicillin, O = oxytetracycline, SU = sulphonamide, PH = phenethicillin, CH = chloramphenicol, SUL = sulphormethoxine, TR = trimethoprim.

§All p values given are for between-group comparisons (antibiotic vs. placebo).

NR = Data were not reported.

¶Fischer's exact test (2-sided) was calculated on the basis of published data.

**NS = Not significant.

††FEV_1/FVC = Forced expiratory volume in 1 second/forced vital capacity.

Main outcome measures	Findings (antibiotic vs. placebo)[§]
• Proportion developing fewer respiratory infections • Hospitalization • Subjective improvement	81 vs. 22% (p = 0.004)[¶] 9.5 vs. 33.3% (p = 0.14) 80 vs. 30% (p = 0.03)
Number of exacerbations (mean per year)	0.33 vs. 1.13 (p <0.01)
• Episodes of upper respiratory illness (mean) • Episodes of lower respiratory illness (mean) • Vital capacity (mean change in percent predicted) • FEV_1/FVC[††] (mean change)	**T vs. OL and P vs. P vs. placebo** 2.88 vs. 2.52 vs. 3.00 vs. 4.2 (p = NS**) 1.32 vs. 1.92 vs. 2.28 vs. 3.36 (p <0.001 for T vs. placebo) 9 vs. 5 vs. 9 vs. 0% (p = NS) -4 vs. -3 vs. -10 vs. 0% (p = NS)
Days of missed work (mean per person-day of observation)	**P vs. T vs. placebo** 0.0657 vs. 0.0838 vs. 0.1713
• Change in 24-hour sputum volume (mean mL) • Proportion with ≥10% increase in FEV_1 • Proportion developing exacerbations • Days of missed work (mean per worker)	**O vs. P and SU vs. placebo** 14.9 vs. 14.3 vs. 9.5 (p = NS) 23 vs. 22 vs. 14.6% (p = NS) 56 vs. 56 vs. 63% (p = NS) 10.8 vs. 12.4 vs. 13.4 (p = NS)
• Subjective improvement at 6 months (%) • Subjective improvement at 12 months (%) • Number of infections per person (mean) • Change in vital capacity (percent predicted)	68.8 vs. 61.5% (p = 0.71) 68.8 vs. 46.2% (p = 0.27) 1.8 vs. 2.7% (p <0.05) -6.2 vs. -1.8% (p = NS)
• Days of missed work (mean per 100 days) • Proportion taking additional antibiotics • Visits to a general practitioner (mean number)	**Daily T vs. daily P vs. intermittent T vs. intermittent P** 4.039 vs. 8.127 vs. 9.339 vs. 8.311 (p = 0.01 for daily T) 90 vs. 83 vs. 82 vs. 87% (p = NS) 0.10 vs. 0.10 vs. 0.13 vs. 0.10 (p = NS)
• Workdays lost (mean per patient) • Physician-assessed improvement	19.5 vs. 31 (p >0.6) 56 vs. 44% (p = 0.74)[¶]
• Clinical score at 6 months, based on physician assessment and patient diary (mean)	159 vs. 35 (p <0.01) (higher scores = better status)

Table 4.12   Continued

Study	N	Subjects[†]	Duration of treatment	Smoking	Antibiotic[‡]
Davis et al. 1965	40	E	4–14 months	NR	CH
Medical Research Council 1966	373	CB	7 months	95% ever smoked 79% current smokers	O
Pines 1967	104	CB	4–8 months	NR	SUL
Johnston et al. 1969	79	CB	Each winter for 5 years	75% current smokers	T
Liippo et al. 1987	24	CB	6 months	79% ever smoked 29% current smokers	TR

[†]CB = chronic bronchitis, E = emphysema, B = bronchiectasis, A = asthma.
[‡]C = co-trimoxazole, T = tetracycline, OL = oleandomycin, P = penicillin, O = oxytetracycline, SU = sulphonamide, PH = phenethicillin, CH = chloramphenicol, SUL = sulphormethoxine, TR = trimethoprim.

colleagues (1997) conducted a multicenter trial that enrolled patients with COPD, a history of heavy smoking (20 or more pack-years[1]), and airway obstruction (FEV_1 less than 70 percent predicted). There was no difference in the cumulative incidence of acute symptomatic exacerbation between the placebo group and the treatment group (44.5 percent versus 43.7 percent, RR = 1.02 [95 percent CI, 0.81–1.28]). The risk of hospitalization for a respiratory problem was lower in the treatment group (16.2 percent versus 23.2 percent, RR = 0.70 [95 percent CI, 0.46–1.06]). Moreover, the average duration of hospitalization for a respiratory problem was lower in the oral vaccination group (1.5 versus 3.4 days per person). The treatment had no impact on FEV_1 levels, which declined 5.5 mL in the treatment group and 7.5 mL in the placebo group, or on a health-related quality-of-life index (health status questionnaire SF-36 physical and mental component summary scores and eight subscales). Although the evidence is mixed, the oral vaccination trials suggest that bacterial infections play a role in COPD exacerbations and that smoking, as the major cause of COPD, acts on the causal pathway to acute infections.

Antibiotics and Acute Bronchitis. Clinical trials assessing the efficacy of antibiotic treatments for acute bronchitis also indirectly addressed the role of smoking in acute respiratory infections among persons with chronic lung disease (Howie and Clark 1970; Stott and West 1976; Franks and Gleiner 1984; Williamson 1984;

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Main outcome measures	Findings (antibiotic vs. placebo)[§]
• Self-reported subjective improvement	29 vs. 31% (p = NS**)
• Proportion of patients with acute infection	67 vs. 68% (p = NS)
• Proportion hospitalized	33 vs. 42% (p = NS)
• Proportion with purulent sputum	62 vs. 79% (p = NS)
• Vital capacity during treatment (mean percent predicted)	59 vs. 64% (p = NS)
• Proportion with exacerbation of bronchitis	81 vs. 85% (p = NS)
• Days off from work (percent reduction in median length of sickness absence)	22 (95% confidence interval [CI], 55 to -4%)
• Decline in forced expiratory volume in 1 second (FEV_1) (slope)	-0.076 vs. -0.086 (p = NS)
• Reduction in proportion experiencing exacerbations	35 (95% CI, 16–54%)
• Number of exacerbations (mean)	2.1 vs. 5.1 (p = NS)
• Days lost from work (mean days per winter)	47.9 vs. 55 (p = NS)
• Reduction in sputum volume (mL)	-17.7 vs. -8.7 (p = NS)
• Change in FEV_1 over 5 years (percent predicted)	-7.2 vs. -16.5 (p = NS)
• Change in mean number of exacerbations	3.2 vs. 2.4 (p = NS)
• Change in FEV_1 (mean liters)	0.08 vs. 0.09 (p = NS)

**NS = Not significant.

[§]All p values given are for between-group comparisons (antibiotic vs. placebo).

Brickfield et al. 1986; Dunlay et al. 1987; Scherl et al. 1987; Hueston 1994; Verheij et al. 1994; King et al. 1996). Although these clinical trials excluded persons with overt COPD, the prevalence of current smoking among patients was substantial (32 to 55 percent). In three trials, at least 50 percent of patients indicated current smoking (Howie and Clark 1970; Franks and Gleiner 1984; Hueston 1994). Other reviews have established the strong association between current smoking and a decrement in pulmonary function (USDHHS 1990; see "Chronic Respiratory Diseases" later in this chapter). Epidemiologic studies also indicate a higher risk of acute bronchitis in persons with COPD (Monto and Ross 1977, 1978). As a consequence, these clinical trials of acute bronchitis likely included persons with smoking-related airway obstruction.

Taken together, these randomized, double-blind, controlled clinical trials suggest that antibiotic treatments provide a small clinical benefit compared with a placebo (Howie and Clark 1970; Stott and West 1976; Franks and Gleiner 1984; Williamson 1984; Brickfield et al. 1986; Dunlay et al. 1987; Scherl et al. 1987; Hueston 1994; Verheij et al. 1994; King et al. 1996). A meta-analysis of these clinical trials indicated that antibiotic treatments were associated with a duration of cough and sputum production that was one-half day shorter (Bent et al. 1999). The efficacy of antibiotics supports a causal role of bacterial infections in acute bronchitis.

Of the five clinical trials that used current smoking status to stratify analyses of clinical outcomes (Franks and Gleiner 1984; Brickfield et al. 1986; Dunlay et al. 1987; Verheij et al. 1994; King et al. 1996), all but one found no evidence of an effect modification from smoking (Brickfield et al. 1986). All of the studies found a similar salutary effect from antibiotics on

the duration of respiratory symptoms in both smokers and nonsmokers (Franks and Gleiner 1984; Brickfield et al. 1986; Dunlay et al. 1987; Verheij et al. 1994; King et al. 1996). In a randomized, placebo-controlled trial of erythromycin for acute bronchitis involving 50 patients from a family practice clinic, antibiotics appeared to attenuate the duration of coughing and sputum production only among nonsmokers (Brickfield et al. 1986). Although these studies are limited by low power for stratified analysis, the overall evidence suggests no difference in antibiotic efficacy between smokers or nonsmokers.

These findings suggest that the incidence of bacterial infection as a cause of acute bronchitis is similar in smokers and nonsmokers. As a consequence, these studies provide indirect evidence that current smoking does not cause acute bacterial bronchitis in persons who, on average, are likely to have decreased pulmonary function. A major limitation of these studies is the absence of any evaluation of viral respiratory infections.

Evidence Synthesis

Although previous Surgeon General's reports have examined the effects of smoking on acute respiratory infections (USDHHS 1990, 1994), the impact of smoking on persons with a preexisting chronic lung disease was not previously reviewed. The preponderance of evidence presented in this section implicates smoking as a cause of acute respiratory infections among persons with COPD. The Tecumseh study indicated that COPD predisposes smokers to a greater risk of acute respiratory infections, and more recent data confirm that COPD is strongly associated with the development of invasive pneumococcal disease (Nuorti et al. 2000). Although the epidemiologic data are not consistent across studies and study outcomes (i.e., self-reported acute respiratory infection, serologic evidence, pulmonary function decrement, and death from respiratory infection), controlled clinical trials have established the efficacy of antibiotics in treating acute COPD exacerbations. Clinical trials of antibiotics as a prophylaxis against acute infections yielded conflicting results and did not clearly establish efficacy in persons with COPD. The evidence did not clearly establish efficacy in persons with COPD, or whether smoking increases the frequency of acute bacterial bronchitis or modifies the effects of antibiotics in persons with reduced lung function. The oral vaccination trials indicated a reduction in the risk of acute infections. However, none of these studies explicitly evaluated the interaction between COPD and smoking, which would directly address the specific effects of smoking on acute respiratory infections in persons with chronic lung diseases.

Taken together, the epidemiologic and clinical trial evidence indicates that smoking probably acts on the causal pathway to an acute respiratory infection in persons with COPD. However, studies did not clearly separate the risk from remote effects of cigarette smoking (mediated by chronic airway obstruction and its attendant complications) from the immediate effects (through the alteration of immune or inflammatory functions). In vitro and in vivo studies support a biologic basis for the immediate adverse impact of smoking on acute respiratory infections.

The data also support an exposure-response relationship between smoking intensity and the risk of chronic bronchitis (Monto and Ross 1978) and the risk of self-reported acute lower respiratory tract infections among persons with chronic bronchitis (Monto and Ross 1978). For other outcome measures, exposure-response relationships have not been clearly demonstrated (Monto and Ross 1977). One investigation demonstrated an association between smoking intensity and the risk of death from an infection among persons with COPD (Prescott et al. 1995).

The evidence supports the causal role of cigarette smoking in acute asthma exacerbations, and acute respiratory viral infections are an important cause of asthma exacerbations. As a consequence, smoking may precipitate an exacerbation by promoting a viral infection. However, evidence does not directly address this possible mechanism, and further research is needed to clarify the precise impact of smoking on acute asthma.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.

2. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.

Implications

Both COPD and asthma are chronic respiratory conditions associated with substantial morbidity, activity limitation, and economic costs. Although sufficient data exist to infer a causal relationship between

smoking and an increased risk for acute respiratory infections in persons without chronic respiratory diseases, effects in persons with chronic lung diseases are less clearly established. Further research should specifically evaluate the impact of current smoking status on acute respiratory infections among persons with COPD and asthma. Particularly in persons with COPD, the effects of past and current smoking should be evaluated both separately and together. The effects of current and past smoking intensity also should be examined.

Conclusive data confirming the health care costs of smoking-related respiratory infections would place the problem in a larger public health context. Clinical practice guidelines could then incorporate more precise information about the potential benefits of smoking cessation.

Chronic Respiratory Diseases

Chronic respiratory diseases are a heterogeneous group of disorders that affect mainly the conducting airways and alveoli, two main components of the respiratory system. A major function of the airways is to conduct air to the alveoli, also known as the lung parenchyma, where gas exchange occurs. There, oxygen is taken up by red blood cells, and carbon dioxide is removed from the bloodstream. In addition, the airways provide defenses against inhaled particles and other agents that impact the airway walls.

Conclusions of Previous Surgeon General's Reports

Past reports of the Surgeon General on active cigarette smoking and chronic respiratory diseases have emphasized respiratory symptoms, lung function, and COPD. Key conclusions of those reports relevant to these topics are summarized in Table 4.13. Although these topics continue to be important public health concerns and are updated in this review, this report also addresses other chronic respiratory diseases including diseases of the airways, such as asthma, and diffuse parenchymal lung diseases, such as pulmonary fibrosis. The rationale for broadening the scope of diseases discussed in this report is based on a growing body of research on associations of cigarette smoking with other chronic respiratory diseases. The potential for synergism between cigarette smoking and specific occupational exposures, which was reviewed in the 1985 Surgeon General's report (USDHHS 1985), is not considered in this report.

Because of the extensive literature reviews in previous Surgeon General's reports on chronic respiratory diseases, this section is limited largely to research published between 1989 and January 2000. The search strategy used to identify references in the MEDLINE database included smoking as a major MEDLINE term, or smoking as a descriptor with tobacco or smoking in the title field. These terms were then linked to lung growth and development, lung function, respiratory symptoms, obstructive lung diseases, asthma, and pulmonary fibrosis. In addition, tables of contents were reviewed from two publications, *American Journal of Respiratory and Critical Care Medicine* and *Thorax*, for issues published through April 2000.

The organization of this review follows lung growth and development through developmental periods (i.e., childhood versus adulthood) during which time the various respiratory diseases become clinically apparent. The available evidence suggests that the development of chronic respiratory diseases, particularly chronic airflow obstruction, may result from impaired lung development and growth, a premature onset of declining lung function, an accelerated decline in lung function, or any combination of these conditions (Figure 4.1).

Biologic Basis

Airway development in utero, alveolar proliferation during the first 12 through 24 months of life (Burri 1997), and lung growth to adulthood are critical to the level of mechanical functioning of the lungs. Impaired growth in utero from exposure to maternal smoking may begin a process that predisposes the infant to chronic respiratory diseases in childhood or adulthood. Exposure to secondhand smoke in infancy and childhood, and active smoking during childhood and

Table 4.13   Conclusions from previous Surgeon General's reports concerning smoking as a cause of chronic respiratory diseases

Risk and statement	Surgeon General's report
Childhood	
"Cigarette smoking during childhood and adolescence produces significant health problems among young people, including cough and phlegm production, an increased number and severity of respiratory illnesses, decreased physical fitness, an unfavorable lipid profile, and potential retardation in the rate of lung growth and the level of maximum lung function." (p. 9)	1994
"In utero exposure to maternal smoking is associated with reduced lung function among infants, and exposure to environmental tobacco smoke during childhood and adolescence may be associated with impaired lung function among girls." (p. 14)	2001
"Adolescent girls who smoke have reduced rates of lung growth, and adult women who smoke experience a premature decline of lung function." (p. 14)	2001
Adulthood	
Chronic Obstructive Pulmonary Disease (COPD)	
"Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis. A relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema." (p. 38)	1964
"Cigarette smoking is the major cause of COLD [chronic obstructive lung disease] morbidity in the United States; 80 to 90 percent of COLD in the United States is attributable to cigarette smoking." (p. 9)	1984
"There was no change in the age-adjusted death rates for lung cancer and COPD between CPS-I [Cancer Prevention Study I, 1959–1965] and CPS-II [Cancer Prevention Study II, 1982–1986] among men and women who never smoked regularly." (p. 21)	1989a
"The two-decade interval witnessed a two- to threefold increase in death rates from chronic obstructive pulmonary disease (COPD) in female smokers aged 55 years or older." (p. 21)	1989a
"In 1985, smoking accounted for. . .82 percent of COPD deaths. . . ." (p. 21)	1989a
"Cigarette smoking is a primary cause of COPD among women, and the risk increases with the amount and duration of smoking. Approximately 90 percent of mortality from COPD among women in the United States can be attributed to cigarette smoking." (p. 14)	2001

Table 4.13   Continued

Risk and statement	Surgeon General's report
Adulthood	
"Mortality rates for COPD have increased among women over the past 20 to 30 years." (p. 14)	2001
Occupational Lung Diseases	
"For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment." (p. 11)	1985
"In those worksites where well-established disease outcomes occur, smoking control and reduction in exposure to hazardous agents are effective, compatible, and occasionally synergistic approaches to the reduction of disease risk for the individual worker." (p. 11)	1985
Asbestos	
"Cigarette smoking and asbestos exposure appear to have an independent and additive effect on lung function decline. Nonsmoking asbestos workers have decreased total lung capacities (restrictive disease). Cigarette-smoking asbestos workers develop both restrictive lung disease and chronic obstructive lung disease (as defined by an abnormal FEV_1/FVC [forced expiratory volume in one second/forced vital capacity]), but the evidence does not suggest that cigarette-smoking asbestos workers have a lower FEV_1/FVC than would be expected from their smoking habits alone." (pp. 13–14)	1985
"Both cigarette smoking and asbestos exposure result in an increased resistance to airflow in the small airways. In the absence of cigarette smoking, this increased resistance in the small airways does not appear to result in obstruction on standard spirometry as measured by FEV_1/FVC." (p. 14)	1985
"Asbestos exposure is the predominant cause of interstitial fibrosis in populations with substantial asbestos exposure. Cigarette smokers do have a slightly higher prevalence of chest radiographs interpreted as interstitial fibrosis than nonsmokers, but neither the frequency of these changes nor the severity of the changes approach levels found in populations with substantial asbestos exposure." (p. 14)	1985
Silica	
"Silicosis, acute silicosis, mixed-dust silicosis, silicotuberculosis, and diatomaceous earth pneumoconiosis are causally related to silica exposure as a sole or principal etiological agent." (p. 15)	1985

Table 4.13 Continued

Risk and statement	Surgeon General's report
Adulthood	
"Epidemiological evidence, based on both cross-sectional and prospective studies, demonstrates that silica dust is associated with chronic bronchitis and chronic airways obstruction. Silica dust and smoking are major risk factors and appear to be additive in producing chronic bronchitis and chronic airways obstruction. Most studies indicate that the smoking effect is stronger than the silica dust effect." (p. 15)	1985
"Pathological studies describe mineral dust airways disease, which is morphologically similar to the small airways lesions caused by cigarette smoking." (p. 15)	1985
Coal	
"Coal dust exposure is clearly the major etiologic factor in the production of the radiologic changes of coal workers' pneumoconiosis (CWP). Cigarette smoking probably increases the prevalence of irregular opacities on the chest roentgenograms of smoking coal miners, but appears to have little effect on the prevalence of small rounded opacities or complicated CWP." (p. 14)	1985
"Increasing category of simple radiologic CWP is not associated with increasing airflow obstruction, but increasing coal dust exposure is associated with increasing airflow obstruction in both smokers and nonsmokers." (p. 14)	1985
"Since the introduction of more effective controls to reduce the level of coal dust exposure at the worksite, cigarette smoking has become the more significant contributor to reported cases of disabling airflow obstruction among coal miners." (p. 14)	1985
"Cigarette smoking and coal dust exposure appear to have an independent and additive effect on the prevalence of chronic cough and phlegm." (p. 14)	1985
"Increasing coal dust exposure is associated with a form of emphysema known as focal dust emphysema, but there is no definite evidence that extensive centrilobular emphysema occurs in the absence of cigarette smoking." (p. 14)	1985
"Reduction in the levels of coal dust exposure is the only method available to reduce the prevalence of simple or complicated CWP. However, the prevalence of ventilatory disabilities in coal miners could be substantially reduced by reducing the prevalence of cigarette smoking and efforts aimed at reducing ventilatory disability should include efforts to enhance successful smoking cessation." (pp. 14–15)	1985

Table 4.13 Continued

Risk and statement	Surgeon General's report
Smoking cessation	
"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (p. 11)	1990
"For persons without overt chronic obstructive pulmonary disease (COPD), smoking cessation improves pulmonary function about five percent within a few months after cessation." (p. 11)	1990
"Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers." (p. 11)	1990
"With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers." (p. 11)	1990
"The rate of decline in lung function is slower among women who stop smoking than among women who continue to smoke." (p. 14)	2001

Sources: U.S. Department of Health, Education, and Welfare 1964; U.S. Department of Health and Human Services 1984, 1985, 1989a, 1990, 1994, 2001.

adolescence, further contribute to impaired lung growth and the risk of developing respiratory diseases (Fletcher et al. 1976; Samet et al. 1983; USDHHS 1984; Tager et al. 1988; Sherrill et al. 1991; Helms 1994; Samet and Lange 1996). Active smoking in adulthood leads to an accelerated decline of FEV_1 in some smokers and ultimately to the development of clinically apparent COPD (USDHHS 1984).

Lung Development In Utero

Epidemiologic Evidence

Although measuring lung function during infancy to detect in utero effects presents many challenges and is an evolving technique, during the past decade our knowledge about the effects of maternal smoking during pregnancy has grown (Dezateux and Stocks 1997; Morgan and Martinez 1998). Studies have consistently documented evidence of impaired lung function in early infancy following in utero exposure to maternal smoking (Table 4.14) (Young et al. 1991;

Hanrahan et al. 1992; Tager et al. 1995; Stick et al. 1996; Lødrup Carlsen et al. 1997; Hoo et al. 1998; Dezateux et al. 1999; Milner et al. 1999). A number of measures of ventilatory function have been used, including (1) measures of expiratory flow: maximal flow at functional residual capacity ($V_{max}FRC$) and the ratio of time to peak tidal expiratory flow to expiratory time (tPTEF/tE); (2) airway resistance and respiratory system conductance; and (3) respiratory system compliance. In addition, bronchial responsiveness to pharmacologic agents has been measured in a smaller number of studies (Young et al. 1991; Clarke et al. 1995).

To determine the effects of in utero exposures to maternal smoking, separate from later exposures to secondhand smoke and lower respiratory tract infections, pulmonary function tests have been performed in healthy infants soon after birth and even before hospital discharge (Stick et al. 1996; Lødrup Carlsen et al. 1997; Hoo et al. 1998; Milner et al. 1999). Three studies that looked at examinations conducted before hospital discharge identified decrements in tPTEF/tE in relation to maternal smoking during pregnancy (Stick et al. 1996; Lødrup Carlsen et al. 1997; Hoo et al.

Figure 4.1 Theoretical curves depicting varying rates of decline of forced expiratory volume in one second (FEV$_1$)
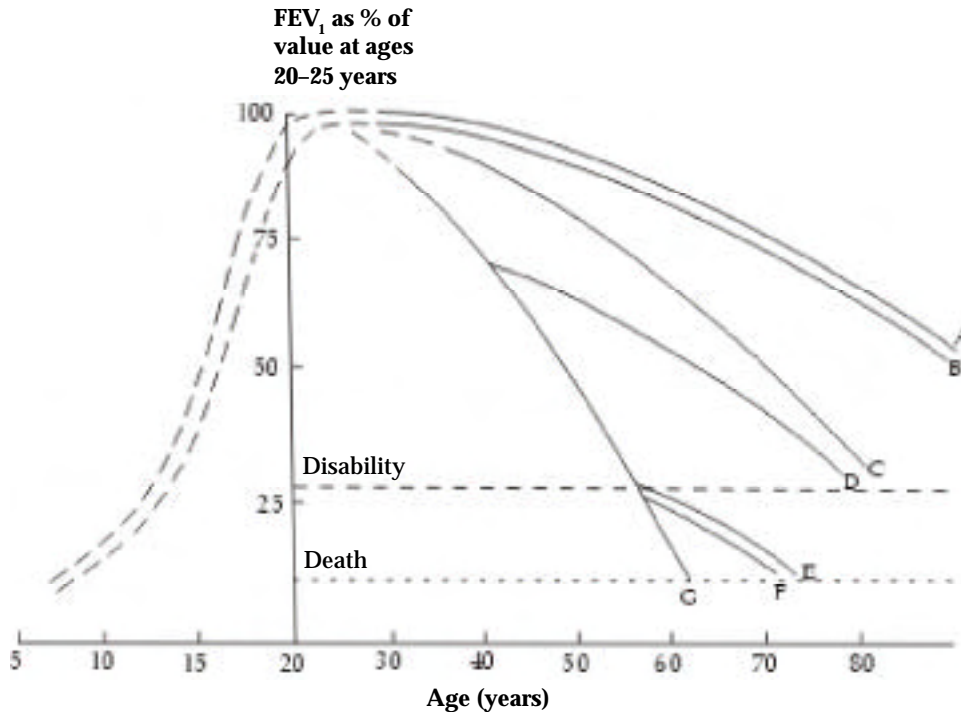
Note: Curves A and B represent never smokers and smokers, respectively, declining at normal rates. Curve C shows increased declines without the development of chronic obstructive pulmonary disease (COPD). Rates of decline for former smokers are represented by curves D and E for those without and with clinical COPD, respectively. Curves F and G show rates of decline with continued smoking after developing COPD.
Sources: Speizer and Tager (1979); U.S. Department of Health and Human Services 1990, p. 281.

1998). Instead of using a measure of airflow, Milner and colleagues (1999) measured respiratory system conductance and respiratory system compliance and found decrements in these parameters that differed between male and female infants (Table 4.14). An inverse dose-response relationship between the number of cigarettes smoked per day during pregnancy and the level of pulmonary function was found in two of the investigations (Stick et al. 1996; Lødrup Carlsen et al. 1997).

Further evidence for an adverse effect from maternal smoking during pregnancy has been found in infants who had pulmonary function measurements later in infancy but before having any LRI (Young et al. 1991; Hanrahan et al. 1992; Tager et al. 1995; Dezateux et al. 1999). Young and colleagues (1991) measured pulmonary function and airway hyper-responsiveness to histamine in 63 healthy infants from

a prenatal clinic in Perth, Australia. The infants were categorized into four groups on the basis of a family history of asthma and parental cigarette smoking during pregnancy, but prenatal and postnatal exposures to cigarette smoke could not be separated. At a mean age of 4.5 weeks, rates of forced expiratory flow (FEF) did not differ among the four groups. However, airway responsiveness was greater in infants whose parents had smoked during pregnancy.

An increased risk of lower respiratory tract illnesses, including wheezing, and subsequent reductions in expiratory airflow and airway hyperresponsiveness during infancy may be consequences of maternal smoking during pregnancy (Martinez et al. 1988; Stick et al. 1991; Tager et al. 1993; Clarke et al. 1995; Dezateux et al. 1999). Martinez and colleagues (1988) measured pulmonary function in 124 infants from Tucson, Arizona, before any lower respiratory

tract illness had occurred, and found that infants whose total respiratory conductance was in the lowest third of the group had an increased risk of a subsequent wheezing illness (OR = 3.7 [95 percent CI, 0.9–15.5]). In a sample of 97 infants from the East Boston, Massachusetts, Neighborhood Health Center, Tager and colleagues (1993) found an association between maternal smoking during pregnancy and an elevated risk for lower respiratory tract illnesses (OR = 1.47 [95 percent CI, 1.08–1.99]). Clarke and colleagues (1995) conducted pulmonary function studies on 79 healthy infants approximately one month of age and followed them during their first year of life. Lower expiratory airflow was associated with a wheezing illness in boys but not in girls, and bronchial hyperreactivity was associated with a wheezing illness in girls but not boys. Dezateux and colleagues (1999) found a significantly higher expiratory airway resistance before there was any evidence of a lower respiratory tract illness in 28 infants who had developed at least one subsequent wheezing illness by one year of age or less, compared with 73 infants who did not have a wheezing illness.

The decrement in pulmonary function associated with in utero exposure to tobacco smoke that is detectable at birth and throughout infancy may persist across childhood and into adulthood. In a cross-sectional survey, Cunningham and colleagues (1994) measured pulmonary function in 8,863 children aged 8 through 12 years from 22 North American communities. In multivariate analyses the children whose mothers reported smoking during pregnancy had significantly lower FEFs and reductions in $FEV_{0.75}$ and FEV_1/FVC, compared with the children of mothers who did not smoke during pregnancy. After adjusting for maternal smoking during pregnancy, current maternal smoking was not associated with a significant decrement in lung function. Gilliland and colleagues (2000) examined the relationship between maternal smoking and pulmonary function among 3,357 school children (grades 4, 7, and 10) living in 12 southern California communities. After adjusting for second-hand smoke exposure and other potential confounders, maternal smoking during pregnancy was associated with significant decrements in peak expiratory flows, maximum midexpiratory flows, and FEFs at 75 percent of FVC, but not in FEV_1 levels.

Evidence Synthesis

These findings consistently show the effects of maternal smoking during pregnancy, including impaired pulmonary function and lower respiratory tract illnesses during infancy and childhood. Evidence for a causal role of maternal smoking is further strengthened by the dose-response relationship between maternal smoking during pregnancy and the magnitude of decrements in pulmonary function (Stick et al. 1996; Lødrup Carlsen et al. 1997). Because these studies have been restricted to healthy full-term infants, it is unlikely that the findings are a result of other factors that may adversely affect in utero development including poor maternal nutrition, alcohol use, or the intake of other potentially toxic agents.

In utero exposure to maternal smoking may be associated with lower respiratory tract illnesses in childhood, and the subsequent risk for chronic respiratory diseases in adulthood through its effect on birth weights. Lower birth weight has been associated with reduced lung function in childhood. Data on the relationship between birth weight and adult lung function also provide similar indirect evidence (Chan et al. 1989; Barker et al. 1991; Rona et al. 1993). Maternal smoking during pregnancy has been associated with decreased birth weights (see Chapter 5, "Reproductive Effects"), and several studies indicate that birth weight is directly related to the level of expiratory airflow during childhood (Chan et al. 1989; Rona et al. 1993) and adulthood (Barker et al. 1991). Furthermore, self-reports of childhood lower respiratory tract illnesses are associated with chronic airflow obstruction in adulthood (Berglund et al. 1999).

Conclusions

1. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy.

3. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood.

Implication

Although the biologic basis for impaired infant lung function from maternal smoking during pregnancy is not yet fully understood, the causal link provides yet another strong rationale for smoking cessation during pregnancy.

Table 4.14   Studies on the association between maternal smoking during pregnancy and infant lung function

Study	Population	Age at measurement
Young et al. 1991	63 full-term infants with no perinatal problems, major congenital problems, or lower respiratory infections Perth, Australia	Mean, 4.5 weeks; range, 2–10 weeks
Hanrahan et al. 1992	80 healthy infants East Boston, Massachusetts	Mean, 4.2 weeks; range, ±1.9 weeks
Tager et al. 1995	159 healthy infants East Boston, Massachusetts	2–6 weeks 4–6 months 9–12 months 15–18 months
Stick et al. 1996	500 healthy infants Perth, Australia	Median, 58 hours after birth; range, 26–159 hours
Lødrup Carlsen et al. 1997	803 healthy infants Oslo, Norway	Mean, 2.7 days
Hoo et al. 1998	108 preterm infants (mean gestational age 33.5 weeks) without major congenital abnormalities or neonatal respiratory distress London, United Kingdom	Before hospital discharge
Dezateux et al. 1999	108 healthy infants >35 weeks gestational age, without major congenital abnormalities or neonatal respiratory distress London, United Kingdom	Mean 7.7 weeks (range, 4.9–12.6) before any upper or lower respiratory symptoms
Milner et al. 1999	289 full-term, healthy infants London, United Kingdom	Within 72 hours of delivery

*FEV_1 = Forced expiratory volume in 1 second.
†tPTEF/tE = Time to peak tidal expiratory flow as a proportion of expiratory time.

Findings

- Maximal flow at functional residual capacity (V_{max}FRC) percent predicted values were not associated with maternal smoking during pregnancy
- Airway responsiveness to histamine increased significantly with maternal smoking during pregnancy and with a family history of asthma

Maternal smoking	VFRC (mL/sec)	FEV_1* (mL)
Nonsmokers (n = 47)	150.4 ± 8.9	51.8 ± 1.2
Continuous smokers (n = 21)	74.3 ± 15.9	44.5 ± 2.0
Variable smokers (n = 12)	135.1 ± 18.3	44.6 ± 2.4

- For infants 12 months of age, maternal smoking during pregnancy was associated with a 16% reduction in VFRC in girls and a 5% reduction in boys
- Secondhand smoke exposure in the neonatal period was not significantly associated with decreased pulmonary function

Maternal smoking	Estimated β-coefficient (95% confidence interval [CI]) from multivariate regression on tPTEF/tE[†]
1–10 cigarettes/day	-0.025 (-0.059 to -0.007)
>10 cigarettes/day	-0.049 (-0.005 to -0.092)

Other factors independently associated with decrement of tPTEF/tE were family history of asthma and maternal hypertension, age, and respiratory rate

- In a multivariate regression, tPTEF/tE was estimated to decline -0.0021 (95% CI, -0.004–0.000) per unit increase in cigarettes/day
- In a multivariate regression, total respiratory compliance was estimated to decline -0.026 mL/cm H_2O (95% CI, -0.45 to -0.007) per unit increase in cigarettes/day

	Maternal smoking	No maternal smoking
V_{max}FRC (mL/sec)	85.2	103.8
tPTEF/tE	0.37	0.43

	Maternal smoking	No maternal smoking
Expiratory raw (airway resistance)	5.29	4.1
Airway resistance (increased maximum pressure/liter/second)	0.32	0.34

The odds ratio (OR) of wheezing in the first year of life was associated with maternal smoking during pregnancy: OR = 4.9 (95% CI, 1.6–15.0)

- No reduction in expiratory flow was associated with maternal smoking
- There was reduced respiratory system compliance in boys whose mothers smoked
- There was reduced respiratory system conductance in girls whose mothers smoked

Pathogenesis of Smoking-Induced Lung Injury

Epidemiologic Evidence

The rate of expiratory airflow depends on elastic recoil forces of the alveoli and on the diameter of the small airways. Complex interactions between smoking-caused changes in the structure and function of small airways and lung parenchyma result in the physiologic finding of chronic airflow limitation (Wright 1992; Thurlbeck 1994). The literature relevant to understanding the mechanisms of smoking-induced COPD has grown substantially in recent years, and points to a complex interplay among a number of biologic processes including oxidative stress, inflammation, protease-antiprotease imbalances, repair processes, and the genetic variations that control these processes (Figure 4.2) (Sandford et al. 1997; Barnes 1999; MacNee and Rahman 1999). The inhalation of cigarette smoke exposes the lungs to high concentrations of oxidant agents and free radicals, which decrease the antioxidant capacity that normally protects epithelial cells from oxidant injury (Repine et al. 1997; Rahman and MacNee 1999). Moreover, several enzymes found in the lungs generate reactive oxygen molecules that may contribute further to the oxidative stress in the lungs. Genetic variations that alter the function of enzymes that generate reactive oxygen molecules, or that affect the activity of antioxidant enzymes, may determine individual susceptibility to COPD from cigarette smoking (Barnes 1999).

Epithelial injury results in the release of proinflammatory mediators (i.e., cytokines) from epithelial cells and inflammatory cells in the airway walls (i.e., lymphocytes and macrophages). These mediators lead to an influx of neutrophils, which also release mediators that perpetuate the cycle of injury and inflammation (Figure 4.2) (MacNee and Rahman 1999; Mills et al. 1999). The inflammatory process is found in the central airways, peripheral airways, and lung parenchyma, even in smokers with normal lung function (Saetta 1999; Saetta et al. 2001). Although an inflammatory process in the small airways (respiratory bronchiolitis) appears to develop in all cigarette smokers, in susceptible smokers the injury progresses and leads to a narrowing of these airways (Bosken et al. 1990; USDHHS 1990; Aguayo 1994). Available evidence suggests that changes in the structure and function of small airways (bronchioles) are fundamental to the development of smoking-induced COPD (Wright 1992; Thurlbeck 1994). Genetic variations that alter the function of several inflammatory mediators, and thus the type of inflammatory response, probably contribute in part to susceptibility to COPD (Barnes 1999). For example, smokers with COPD have a predominance of CD8-positive T lymphocytes in the central and peripheral airways compared with smokers without COPD (O'Shaughnessy et al. 1997; Saetta et al. 1998, 2001).

The inflammatory process may extend into the peribronchiolar alveoli and destroy the alveolar walls—the hallmark of emphysema—when there is an imbalance between proteases and antiproteases. Proteases are enzymes released from neutrophils and macrophages that degrade structural proteins (e.g., elastin and collagen) of the airways and lung parenchyma. Evidence for increased elastin degradation was

Figure 4.2 Summary diagram of cigarette-related mechanisms of lung injury
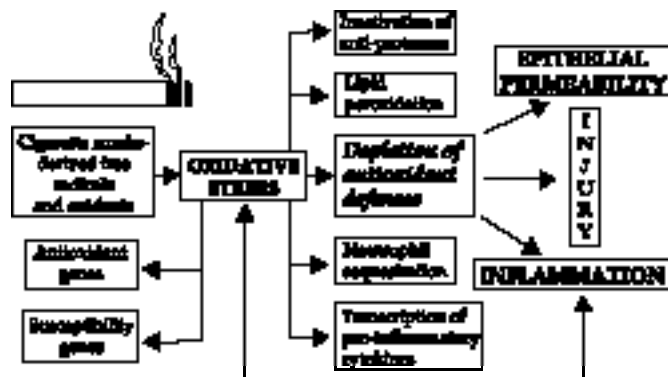
Source: MacNee and Rahman 1999, p. S63. Reprinted with permission.

reported by Gottlieb and colleagues (1996), who found increased urine desmosine (a by-product of elastin degradation) in smokers who had rapid declines in lung function. Antiproteases released from macrophages and the liver provide a natural defense against proteases. A deficiency in alpha$_1$-antitrypsin, an antiprotease, is a rare genetic variation that causes emphysema, but it is found only in 1 to 2 percent of patients with COPD.

Evidence Synthesis

To date, except for an alpha$_1$-antitrypsin deficiency, the role of genetic variations in the development of COPD has received limited attention (Sandford et al. 1997; Barnes 1999; Takizawa et al. 2001). Family studies have demonstrated a genetic influence on the level of FEV$_1$, and segregation analysis has provided evidence that the effect is polygenic. Moreover, in case-control studies of COPD patients, a family history of COPD has proven to be a risk factor for COPD. Candidate genes for susceptibility to cigarette smoke and COPD that are under active investigation include the numerous genes that control peripheral airway inflammation, oxidant levels, and the protease-antiprotease balance (Higham et al. 2000; Sakao et al. 2001; Sandford et al. 2001).

Conclusion

1. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.

Implication

Although smoking prevention and cessation remain the cornerstones for preventing smoking-induced chronic respiratory diseases (USDHHS 1990), further research on the biologic mechanisms of airway and alveolar injury caused by smoking may provide new approaches for preventing smoking-induced lung diseases among smokers unable to quit.

Growth of Lung Function in Infancy and Childhood

Epidemiologic Evidence

In addition to the adverse effects on pulmonary function of in utero exposure to maternal smoking and postnatal exposure to parental smoking (National Research Council 1986; USDHHS 1986; U.S. Environmental Protection Agency 1992), active cigarette smoking during childhood and adolescence has the potential for retarding the rate of lung growth and the level of maximum lung function (Table 4.13) (USDHHS 1994), thus increasing the risk for COPD in adulthood (Figure 4.1). Results from six cohort studies of lung function in children and adolescents published from 1982–1992 were reviewed in the 1994 Surgeon General's report (USDHHS 1994). Two representative publications from that report (Tager et al. 1985, 1988) are summarized here along with two investigations that were not reviewed in the 1994 report (Sherrill et al. 1991; Gold et al. 1996).

In a longitudinal study of 669 children and adolescents aged 5 through 19 years in East Boston, Massachusetts, Tager and colleagues (1985) found that among adolescents who started to smoke at 15 years of age and continued to smoke, the percent predicted FEV$_1$ level at 20 years of age was only 92 percent of the expected FEV$_1$ level for nonsmokers. Subsequently, Tager and colleagues (1988) analyzed spirometric measurements from at least one FVC test performed during 1975–1985 in each of 974 females and 913 males aged 5 years and older. For girls, a linear increase in FEV$_1$ levels ended approximately one year earlier for current smokers (at 17 years of age) than for nonsmokers without respiratory symptoms (at 18 years of age); the average maximal FEV$_1$ values were 2.9 L and 3.1 L, respectively. For nonsmokers with respiratory symptoms, the estimated maximal FEV$_1$ level was identical to that for current smokers (2.9 L). For boys, the estimated maximal FEV$_1$ level was identical for asymptomatic nonsmokers (those who do not have a diagnosis of chronic bronchitis or emphysema, or evidence of chronic respiratory symptoms), symptomatic nonsmokers, and current smokers (4.9 L), but was attained at a much earlier age for current smokers (at 18 through 19 years of age) compared with asymptomatic nonsmokers (aged 20 through 34 years) and symptomatic nonsmokers (21 years). Sherrill and colleagues (1991) assessed growth curves in smokers classified as asymptomatic. They found that among women, cessation of lung function growth occurred at 22 years of age in asymptomatic smokers and at 23 years of age in asymptomatic women who had never smoked. Among female smokers with respiratory symptoms, lung function growth ended at 21 years of age, three years earlier than for those who had never smoked. Among asymptomatic men, the authors found no differences in the age of lung growth cessation between nonsmokers and smokers (23 years of age). Among

symptomatic male smokers, however, lung growth cessation occurred at a younger age (25 years of age) compared with symptomatic nonsmokers (27 years of age).

In a cohort of 4,902 girls and 5,158 boys from 10 to 18 years of age tested annually with spirometry, Gold and colleagues (1996) examined the effects of cigarette smoking on the rate of lung function growth and the level of lung function attained. Among girls smoking five or more cigarettes per day, the rate of increase in FEV_1 levels was slower by 31 mL/year (95 percent CI, 16.0–46.0 mL/year) than among girls who had never smoked. At 17 to 18 years of age, FEV_1 levels began to decline among girls who smoked while staying at a plateau among girls who did not smoke. Although smoking five or more cigarettes per day slowed the rate of increase in FEV_1 levels in boys, the magnitude of the effect (slower by 9 mL/year; 95 percent CI, -6.0 to 24.0 mL/year) was less than that in girls. There was an inverse association between the amount smoked and the level of FEV_1/FVC and FEF between 25 and 75 percent of the FVC ($FEF_{25-75\%}$). The number of cigarettes smoked was not associated with FVC or FEV_1 levels.

Evidence Synthesis

There have been only a limited number of longitudinal investigations of active smoking during childhood and adolescence because of the complex logistics of such studies. However, the findings are consistent for various populations. In smokers, lung function growth is slower during childhood and adolescence, prematurely ceases, and begins to decline in late adolescence and early adulthood. The evidence suggests a causal role for active smoking. This causal link is strengthened by the finding of a dose-response relationship between smoking and the level of FEV_1/FVC and between smoking and $FEF_{25-75\%}$. Additionally, the inflammatory process caused by smoking would be initiated at any age, and the lungs of young smokers show evidence of airways inflammation and injury.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence.

2. The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood.

Implications

These conclusions provide a strong rationale for interventions to prevent children and adolescents from starting to smoke and for helping young smokers to quit. Future studies should determine the effects of smoking cessation on the rate of lung growth, and they should follow smokers from adolescence into their fourth and fifth decades of life when COPD is first diagnosed. Addressing these gaps in knowledge could provide further evidence of a causal link between active smoking during childhood and the risk for later development of COPD.

Decline of Lung Function

Epidemiologic Evidence

Results from longitudinal investigations of adults between their second and third decades—the period of transition from lung growth to a plateau of variable length and then to decline—suggest that cigarette smoking causes a premature onset of lung function decline and, to a lesser extent, a more rapid decline (Tager et al. 1988; Sherrill et al. 1991). In the East Boston study, estimates of the age range when lung function begins to decline were wide but tended to be earlier for current smokers compared with asymptomatic or symptomatic nonsmokers (Tager et al. 1988). After the period of maximal lung growth, there is a prolonged plateau period for the FEV_1 level in nonsmoking men before the FEV_1 declines (late in the fourth decade of life). This decline is estimated to begin 10 years earlier (i.e., late in the third decade of life) in asymptomatic nonsmokers and 15 years earlier in current smokers (i.e., in the middle of the third decade). Among all women, the onset of decline begins at an earlier age compared with that of men, and female current smokers had a more rapid earlier decline (-20 mL/year) and an earlier age of onset of a more rapid decline compared with nonsmoking women. In the population-based study of respiratory diseases in Tucson, Arizona, Sherrill and colleagues (1991) also found that symptom status modified the rate of decline. The rate of decline was similar for asymptomatic male smokers and nonsmokers until approximately 48 years of age, when the average rate of decline for smokers increased from -29 mL/year to -46 mL/year. Among symptomatic smokers, the increased rate of decline occurred at a younger age (34 years of age). The FEV_1 level was lower for symptomatic female smokers beginning in the late teenage years, but there

was little difference in the subsequent rate of FEV$_1$ decline between smokers and nonsmokers.

In cross-sectional and cohort studies of ventilatory function, a higher average rate of FEV$_1$ decline has been consistently found in current cigarette smokers compared with former smokers and nonsmokers (Table 4.15) (USDHHS 1984, 1990). In cohort studies the average rate of FEV$_1$ decline among nonsmokers ranged from 17 to 61 mL/year, and the decline among smokers exceeded the decline among nonsmokers by 7 to 27 mL/year (USDHHS 1990). Furthermore, while the rate of FEV$_1$ decline for smokers and nonsmokers is highly variable, the distribution of FEV$_1$ decline rates is shifted toward a higher proportion of sustained smokers with rapid rates of decline. As the amount of cigarette smoking increases, the rate of decline increases (Xu et al. 1992, 1994; Burchfiel et al. 1996; Vestbo et al. 1996; Belousova et al. 1997; Scanlon et al. 2000; Vollmer et al. 2000). For some smokers, the increased rate of decline eventually results in a FEV$_1$ level associated with dyspnea and a limitation of activities; at this level, the clinical diagnosis of COPD is usually made (Figure 4.1).

Because not all smokers develop COPD, research is increasingly directed at identifying factors that may heighten susceptibility to rapid rates of FEV$_1$ decline. Factors that have been examined include gender (Xu et al. 1994; Scanlon et al. 2000; Vollmer et al. 2000), race and ethnicity (Scanlon et al. 2000; Vollmer et al. 2000), alcohol use (Burchfiel et al. 1996), diet and use of nutritional supplements (Carey et al. 1998), anthropometric characteristics (Burchfiel et al. 1996), respiratory symptoms (Jaakkola et al. 1991a,b; Sherman et al. 1992; Burchfiel et al. 1996; Scanlon et al. 2000), FEV$_1$ levels (Burrows et al. 1987; Scanlon et al. 2000), airways hyperresponsiveness (Frew et al. 1992; Tashkin et al. 1996), comorbid conditions such as asthma and coronary heart disease (Burchfiel et al. 1996; Lange et al. 1998), and occupational and environmental exposures (Xu and Wang 1998). Investigations of these factors are ongoing and firm conclusions cannot yet be reached on their roles in modifying the risk for COPD in smokers.

Available investigations provide conflicting results about the relative rates of FEV$_1$ decline among women who smoke compared with men who smoke (Xu et al. 1994; Scanlon et al. 2000; Vollmer et al. 2000). Xu and colleagues (1994) suggested that women may have a higher rate of FEV$_1$ decline. They hypothesized that different distributions of unhealthy participants by gender in nonsmoking reference groups may explain conflicting results in studies that compared rates

of FEV$_1$ decline in women and men. Other factors that may modify the effects of smoking and contribute to gender differences in study findings include the year of birth of study participants (birth cohort) and the time period of a study (Samet and Lange 1996). In a study from the Netherlands, Xu and colleagues (1995) reported a significant interaction between age and birth cohorts in relation to declines in FEV$_1$ levels in women but not in men. The modifying effects of a birth cohort may partially reflect changes in smoking behavior and perhaps in the products smoked.

Several studies have shown that women have a higher prevalence and degree of bronchial hyperreactivity (Leynaert et al. 1997), associated with an accelerated rate of decline in FEV$_1$ levels, compared with men (Tashkin et al. 1996; Scanlon et al. 2000). This gender difference in bronchial hyperreactivity may contribute to a higher risk in women for developing COPD. Scanlon and colleagues (2000) found in the Lung Health Study that women who continued to smoke over a five-year period had a greater annual decline in FEV$_1$ levels than did men with comparable levels of smoking (-1.08 percent predicted and -0.77 percent predicted, respectively), but the statistical significance of the difference was not reported. The increased rate of decline among women was associated with a greater degree of bronchial hyperreactivity.

Biologic differences between women and men, including differences in lung mechanics and hormonal factors, may affect susceptibility to the adverse effects of cigarette smoke, but limited data are available to test these hypotheses. Whether there are gender differences from the effects of smoking on changes in lung function remains unclear.

Scant data are available on racial and ethnic differences in the rates of FEV$_1$ decline (Scanlon et al. 2000; Vollmer et al. 2000). In the Lung Health Study, Vollmer and colleagues (2000) combined spirometric data from eight population-based observational studies or clinical trials conducted in North America to examine the relationship between smoking, lung function, race, and ethnicity. Overall, this cross-sectional analysis included 23,812 men (66 percent white, 14 percent black, 4 percent Hispanic, 12 percent Asian/Pacific Islander, and 3 percent American Indian) and 16,921 women (62 percent white, 25 percent black, 6 percent Hispanic, and 7 percent American Indian). The estimated average excess FEV$_1$ decline attributed to smoking was highest among whites (-6 mL/pack-year) and similar in the other racial and ethnic groups (-3 to -4 mL/pack-year). However, the greatest differences among racial and ethnic groups were limited to the heaviest

Table 4.15   Studies on the association between smoking and rates of forced expiratory volume in one second (FEV$_1$) decline

Study	Population	Period of study/follow-up
Jaakkola et al. 1991a	214 white women 177 white men Aged 15–40 years at baseline Montreal, Canada	Baseline: 1980–1981 Follow-up: 1988–1989
Jaakkola et al. 1991b	626 women 418 men Aged 15–40 years Montreal, Canada	1980
Frew et al. 1992	733 men from 4 worksites Mean age 37.2–42.4 years Vancouver, Canada	Baseline: 1981–1983 Mean follow-up: 5.64 years
Sherman et al. 1992	2,191 women 1,757 men Aged 25–74 years United States (6 cities)	Baseline: 1974 Mean follow-up: 12 years
Buist et al. 1995	3,135 women 2,093 men Aged 35–56 years China	1984–1985
Sandvik et al. 1995	1,393 men Aged 40–59 years Oslo, Norway	Baseline: 1972–1975 Follow-up: 1980–1982
Burchfiel et al. 1996	4,451 Japanese American men Aged 45–68 years Honolulu, Hawaii	Baseline: 1965–1968 Follow-up: 1971–1975
Belousova et al. 1997	860 women 639 men Aged 18–73 years Australia	1991–1992

*Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Rate of FEV$_1$ decline	Type of study/comments
-0.42 mL/year/cigarettes/day	Longitudinal; participation was 38% at follow-up
-0.35 mL/year/cigarettes/day	Cross-sectional; significant interaction between smoking and wheezing
Current smokers: -29.3 mL/year Former smokers: -25.5 mL/year Never smokers: -23.3 mL/year	Longitudinal; bronchial hyperresponsiveness was associated with a rapid FEV$_1$ decline only in current smokers

Women
  Continuing smokers: -34.3 mL/year
  Former smokers: -27.1 mL/year
  Never smokers: -28.0 mL/year
Men
  Continuing smokers: -44.6 mL/year
  Former smokers: -35.7 mL/year
  Never smokers: -32.9 mL/year
	Longitudinal; respiratory symptoms were associated with a more rapid decline

-4.0 mL/year of smoking	Cross-sectional
Smokers: -38.7 mL/year Nonsmokers: -16.6 mL/year	Longitudinal

Continuous smokers: -34 mL/year
Never smokers: -22 mL/year
 	
FEV$_1$ decline (mL/year)   % current smokers
    <30   40.0
    30–59   50.5
     60   59.9
	Longitudinal; rapid FEV$_1$ decline was independently associated with pack-years*, wheezing, and reduced subscapular skinfold

-2.0 mL/cigarettes/day	Cross-sectional

Table 4.15 Continued

Study	Population			Period of study/follow-up
Xu and Wang 1998	1,618 women 1,669 men Aged 40–69 years Beijing, China			1986
Scanlon et al. 2000	1,374 women 2,444 men Mild-to-moderate COPD[†] Aged 35–60 years 10 centers United States and Canada			Baseline: 1986–1989 Annual follow-up for 5 years
Vollmer et al. 2000		Men	Women	NR[‡]
	White	15,771	10,468	
	Black	3,308	4,203	
	Hispanic	1,004	1,039	
	Asian/Pacific Islander	2,954	0	
	American Indian	775	1,211	
	Aged 30–85 years United States			

*Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[†]COPD = Chronic obstructive pulmonary disease.
[‡]NR = Data were not reported.

smokers (more than 10 cigarettes per day). Overall, during the five-year period of the Lung Health Study, there were no differences in the rates of change in FEV_1 declines among these participants (Scanlon et al. 2000).

The presence of respiratory symptoms, particularly coughing, phlegm, and wheezing, has been associated with an accelerated decline in FEV_1 levels in cigarette smokers and nonsmokers in a number of studies (Jaakkola et al. 1991a,b; Sherman et al. 1992; Burchfiel et al. 1996; Vestbo et al. 1996). Among Japanese American men in the Honolulu Heart Program who were continuous smokers, Burchfiel and colleagues (1996) found an increased risk of rapid FEV_1 declines (-60 mL/year or greater) associated with wheezing (OR = 3.9 [95 percent CI, 1.8–8.3]). However, respiratory symptoms have not been predictive of FEV_1 declines in all studies. Although Scanlon and colleagues (2000) did not find an association between respiratory symptoms and the rate of FEV_1 declines in the Lung Health Study, their ability to detect an association may have been limited because participants in this study were restricted to smokers with mild to moderate chronic airflow obstruction.

The presence of other diseases including asthma (Lange et al. 1998) and coronary heart disease (Burchfiel et al. 1996) has been associated with an accelerated FEV_1 decline among smokers. In the Copenhagen City Heart Study, Lange and colleagues (1998) followed 9,370 women and 8,136 men, 20 to 79 years of age, over a 15-year period. Except for the youngest women (20 to 39 years of age) and the oldest men (60 to 79 years of age), smokers with asthma averaged greater FEV_1 reductions than smokers without asthma. In the Honolulu Heart Program, Japanese American men with coronary heart disease who continued to smoke had an increased risk for a rapid FEV_1 decline (-60 mL/year or greater) (OR = 1.99 [95 percent CI, 0.96–4.14]).

Nutritional factors such as dietary intake (Carey et al. 1998) and anthropometric characteristics

Rate of FEV$_1$ decline	Type of study/comments
-6.5 mL/year of smoking in excess of decline in nonsmokers	Cross-sectional; significant interaction between smoking and occupational exposures and ambient pollution
Continuing smokers: -62 mL/year Intermittent quitters: -42 mL/year Sustained quitters: -31 mL/year	Randomized clinical trial
Excess decline attributed to smoking (mL/pack-year*)	Cross-sectional

	Men	Women
White	-6	-7
Black	-4	-4
Hispanic	-3	-5
Asian/Pacific Islander	-3	NR
American Indian	-4	-5

(Burchfiel et al. 1996) have been associated with rates of FEV$_1$ decline. In a national sample of 2,171 British adults aged 18 through 73 years, Carey and colleagues (1998) found that current smokers who consumed the smallest quantities of fresh fruits (sources of antioxidant vitamins) over a seven-year period had a higher rate of FEV$_1$ decline than lifetime nonsmokers, with adjustments for social class, region, pack-years, and average fresh fruit scores (by rating consumption as more than one per day, one per day most days, once or twice per week, less than one per week, or never).

Anthropometric characteristics have been associated with a rapid FEV$_1$ decline among cigarette smokers (Burchfiel et al. 1996). Burchfiel and colleagues (1996) found that increasing body mass, measured by subscapular skinfold thickness, was associated with a lower risk for rapid FEV$_1$ declines (-60 mL/year or greater). A 10-mm increase in subscapular skinfold thickness was associated with a 30 percent decrease in the risk for a rapid FEV$_1$ decline (OR = 0.70 [95 percent CI, 0.55–0.88]).

The relationship between a single measure of and a subsequent rate of change in the FEV$_1$ level has been termed the "horse-racing effect"; a low FEV$_1$ level is a predictor of a rapid decline in the FEV$_1$ (Fletcher et al. 1976; Burrows et al. 1987). The term "horse-racing" was proposed because a low FEV$_1$ level at any point reflects a high rate of prior loss and hence is predictive of a future decline. As an integrated consequence of a prior decline, the FEV$_1$ level is also a potential marker for susceptibility to the factors driving the decline.

Burrows and colleagues (1987) proposed that a low FEV$_1$ level may be an early marker for identifying smokers who are susceptible to COPD. The investigators examined relationships between FEV$_1$ levels and other spirometric parameters and the rates of FEV$_1$ decline in 620 women and 475 men from Tucson, Arizona. For both men and women, a low initial FEV$_1$ level was not associated with a rapid FEV$_1$ decline. In men, however, an initially low ratio of FEV$_1$/FVC (less than 70 percent) was associated with a rapid FEV$_1$

decline; trends in women were reported to be similar but less marked, although the data were not provided. Similarly, in the Lung Health Study, Scanlon and colleagues (2000) found no differences in the rates of FEV_1 decline over four years of follow-up when comparing continuing smokers with a baseline FEV_1 in the lowest quintile (-63 mL/year) with those in the highest quintile (-61 mL/year). However, the investigators did find a significant association between the baseline FEV_1 percent predicted and the rate of decline. These findings need to be interpreted with attention to the characteristics of the study participants: middle-aged smokers with mild-to-moderate airflow obstruction. Overall, the available results suggest that various indicators of impaired ventilatory function predict subsequent FEV_1 declines.

Among cigarette smokers, bronchial hyperresponsiveness to a variety of stimuli (e.g., histamine and methacholine) has been associated with an accelerated rate of decline in FEV_1 levels (Frew et al. 1992; Rijcken et al. 1995; Villar et al. 1995; Tashkin et al. 1996). In the Lung Health Study, Tashkin and colleagues (1996) examined the relationship between bronchial hyperreactivity to methacholine and FEV_1 declines among 5,733 smokers aged 35 through 60 years with mild COPD (mean FEV_1/FVC, 65 percent; FEV_1, 78 percent predicted). After adjusting for age, gender, baseline smoking history, changes in smoking status, and baseline lung function levels, the investigators found that airway hyperreactivity during the five-year follow-up was a strong predictor of changes in FEV_1 levels percent predicted. The greatest decline of 2.2 percent predicted was in women who had the highest degree of hyperreactivity and who continued to smoke. The corresponding value in men was 1.7 percent predicted.

In addition to cigarette smoking, exposures to ambient air pollutants or workplace exposures may accelerate FEV_1 declines and increase future risks for COPD (Garshick et al. 1996; Xu and Wang 1998). For example, Xu and Wang (1998) examined the effects of smoking, urban air pollution, and workplace exposures on lung function levels in a 1986 cross-sectional survey of 3,287 randomly selected adults 40 to 69 years of age residing in Beijing, China. The investigators found that smokers had an increased reduction in FEV_1 levels of 6.5 mL for each year of smoking compared with adults who had never smoked; smokers living in residential and industrial areas with high levels of ambient pollutants had further decrements in pulmonary function.

Effects of Smoking Cessation

The beneficial effects of smoking cessation on the rates of FEV_1 decline were extensively reviewed in the 1990 Surgeon General's report. A major conclusion of that report relevant to FEV_1 declines and smoking cessation was that "cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers" (Table 4.13) (USDHHS 1990, p. 11). Since that report, there have been additional studies supporting these conclusions (Townsend et al. 1991; Anthonisen et al. 1994; Sherrill et al. 1994; Xu et al. 1994; Burchfiel et al. 1995; Frette et al. 1996; Murray et al. 1998; Berglund et al. 1999; Scanlon et al. 2000). These studies also have advanced an understanding of factors that modify the effects of smoking cessation on rates of FEV_1 decline.

The Lung Health Study provides powerful clinical trial data on the effects of smoking cessation on the rates of FEV_1 decline and lung function levels (Anthonisen et al. 1994; Scanlon et al. 2000). This five-year, multicenter clinical trial of smoking cessation interventions was conducted in 10 North American centers. Between 1986 and 1989, 5,887 women (37 percent) and men (63 percent) aged 35 through 60 years who were current smokers with mild to moderate airflow obstruction (FEV_1/FVC of 70 percent or less and FEV_1 between 55 percent and 90 percent of predicted normal) were randomized into three groups: usual care, smoking cessation intervention with a placebo inhaler, and smoking cessation intervention with an inhaled bronchodilator (ipratropium bromide). Participants in the smoking cessation intervention placebo group and the usual care group who stopped smoking in the first year of the trial had an average increase in FEV_1 levels of 47 mL compared with a 49 mL decrease among persons who continued to smoke (Scanlon et al. 2000). Between year one and year five of the trial, the average rate of FEV_1 reduction among continuous smokers was -62 mL/year, twice that of sustained quitters (-31 mL/year) during the same time period. Quitting intermittently during the follow-up period was associated with an intermediate rate of decline (-43 mL/year). The degree of improvement during the first year of cessation and the rates of FEV_1 decline after cessation varied with age at cessation, gender, amount of smoking, level of baseline lung function, and airways hyperreactivity.

Results from several investigations suggest that the benefits of smoking cessation are greatest for persons who stop smoking at younger ages (Camilli et al.

1987; Sherrill et al. 1994; Xu et al. 1994; Frette et al. 1996; Scanlon et al. 2000). In the Lung Health Study, Scanlon and colleagues (2000) found that sustained quitters younger than 50 years of age had the slowest rates of FEV_1 decline during the five-year follow-up period compared with sustained quitters 50 years of age and older (Figure 4.3). Among 147 women and 141 men who were new quitters in the prospective Tucson Epidemiological Study of Airways Obstructive Disease, Sherrill and colleagues (1994) estimated that smoking cessation among women improved FEV_1 levels by 4.3 percent at 20 years of age and by 2.5 percent at 80 years of age. For men, FEV_1 improvements were less at both ages: 1.2 percent at 20 years of age and zero at 80 years of age. During the 24 years of follow-up in the Dutch Vlagtwedde-Vlaardingen Study (Xu et al. 1994), the mean FEV_1 loss in former compared with current smokers was 20 mL/year less for women who stopped smoking before 45 years of age, but only 5.4 mL/year less for women who stopped smoking at 45 years of age or older. The corresponding values for men were 28.2 mL/year less for men younger than 45

years of age, and 10.4 mL/year less for men 45 years of age and older. In the Rancho Bernardo (California) Heart and Chronic Disease Study, 826 women and 571 men aged 51 through 95 years had spirometry testing from 1988–1991 (Frette et al. 1996). Women who were former smokers who stopped smoking before 40 years of age had FEV_1 levels similar to those for women who had never smoked (2.09 L and 2.13 L, respectively). The average FEV_1 level for women who stopped smoking at 40 through 60 years of age was 2.02 L, which was between that for female nonsmokers (2.13 L) and female current smokers (1.71 L). Women who stopped smoking at 60 years of age or older had a FEV_1 level similar to that of current smokers (1.72 L and 1.71 L, respectively); the same pattern in relation to age at smoking cessation was found for men.

Limited data suggest that smoking cessation more significantly benefits lung function and the rate of FEV_1 decline in women than in men (Sherrill et al. 1994; Scanlon et al. 2000). The Tucson Epidemiological Study of Airways Obstructive Disease (Sherrill et al. 1994) estimated that the average improvement in

Figure 4.3 Mean change and 95 percent confidence interval in forced expiratory volume in one second (FEV_1) percent predicted from years 1–5 of the Lung Health Study for sustained quitters, intermittent quitters, and continuous smokers, by quintile of age
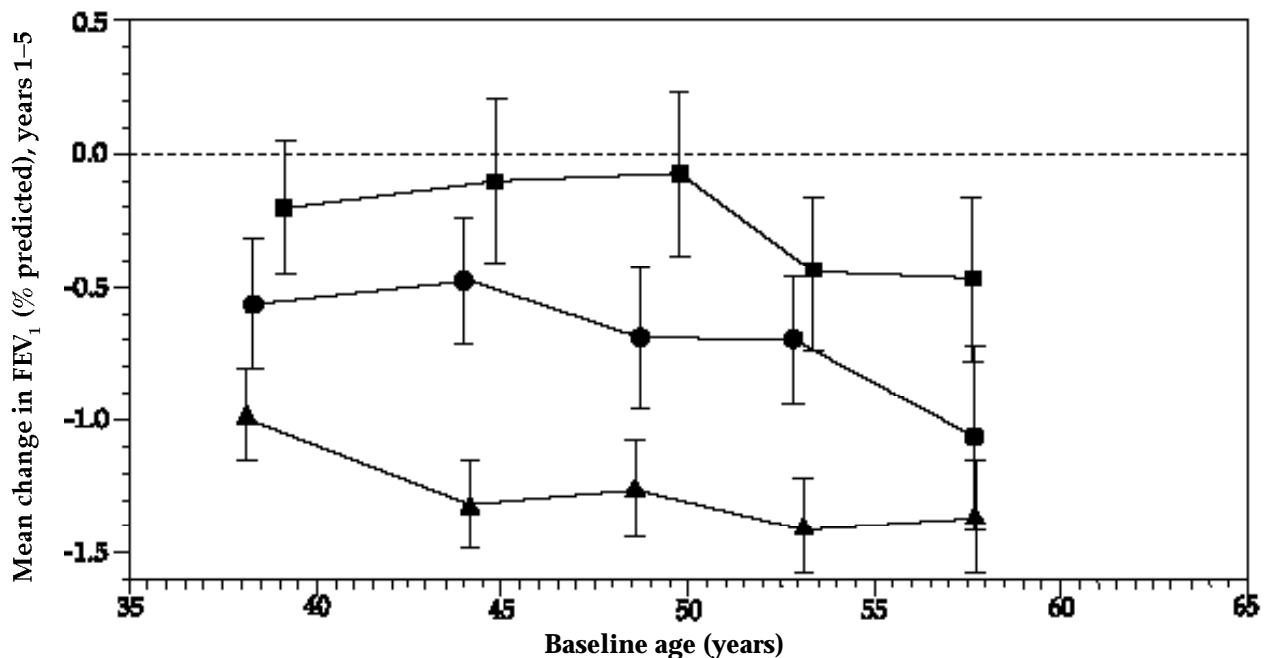
Source: Scanlon et al. 2000, p. 387. Reprinted with permission.

FEV_1 levels at 80 years of age was higher among women who had quit smoking (2.5 percent) than among men who had stopped smoking (0.0 percent). Women who were sustained quitters in the Lung Health Study had improvements in FEV_1 levels in the first year of cessation 2.5 times greater than did men (Scanlon et al. 2000). The report from Scanlon and colleagues (2000) did not provide gender-specific effects on subsequent FEV_1 rates of decline.

The amount of exposure to cigarette smoke, which may be measured in several ways, may also influence the effects of smoking cessation (Burchfiel et al. 1995; Scanlon et al. 2000). Burchfiel and colleagues (1995) found slower FEV_1 declines after quitting in Japanese American men with the highest level of baseline smoking (-9.1 mL/year) compared with men with the lowest level (-24.1 mL/year). In the Lung Health Study, Scanlon and colleagues (2000) found no differences in the rates of FEV_1 decline among sustained quitters from year one through year five of follow-up in relation to the number of cigarettes smoked at baseline. However, they did find that the largest improvements in FEV_1 levels after smoking cessation for the first year were among persons who smoked the most cigarettes per day before quitting (Figure 4.4) (Scanlon et al. 2000). Among sustained quitters in the Lung Health Study, for the subgroup with the highest quintile of cigarettes smoked per day before quitting, improvement in FEV_1 levels was 3.33 percent predicted in the first year of cessation compared with only 0.51 percent predicted for the lowest smoking quintile.

Limited data are available on the relationship between the FEV_1 level at quitting and the consequences of smoking cessation (Burchfiel et al. 1995; Scanlon et al. 2000). In the Honolulu Heart Program, Burchfiel and colleagues (1995) found that after adjusting for age, height, and amount smoked, the benefits of quitting were more evident in persons with lower baseline FEV_1 levels. In contrast, Scanlon and colleagues (2000) found that a baseline FEV_1 level was not predictive of subsequent rates of decline in the FEV_1 level and baseline level was not associated with greater improvements after the first year of cessation. The conflicting results between these two studies may reflect differing study populations. The Honolulu Heart Program was population-based and began with middle-aged Japanese American men, whereas the Lung Health Study used volunteer smokers with evidence of mild-to-moderate airflow obstruction.

The degree of bronchial reactivity has been strongly associated with the magnitude of improvements in FEV_1 levels in the first year of cessation, and with the subsequent rates of FEV_1 decline. In the Lung Health Study, Tashkin and colleagues (1996) found that persons with higher airway reactivity had the greatest improvements in FEV_1 levels within the first year after quitting, whereas the slowest rates of FEV_1 decline occurred among sustained quitters with the lowest airway reactivity.

Although the benefits of smoking cessation on rates of decline and lung function levels are well established, weight gain associated with quitting may reduce lung function levels and increase FEV_1 declines, thus counterbalancing the benefits of quitting. In the Lung Health Study, Wise and colleagues (1998) found that the FVC was affected more than the FEV_1 by the weight gain. The estimated loss of FEV_1 was 11.1 mL/kg of weight gain for men and 10.6 mL/kg for women, and the mean weight gains over five years among sustained quitters were 7.6 kg and 8.8 kg, respectively. Furthermore, the average FEV_1 decline was greater in those who gained the most weight during the five years of follow-up (Figure 4.5). However, the effect of weight gain on the rates of FEV_1 decline was relatively small compared with the effects of continued smoking, and the FVC and FEV_1 would be expected to increase with weight loss.

Evidence Synthesis

The adverse effects of active smoking and the benefits of smoking cessation on lung function decline have been firmly established (USDHHS 1984, 1990). Research emphasis has shifted to finding determinants of susceptibility to rapid lung function decline in active smokers and determinants of improvements after smoking cessation. Factors that predict the greatest susceptibility to rapid lung function decline while actively smoking include a greater number of cigarettes smoked, wheezing, asthma, bronchial hyperreactivity, low body mass, low lung-function level (FEV_1 percent predicted or low FEV_1/FVC), occupational exposures, and ambient air pollution. However, there is limited evidence available on how modifying active smoking affects the rate of lung function decline by gender, ethnicity, and antioxidant dietary intake.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function.

Figure 4.4 Mean change and 95 percent confidence interval in forced expiratory volume in one second (FEV$_1$) percent predicted during year 1 of the Lung Health Study, for persons who quit smoking and for persons who continued to smoke during year 1, by quintile of the number of cigarettes smoked at baseline
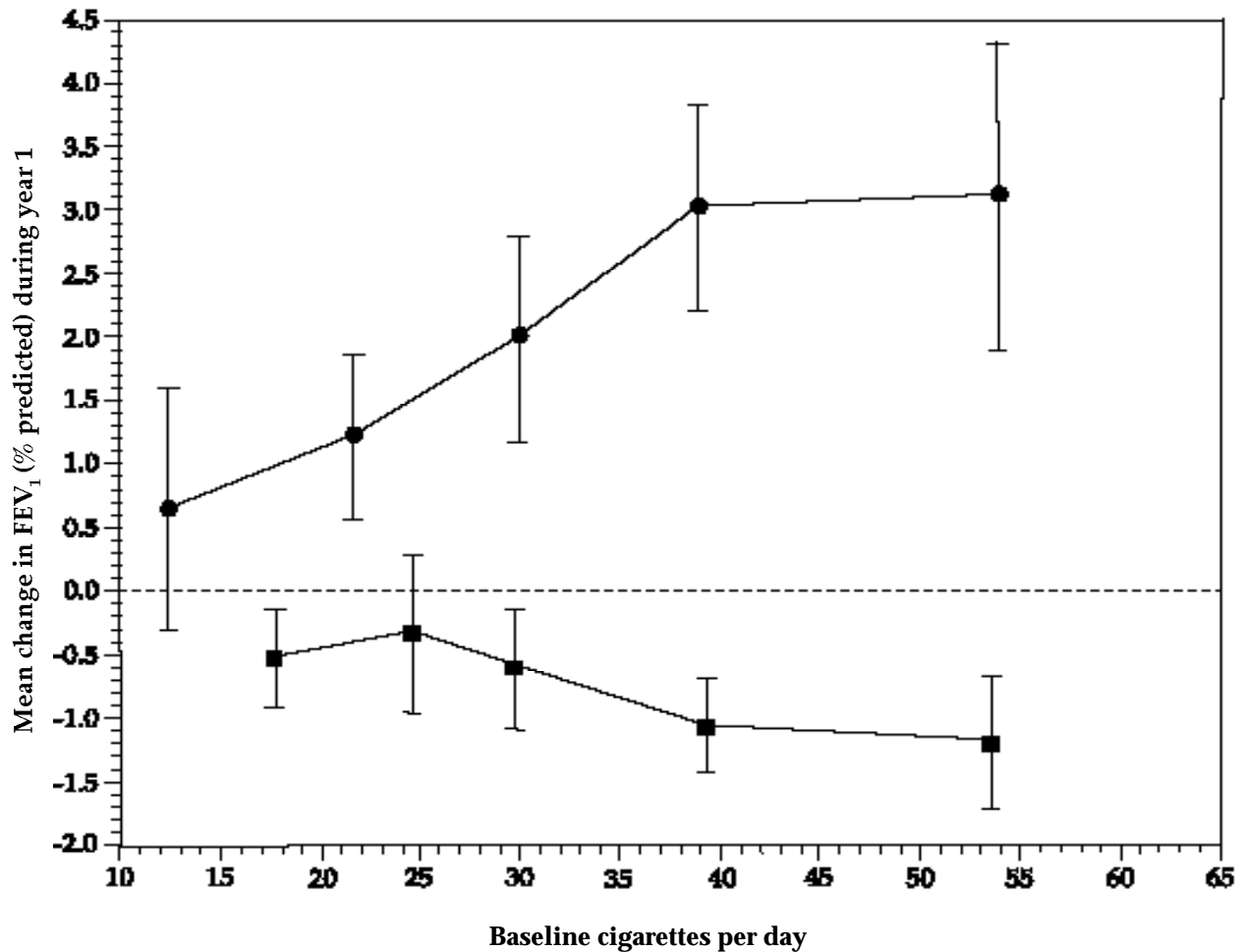
Note: Corrected data presentation shown here. When the smokers were ranked by quintile, the heaviest smokers had the largest functional losses during the first year if they continued smoking (p = 0.028).
Source: Scanlon et al. 2000, p. 389. Reprinted with permission.

2. The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked.

Implications

These conclusions provide a strong rationale for smoking cessation interventions for active smokers.

The greatest benefits from smoking cessation will occur at younger ages, but all smokers benefit from cessation regardless of age. Identifying smokers with the greatest susceptibility for a rapid decline in lung function may lead to more targeted interventions, but cessation for all smokers is central to preventing COPD.

Figure 4.5 The relationship between mean changes in forced expiratory volume in one second (FEV$_1$) percent predicted to quintiles of mean changes in weight for each smoking category
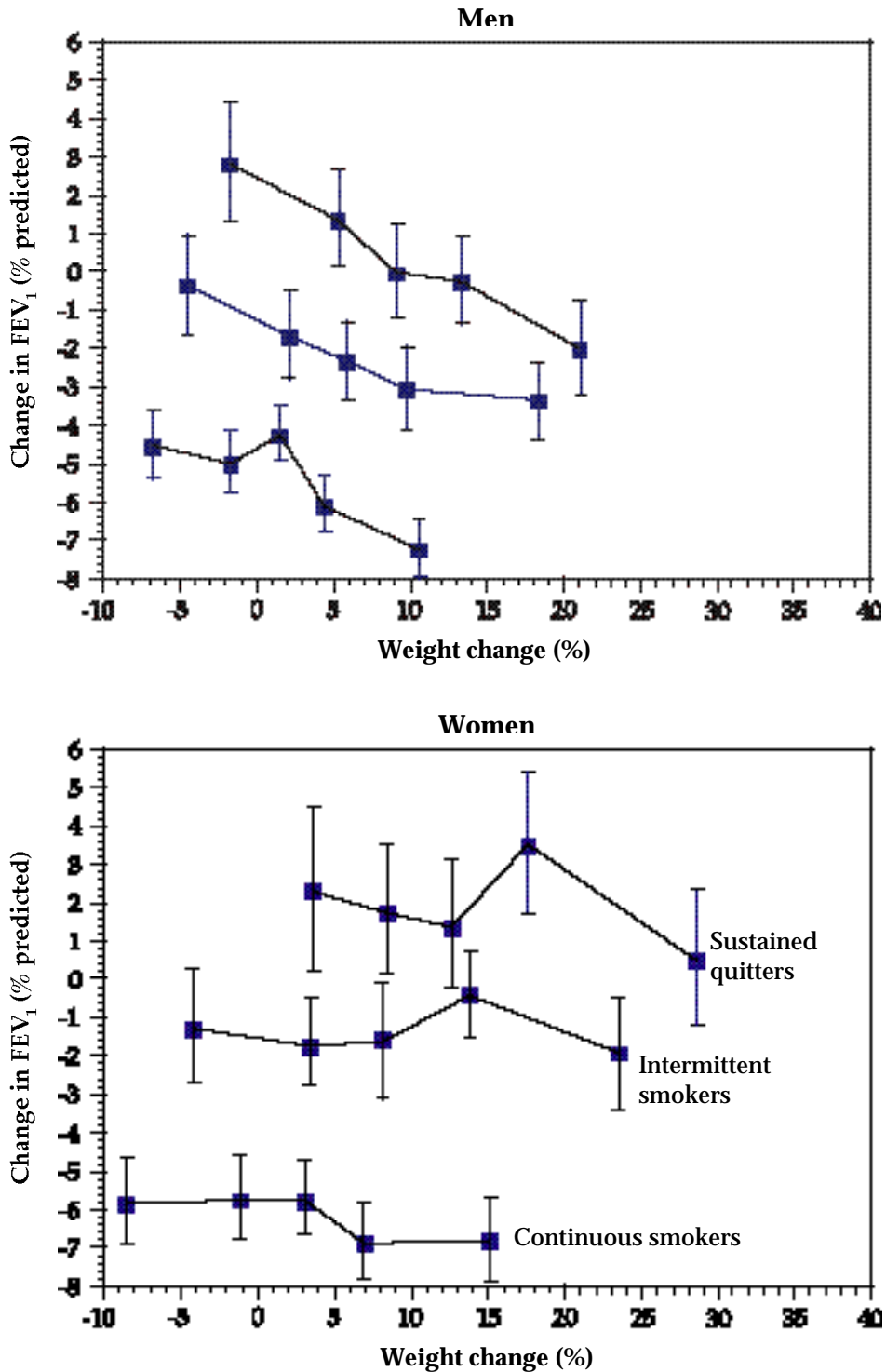
Note: Corrected data presentation shown here. The interval for changes in FEV$_1$ percent predicted and weight are between baseline and the fifth annual visit. The top panel shows men and the bottom panel shows women. Error bars represent a standard error of ±2.

Source: Wise et al. 1998, p. 869. Reprinted with permission.

Chronic Respiratory Symptoms and Diseases

Substantial observational evidence has long shown that respiratory symptoms and diagnoses, the most relevant health outcomes to patients, are causally associated with smoking. Respiratory symptoms—coughing, productive coughing, wheezing, and dyspnea (difficulty breathing and shortness of breath)—are nonspecific and are associated with a number of acute and chronic respiratory diseases and even nonrespiratory diseases. Despite the nonspecificity of respiratory symptoms, their presence is a sensitive indicator of underlying lung injury and disease (Torén et al. 1993), and they have clinical relevance because they may impair functioning and reduce the quality of life. Selected diseases, particularly asthma and respiratory symptoms such as wheezing, may be sufficiently specific in children to be used to define the disease. However, the specificity of wheezing for asthma declines with age because of the increasing prevalence of COPD.

Respiratory Symptoms: Childhood and Adolescence

Overall, the frequency of respiratory symptoms in children and adolescents is greater in current smokers compared with nonsmokers or former smokers, and the duration and amount of smoking further increase the frequency of symptoms (USDHHS 1994; Arday et al. 1995; Larsson 1995; Lam et al. 1998; Withers et al. 1998). A major conclusion of the 1994 Surgeon General's report was that "Cigarette smoking during childhood and adolescence produces significant health problems among young people, including cough and phlegm production, an increased number and severity of respiratory illnesses" and "decreased physical fitness" (USDHHS 1994, p. 41). Since the 1994 report, several investigations have confirmed and extended the conclusions relevant to respiratory symptoms in childhood and adolescence (Arday et al. 1995; Lam et al. 1998; Withers et al. 1998).

Epidemiologic Evidence

To examine the relationship between smoking status and respiratory symptoms, Arday and colleagues (1995) used self-reported questionnaire data obtained from a random sample of 26,504 high school seniors in the 48 contiguous United States from 1982–1989. Compared with students who had never smoked or who had smoked only once or twice in the past, current regular smokers (i.e., reported smoking at least

one cigarette within the past 30 days) who began to smoke daily by ninth grade were more likely to report at least one episode in the past 30 days of coughing spells (OR = 2.1 [95 percent CI, 1.90–2.33]), shortness of breath when not exercising (OR = 2.67 [95 percent CI, 2.38–2.99]), and wheezing or gasping (OR = 2.58 [95 percent CI, 2.29–2.90]). These risk estimates were adjusted for gender, marijuana and cocaine use, parental education, and the year of the survey. The prevalence of respiratory symptoms increased with the amount and duration of smoking.

Lam and colleagues (1998) conducted a cross-sectional survey of 6,304 students 12 to 15 years of age who were attending school in Hong Kong. Students who reported smoking more than six cigarettes per week had a higher prevalence of coughing for three months compared with students who had never smoked (OR = 3.02 [95 percent CI, 1.95–4.69]), and a higher prevalence of wheezing in the past three months (OR = 2.91 [95 percent CI, 1.99–4.26]). These risk estimates were adjusted for gender, age, area of residence, and type of housing. Statistically significant increases in the prevalence of respiratory symptoms were associated with an increased frequency of smoking.

Withers and colleagues (1998) reported results from following a cohort of 2,289 children from the ages of 6 to 8 years to 14 to 16 years of age; all were registered with 1 of 86 family practitioners in Southampton, United Kingdom. Regular smoking (i.e., smoking at least one cigarette per week during the 12 months before completing the questionnaire) was associated with a current cough (OR = 1.71 [95 percent CI, 1.21–2.43]), the onset of a cough between the surveys (OR = 1.91 [95 percent CI, 1.12–3.25]), a persistent wheeze in boys (OR = 4.35 [95 percent CI, 1.20–14.3]), and a new report of wheezing (OR = 1.65 [95 percent CI, 1.14–2.39]).

In the three investigations published since the 1994 Surgeon General's report, the prevalence of respiratory symptoms was consistently higher among cigarette smokers than among nonsmokers (Arday et al. 1995; Lam et al. 1998; Withers et al. 1998). Furthermore, limited evidence suggests that the prevalence of symptoms increases with the duration and amount of smoking (Arday et al. 1995; Lam et al. 1998). Although the results from these investigations are not directly comparable because the survey questions on smoking status and respiratory symptoms vary across studies, in three distinct settings each study shows an increase in symptom rates for children who smoke.

Other factors that may also contribute to respiratory symptoms include gender, associated diseases (e.g., atopy or asthma), passive exposure to smoking if parents or other household members smoke,

marijuana and cocaine use, ambient air pollution, workplace exposures, and socioeconomic factors. These factors have been considered to an extent in some studies. Arday and colleagues (1995) adjusted for gender, marijuana and cocaine use, and parental education. Lam and colleagues (1998) considered gender, age, area of residence, and housing type. Withers and colleagues (1998) included gender, personal and family history of atopy, passive smoking, other household exposures, and social factors. However, despite inconsistent controls for other factors that may contribute to the occurrence of respiratory symptoms, none is likely to substantially confound the strong association between smoking and respiratory symptoms.

Limited data are available on the relationship between smoking cessation and the occurrence of respiratory symptoms in children and adolescents (Arday et al. 1995; Lam et al. 1998). Compared with nonsmokers, former smokers report more frequent respiratory symptoms, but they generally have fewer occurrences of symptoms than regular smokers. Several factors may partially explain this higher occurrence in former smokers compared with nonsmokers, including a relatively short duration of cessation, false reporting of their smoking status, and the "healthy smoker" effect. This effect refers to the observation that persons who continue to smoke are less likely to have respiratory symptoms, in contrast to former smokers who quit smoking because of frequent respiratory symptoms (Weiss et al. 1989).

Evidence Synthesis

Since the 1994 Surgeon General's report on smoking and health, several investigations have been published that confirm and extend conclusions of that report that are relevant to respiratory symptoms in childhood and adolescence (Table 4.13). These studies establish that respiratory symptoms increase with the amount and duration of smoking. Further, these studies also show that the effects of active smoking on respiratory symptoms are not due to other factors that increase respiratory symptoms. Limited data are available on the effects of smoking cessation on respiratory symptoms among youth.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.

Implication

This conclusion provides yet another strong rationale for smoking cessation interventions among youth.

Asthma. In the *Guidelines for the Diagnosis and Management of Asthma* of the National Heart, Lung, and Blood Institute (NHLBI 1997), asthma is defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role . . . . In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli" (p. 3).

Asthma is the most common chronic respiratory childhood disease, and it has been increasing in frequency in the United States and worldwide for several decades (NHLBI 1997; Warner 1999). This complex disease is associated with a number of environmental exposures, particularly aeroallergens, and with genetic susceptibility. Although the literature documenting the association between secondhand smoke exposure and childhood asthma is extensive (Cook and Strachan 1999), only a limited number of studies on active smoking and childhood asthma have been conducted (Larsson 1995; Kaplan and Mascie-Taylor 1997; Lam et al. 1998; Norrman et al. 1998; Withers et al. 1998; Chen et al. 1999).

Epidemiologic Evidence. Establishing the presence of asthma in epidemiologic studies is one of the greatest challenges in investigating cigarette smoking and asthma, primarily because of the lack of an agreed-upon operational definition of asthma (Torén et al. 1993). However, during childhood and adolescence physician-diagnosed asthma and standardized questions about asthma-related symptoms (i.e., wheezing or wheezing with dyspnea) provide sufficient specificity. Asking such questions has been the main method used to examine active smoking and asthma among youth (Larsson 1995; Kaplan and Mascie-Taylor 1997; Lam et al. 1998; Withers et al. 1998; Chen et al. 1999).

Larsson (1995) examined the association between smoking and self-reported asthma incidence among 2,308 persons aged 16 through 19 years living in

Sweden. Between 1990 and 1993, the overall incidence of physician-diagnosed asthma was 1.3 percent per year, and the incidence among females was higher (1.8 percent per year) than that among males (0.9 percent per year). The risk for physician-diagnosed asthma was also higher among female smokers (OR = 2.0 [95 percent CI, 1.0–4.0]) than among male smokers (OR = 1.7 [95 percent CI, 0.6–4.8]). The risks for asthma-related symptoms and the use of asthma medications also were higher among females than among males. This analysis was limited by the lack of information on other factors associated with asthma, including personal atopy, family history of atopy and asthma, parental smoking, and other potential confounding variables.

Kaplan and Mascie-Taylor (1997) examined smoking and asthma in a cohort of 8,860 participants from England, Wales, and Scotland participating in the National Child Development Study. The analysis was based on self-reports at 16 and 23 years of age. In a univariate analysis that included males and females, regular smoking since 16 years of age was associated with reports of asthma or wheezy bronchitis between 16 and 23 years of age (OR = 1.55). Stratified or multivariate analyses, adjusting for other factors, were not performed.

In a 1994 cross-sectional survey of Hong Kong schoolchildren aged 12 through 15 years, Lam and colleagues (1998) did not find an association between active smoking and physician-diagnosed asthma. The prevalence of asthma was 8.6 percent among children who reported smoking six or more cigarettes per week compared with 8.1 percent among children who had never smoked (OR = 1.18 [95 percent CI, 0.76–1.83]).

In a cohort of persons from 2,150 households in the United Kingdom, Withers and colleagues (1998) obtained questionnaire responses on smoking behaviors and asthma from participants aged 14 through 16 years. Smoking at least one cigarette per week in the 12 months preceding the survey was not associated with physician-diagnosed asthma (26.3 percent) compared with children who did not report smoking (21.9 percent). However, the prevalence of asthma was not examined separately with greater amounts of smoking.

Norrman and colleagues (1998) surveyed 1,112 Swedish eighth graders 13 to 16 years of age in 1987 and again in 1991. Overall, the incidence of self-reported asthma was 1.1 percent per year. The onset of asthma was significantly associated with current smoking (OR = 3.4 [95 percent CI, 1.2–9.3]) but not with former smoking (OR = 2.8 [95 percent CI, 0.4–23.0]).

Among 3,240 persons aged 12 through 24 years who participated in the 1994–1995 Canadian National Population Health Study, Chen and colleagues (1999) found a significant association between asthma diagnosed by a health professional and smoking, but only among females. The OR for asthma among female smokers compared with female nonsmokers, adjusted for age, was 2.18 (95 percent CI, 1.41–3.44). Among males, the OR for smokers was 0.98 (95 percent CI, 0.56–1.70) compared with nonsmokers.

In addition to the potential etiologic role of active smoking in asthma, there is strong evidence that smoking adversely affects the course of the disease in children with asthma (Godden et al. 1994; Lam et al. 1998). Godden and colleagues (1994) examined the prevalence of respiratory symptoms and FEV_1 levels among 360 persons from Scotland aged 34 through 40 years, who were participants in a population-based survey as children and who had been diagnosed with childhood asthma (n = 97), wheezing with an upper respiratory infection (n = 132), or no respiratory symptoms (n = 131). In the entire group, current smoking was associated with an increased risk of a current wheeze (OR = 2.02 [95 percent CI, 1.15–3.52]), cough (OR = 7.24 [95 percent CI, 3.39–15.49]), and phlegm (OR = 3.08 [95 percent CI, 1.27–7.39]). The risk associated with all three respiratory symptoms was substantially lower for former smokers, and only phlegm (OR = 1.68 [95 percent CI, 1.30–10.38]) was significantly associated with past smoking. In addition, current smoking was associated with a lower mean FEV_1 percent predicted level (-5.64 percent [95 percent CI, -19.4 to 1.09]). In the 1994 cross-sectional survey of Hong Kong schoolchildren reported by Lam and colleagues (1998), children with asthma who smoked more than six cigarettes per week were more likely to report using asthma medications during the previous two days compared with children who had never smoked (OR = 3.07 [95 percent CI, 1.58–5.97]).

Evidence Synthesis. Although the prevalence of wheezing, an asthma-related symptom, is consistently higher in current smokers than in former smokers and nonsmokers, available investigations provide inconsistent findings on the relationship between smoking and reports of physician-diagnosed asthma. Moreover, none of the investigations have fully controlled for known risk factors for asthma. There is limited but consistent evidence that active smoking worsens the prognosis of asthma in children.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.

Implications. These conclusions provide a strong rationale for preventing active smoking among children and adolescents to preclude the occurrence of asthma-related symptoms. The promotion of smoking cessation should improve the prognosis for children and adolescents with asthma who smoke. Future studies of causes of childhood asthma should include active smoking as a potential etiologic agent.

Respiratory Symptoms: Adulthood

Epidemiologic Evidence

Evidence continues to accumulate confirming the long-established causal association between active smoking and respiratory symptoms in adults. Among adults, all respiratory symptoms are strongly and consistently associated with cigarette smoking (Freund et al. 1993; David et al. 1996; Bodner et al. 1998; Forastiere et al. 1998; Butland et al. 1999), and smoking cessation reduces their frequency (Kanner et al. 1999). In the Framingham Study, Freund and colleagues (1993) found that among persons aged 45 years and older, the prevalence of a cough was higher among cigarette smokers than among nonsmokers, and the prevalence increased as the amount smoked increased. Persons who smoked more than 30 cigarettes per day were seven times more likely than nonsmokers to report a chronic cough.

Among 677 women 18 to 43 years of age who were seen for prenatal care at an East Boston clinic, David and colleagues (1996) examined the relationship between cigarette smoking and a persistent wheeze without asthma. In a multiple logistic regression model adjusting for ethnicity, parental history of asthma, educational level, and the presence of a cat or dog at home, current smokers had a fivefold increased risk (OR = 4.97 [95 percent CI, 2.46–10.1]) of a persistent wheeze

compared with lifetime nonsmokers. There was no increase in this risk among former smokers (OR = 1.13 [95 percent CI, 0.50–2.55]).

Bodner and colleagues (1998) conducted a nested case-control study of 117 adults aged 39 through 45 years with adult onset of wheezing and 277 randomly selected persons without wheezing who were participants in a population-based cohort study in Scotland. After adjusting for family history, atopy, and social class, the investigators found that current smoking was associated with adult onset of wheezing (OR = 2.01 [95 percent CI, 1.08–3.74]) and with chronic cough and phlegm (OR = 11.48 [95 percent CI, 2.49–52.89]). Former smokers were at a lower risk for adult onset of wheezing (OR = 1.48 [95 percent CI, 0.74–2.95]), but the risk remained significant for chronic cough and phlegm (OR = 5.24 [95 percent CI, 1.00–27.53]).

In a population-based study of 1,226 women aged 55 years and older living in Sonoma, California, Forastiere and colleagues (1998) examined relationships of chronic respiratory symptoms with a number of risk factors. Among women who reported shortness of breath with a wheeze or chronic wheeze during the past 12 months without a physician's diagnosis of asthma or chronic bronchitis/emphysema, the investigators found that the risk for these symptoms was highest in current smokers (OR = 3.8 [95 percent CI, 2.2–6.5]) and that the risk declined but remained statistically significant for former smokers who had quit for 10 or fewer years (OR = 1.8 [95 percent CI, 1.1–3.2]) or for more than 10 years (OR = 1.8 [95 percent CI, 1.2–2.5]). Overall, the population attributable risk for these symptoms in this population of women who had ever smoked was 35 percent.

In a longitudinal study in the Netherlands that included 792 women and 995 men, Jansen and colleagues (1999) found a dose-response relationship between the number of cigarettes smoked and any occurrence of chronic respiratory symptoms. When smokers were compared with nonsmokers, the risk (OR) of any chronic respiratory symptom was 1.89 (95 percent CI, 1.37–2.60) for those who smoked 1 to 14 cigarettes per day, 2.98 (95 percent CI, 2.14–4.29) for those who smoked 15 to 24 cigarettes per day, and 3.57 (95 percent CI, 2.32–5.48) for those who smoked 25 or more cigarettes per day. Among former smokers, the risk was lower but not statistically significant (OR = 1.21 [95 percent CI, 0.85–1.74]).

Butland and colleagues (1999) conducted a cross-sectional survey of 5,770 women and 5,582 men aged 33 years living in the United Kingdom. The prevalence of any wheezing or wheezing five or more times in the past 12 months increased with the amount smoked

Figure 4.6 Proportion (95 percent confidence interval) of participants reporting chronic cough at each annual follow-up visit, stratified by final smoking status
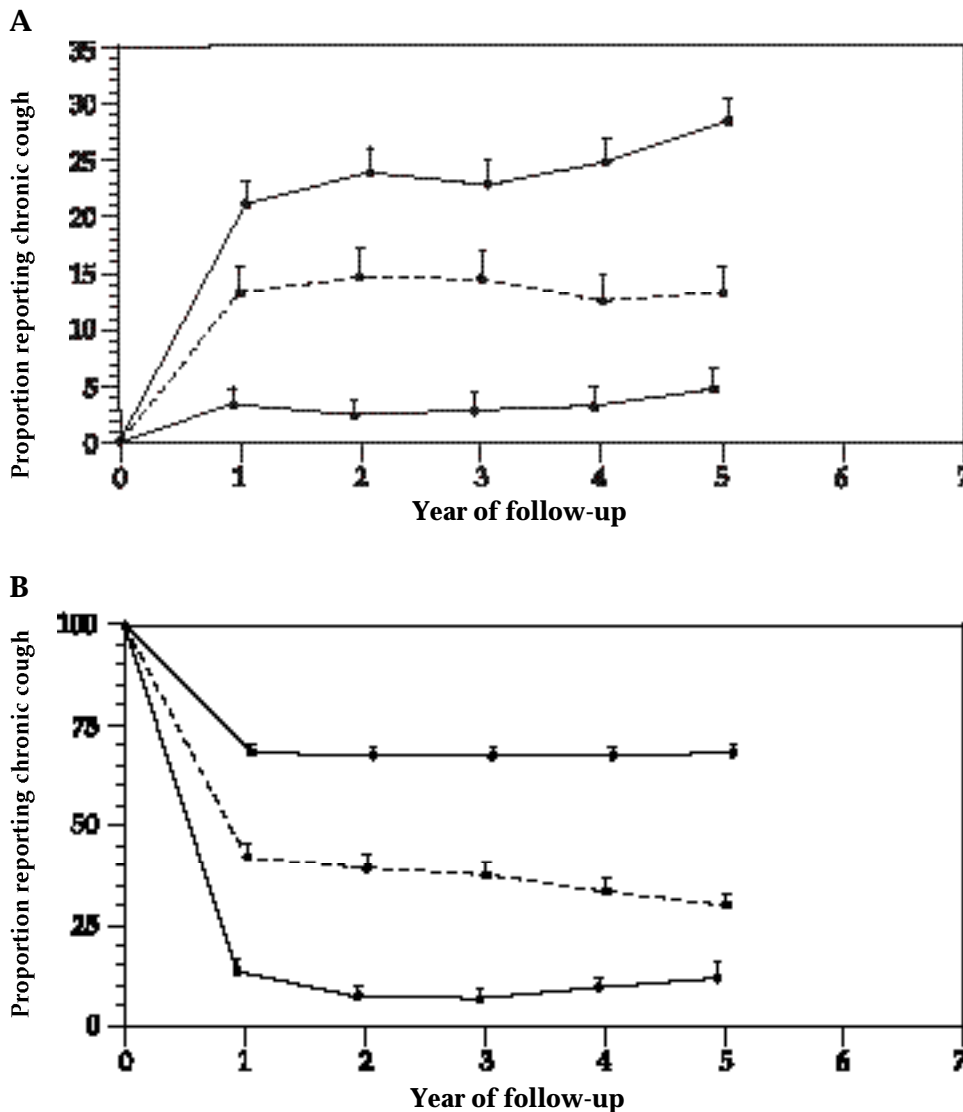
Note: (A) Restricted to participants who did not report the symptom of cough at entry into the study. (B) Restricted to participants who reported the symptom of cough at entry into the study.
Source: Kanner et al. 1999, p. 414. Reprinted with permission.

and was lower for former smokers. The prevalence of these symptoms was similar when comparing non-smokers with former smokers who had quit for more than five years.

In the Lung Health Study (Kanner et al. 1999), the prevalence of all respiratory symptoms significantly decreased during the five-year sustained cessation follow-up period. Compared with current smokers, intermittent quitters had a lower prevalence of respiratory symptoms. When compared with those in the sustained cessation category, intermittent quitters had a greater prevalence of respiratory symptoms (Figure 4.6) (Kanner et al. 1999).

Evidence Synthesis

Active cigarette smoking is consistently associated with an increased risk for respiratory symptoms, including coughing, phlegm, wheezing, and dyspnea.

Moreover, the occurrence of respiratory symptoms increases with the number of cigarettes smoked and decreases with smoking cessation. These symptoms reflect the consequences of the smoking-caused changes throughout the respiratory tract.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.

Implications

Respiratory symptoms are common among cigarette smokers and probably contribute substantially to an impaired quality of life and a higher utilization of health care resources. Thus, a decrease in the occurrence of these symptoms with smoking cessation will provide important benefits to public health and to the well-being of successful quitters.

Asthma. *Epidemiologic Evidence.* Asthma in adults is a complex and heterogeneous disorder, likely caused by a number of occupational and environmental exposures as well as by genetic or other intrinsic predispositions. The majority of asthma begins in childhood and may remit for a number of years before manifesting again in adulthood. This phenomenon may complicate the interpretation of epidemiologic investigations of risk factors for adult-onset asthma, because this condition most likely comprises both childhood asthma and true adult-onset asthma. The role of smoking as an etiologic agent in adults with asthma has been investigated in a number of studies using both longitudinal and cross-sectional designs (Tables 4.16 and 4.17). The results indicate a complicated relationship between cigarette smoking and asthma that may be modified by smoking status (i.e., current, former, or never smoker), gender, age, other established risk factors for asthma (e.g., family history of asthma or personal atopy), and the bias arising from the "healthy smoker effect" (Weiss et al. 1989).

The interpretation of the evidence for cigarette smoking and asthma is constrained by a number of methodologic considerations including varying study designs, different definitions of asthma, and different indexes for defining smoking status. Although the longitudinal design is the strongest for investigating the relationship between smoking and adult-onset asthma, the studies that have been conducted arrived at conflicting results (Table 4.16). In those studies, current smoking was associated with an increased risk of asthma among men (Vesterinen et al. 1988) and among men and women aged 40 years or older (Krzyzanowski and Lebowitz 1992). However, neither Vesterinen and colleagues (1988) nor Troisi and colleagues (1995) found an association between current smoking and asthma in women. Furthermore, Troisi and colleagues (1995) did not find a dose-response relationship between the amount smoked and asthma. The strongest associations between smoking and asthma were reported by Strachan and colleagues (1996) and Plaschke and colleagues (2000). However, their results are difficult to interpret. For example, Strachan and colleagues (1996) combined asthma with wheezy bronchitis, and Plaschke and colleagues (2000) did not define "smokers," which may have included former smokers. Finally, McWhorter and colleagues (1989) only examined ever smoking in their longitudinal investigation and did not find an association with asthma.

A number of cross-sectional studies have examined the association between asthma and smoking, with inconsistent results for both current and former smokers (Table 4.17). Of the 10 publications that provided quantitative results, 3 found an association between current smoking and asthma in men and women (Ben-Noun 1999; Chen et al. 1999; Torén and Hermansson 1999), and 1 found an association only in women (Chen et al. 1999). No association was reported in seven cross-sectional studies (Flodin et al. 1995; David et al. 1996; Bodner et al. 1998; Forastiere et al. 1998; Zhang et al. 1999; de Marco et al. 2000; Kotaniemi et al. 2001). Moreover, two investigations provided indirect evidence that current smoking was not associated with asthma (Hansen et al. 2000; Kilpelainen et al. 2001), and limited data suggest that the risk of asthma may be greater because of a family history of asthma or the presence of other atopic conditions (i.e., hay fever, atopic dermatitis) (Melbostad et al. 1998; Torén and Hermansson 1999). However, this finding was contradicted by the results reported by Plaschke and colleagues (2000).

Among former smokers, an association with asthma has been inconsistent (Table 4.17). Out of nine studies, five found an increased risk for asthma among former smokers compared with current smokers (Flodin et al. 1995; Troisi et al. 1995; Bodner et al. 1998; Forastiere et al. 1998; Siroux et al. 2000), with ORs ranging from 1.4 to 5.24. In contrast, four studies found no association (David et al. 1996; Chen et al. 1999; de Marco et al. 2000; Kotaniemi et al. 2001).

In four cross-sectional studies that examined ever smokers defined as current and former smokers (Table 4.17) (Flodin et al. 1995; Melbostad et al. 1998; Ben-Noun 1999; Siroux et al. 2000), three of the studies

associated asthma with ever smoking (Flodin et al. 1995; Melbostad et al. 1998; Ben-Noun 1999) with ORs ranging from 1.3 to 1.9.

Investigating the relationship between smoking and asthma offers a number of challenges, including diagnostic misclassifications and changes in smoking behaviors because of asthma. Dodge and colleagues (1986) found that among persons aged 40 years or older with newly diagnosed asthma, emphysema, or chronic bronchitis based on self-reports, women were more likely than men to receive a physician's diagnosis of asthma or chronic bronchitis, and men were more likely to receive a diagnosis of emphysema. In the Nurses Health Study, Troisi and colleagues (1995) found that among women diagnosed with chronic bronchitis, smokers were more likely to receive a subsequent diagnosis of asthma than were nonsmokers (RR = 2.02 [95 percent CI, 1.01–4.02]). This labeling pattern in women may tend to bias toward an association of asthma with smoking.

Because the bronchial hyperresponsiveness of asthma may cause an intolerance to tobacco smoke, and because smoking worsens respiratory symptoms in persons with asthma (Althuis et al. 1999; Sippel et al. 1999), some persons alter their smoking habits and thereby obscure a possible causal association (Weiss et al. 1989). The result is that persons with asthma may not start smoking or may be more likely to quit, a phenomenon referred to as the "healthy smoker effect" (Weiss et al. 1989); however, few data support these suggested biases. In a population-based survey of 3,019 persons from Australia, Wakefield and colleagues (1995) found no differences in the prevalence of smoking between persons with asthma (28.5 percent) and persons without asthma (26.9 percent), or in the amount smoked. Moreover, there were no differences between those two groups in reports of ever trying to quit or trying to quit in the past year.

Siroux and colleagues (2000) examined smoking behaviors among 200 adult patients with asthma and 265 controls without asthma, and found that childhood asthma was not associated with a reduced initiation of smoking. However, patients with asthma were more likely than those without asthma to quit smoking (OR = 2.76 [95 percent CI, 1.19–6.42] for men; OR = 2.20 [95 percent CI, 1.11–4.34] for women).

Surrogate evidence for a link between cigarette smoking and asthma may be obtained from investigations of the relationship between smoking and non-specific bronchial hyperresponsiveness (Weiss et al. 1989). Although the results are not entirely consistent, available evidence suggests that current smokers have greater bronchial hyperresponsiveness compared with nonsmokers, thus establishing a biologically plausible link for a causal role for smoking in the development of asthma (Weiss et al. 1989; Kennedy et al. 1990; Rijcken et al. 1993; Sunyer et al. 1997).

A possible biologic link between smoking and asthma was also described by Wang and colleagues (2001) in their case-control study of 128 patients with asthma and 136 controls, identified through a community-based survey of 10,014 patients in China. Patients and controls were all examined for the prevalence of two genetic variations of the β_2-adrenergic receptor gene, which controls airway dilatation. Compared with lifetime nonsmokers, ever smokers who were homozygotes for a specific genetic variation of the β_2-adrenergic receptor gene on chromosome 16 (arginine/arginine-16) had a markedly increased risk for asthma (OR = 7.81 [95 percent CI, 2.07–29.5]). In addition, there was a strong dose-response relationship with the amount smoked.

Although the relationship between active smoking and adult-onset asthma is inconsistent, there is consistent evidence that smoking adversely affects the control and severity of asthma (Prescott et al. 1997; Cassino et al. 1999; Siroux et al. 2000; Beeh et al. 2001). As part of the Copenhagen City Heart Study, Prescott and colleagues (1997) examined 13,540 patients for factors associated with hospital admissions for asthma between 1977 and 1993. Overall, the risk of hospitalization for asthma was 20 percent greater in current and former smokers compared with lifetime nonsmokers (95 percent CI, 1.1–1.4) for each 10-year period of smoking. Cassino and colleagues (1999) examined determinants of emergency department visits for asthma among 1,216 adults with asthma living in New York City. Compared with nonsmokers, the RRs for emergency department visits were 1.07 (95 percent CI, 0.97–1.18) for 1 to 5 pack-years of smoking, 1.69 (95 percent CI, 1.56–1.84) for 6 to 13 pack-years, 0.93 (95 percent CI, 0.84–1.04) for 14 to 30 pack-years, and 1.11 (95 percent CI, 1.00–1.22) for 31 or more pack-years. They also identified heavy cigarette use (13 or more pack-years) as a predictor of emergency department visits following days that had high outdoor ozone levels. In a case-control study of 200 adults with asthma from six specialty clinics in France and 265 controls without asthma, Siroux and colleagues (2000) found that active smoking was associated with an increase in asthma severity. For example, compared with nonsmokers, current smokers more often reported one or more asthma attacks per day (OR = 2.39 [95 percent CI, 1.06–5.36]) and abnormal breathing between attacks (OR = 2.06 [95 percent CI, 0.97–4.36]) than nonsmokers. Among 112 persons with asthma seen at a pulmonary

Table 4.16   Longitudinal studies on the association between smoking and adult asthma

Study	Population	Period of study/follow-up
Vesterinen et al. 1988	7,274 women, 6,971 men Aged 18–64 years Finland	Baseline: 1975 Follow-up: 1981
McWhorter et al. 1989	8,236 women, 5,637 men Aged 25–74 years United States	Baseline: 1971–1975 Follow-up: 1982–1984

Krzyzanowski and Lebowitz 1992	1,818 women, 1,264 men
	Aged 19–70 years
	Cracow, Poland
	
	839 women, 613 men
	Aged 19–70 years
	Tucson, Arizona
		Baseline:
		  Cracow, 1968
		  Tucson, 1972
		Follow-up: 13 years

Troisi et al. 1995	74,072 women Aged 34–68 years United States	Baseline: 1976 Follow-up: 10 years
Strachan et al. 1996	18,559 persons born in 1958 in England, Scotland, and Wales	Baseline: 1958 Follow-up: 1991
Plaschke et al. 2000	699 women, 659 men Aged 20–40 years Sweden	Baseline: 1990 Follow-up: 1993

*OR = Odds ratio.
†CI = Confidence interval.
‡Ages at which persons were asked if they currently smoked.

Findings (OR*)			Asthma definition/comments
	OR (95% CI[†]) compared with never smokers		Self-reported physician-diagnosed asthma
Smoking status	Men	Women	
Former smokers	1.69 (0.88–3.23)	1.05 (0.52–2.14)	
Current smokers	1.73 (1.01–2.96)	1.33 (0.78–2.26)	
	OR (95% CI) compared with never smokers		Self-reported physician-diagnosed asthma
Smoking status	New onset of asthma		
Ever smoked	1.1 (0.9–1.5)		
	Asthma incidence per 1,000 (continuous smokers vs. nonsmokers)		Physician-diagnosed bronchial asthma
Age (years)	Women	Men	
19–40	0.6	0.8	
41–55	1.9	2.2	
56–70	2.1	5.4	
Amount smoked	Age-adjusted relative risk of asthma (95% CI) compared with nonsmokers		Physician-diagnosed asthma; increase in risk among former smokers was only during the first 2 years of cessation
1–14 cigarettes/day	0.80 (0.59–1.09)		
15–24 cigarettes/day	0.69 (0.52–0.90)		
25 cigarettes/day	0.78 (0.57–1.06)		
Smoking ages[‡]	OR (95% CI) compared with nonsmokers		Told they have asthma by a physician; attacks of asthma and wheezy bronchitis
16, 23, and 33 years	2.25 (1.75–2.89)		
16, 23, and 33 years	4.42 (3.31–5.92)		
Smoking status	Asthma onset OR (95% CI) compared with nonsmokers		Self-reported asthma attack in the past 12 months and currently using asthma medication; adjusted for age, gender, area of residence, pets at home, sensitization to allergens, and allergic rhinitis; smokers were not defined
All smokers	3.0 (1.5–5.8)		
Atopic smokers	1.8 (0.8–4.2)		
Nonatopic smokers	5.7 (1.7–19.2)		

Table 4.17   Cross-sectional studies on the association between smoking and adult asthma

Study	Population	Period of study
Flodin et al. 1995	79 persons with asthma Aged 20–65 years 304 population controls Sweden	1990
Troisi et al. 1995	74,072 women Aged 34–68 years United States	1980–1990
David et al. 1996	475 non-Hispanic whites, 371 Hispanic pregnant women Aged 18–43 years Boston, Massachusetts	1986–1992
Bodner et al. 1998	102 patients with adult-onset wheeze, 271 controls from a community cohort Scotland	1995
Forastiere et al. 1998	1,226 women Aged 55 years Sonoma, California	1993–1994
Melbostad et al. 1998	2,914 women, 5,568 men Aged 20–69 years Norway	1991
Ben-Noun 1999	141 persons with asthma, 423 nonasthmatic controls matched for age and gender Aged 18 years Israel	1996
Chen et al. 1999	9,557 females, 8,048 males Aged 12 years Canada	1994–1995

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.

Findings			Asthma definition/comments
Smoking status	Adjusted OR* (95% CI[†]) compared with nonsmokers		Lung specialist determination based on clinical history and bronchial hyperresponsiveness; adjusted for age, gender, atopy, passive smoking, and occupational exposures
Ever smoked	1.9 (1.1–3.4)		
Current smokers	0.7 (0.4–1.3)		
Former smokers	3.3 (1.8–6.0)		
Smoking status	RR[‡] (95% CI)		Physician-diagnosed asthma
Current smokers	0.57 (0.46–0.71)		
Former smokers	0.50 (0.40–0.62)		
Smoking status	OR (95% CI) compared with nonsmokers		Self-reported physician-diagnosed asthma; adjusted for ethnicity, family history of asthma, education, and cat/dog in the home
Former smokers	1.18 (0.58–2.39)		
Current smokers	1.77 (0.85–3.70)		
Smoking status	OR (95% CI) compared with nonsmokers		Physician-diagnosed asthma; adjusted for gender, atopy, family history, and social class
Current smokers	0.65 (0.19–2.20)		
Former smokers	5.24 (1.00–27.53)		
Smoking status	OR (95% CI) compared with nonsmokers		Physician-diagnosed asthma and wheezing in the past 12 months; age adjusted
Nonsmokers	1.0		
Current smokers	1.6 (0.5–4.8)		
Former 10 years	2.9 (1.4–6.2)		
Former >10 years	2.2 (1.2–3.9)		
Smoking status	OR (95% CI) compared with nonsmokers		Physician-diagnosed asthma; adjusted for gender, age, family history of asthma, childhood asthma, and family exposures
Nonsmokers	1.0		
Ever smoked	1.3 (1.0–1.7)		
Ever smoked and asthma in parents or siblings	8.54 (3.67–20.2)		
Smoking status	OR		Asthma in family practice; CIs were not provided
Current smokers	1.7		
Ever smoked	1.9		
Age/smoking status	OR (95% CI) compared with nonsmokers		Asthma was diagnosed by a health professional; adjusted for age
12–24 years	Females	Males	
Nonsmokers	1.0	1.0	
Current smokers	2.18 (1.41–3.44)	0.98 (0.56–1.70)	
Former smokers	1.14 (0.56–2.32)	0.91 (0.37–2.21)	
25 years			
Nonsmokers	1.0	1.0	
Current smokers	1.61 (1.17–2.21)	0.96 (0.66–1.39)	
Former smokers	1.16 (0.83–1.60)	1.40 (1.00–1.96)	

Table 4.17   Continued

Study	Population	Period of study
Torén and Hermansson 1999	8,044 women, 7,769 men Aged 20–50 years Sweden	1993
Zhang et al. 1999	2,051 adult men China	1988
de Marco et al. 2000	105 persons with asthma, 840 controls who did not report asthma in their lifetime Aged 20–44 years from 16 countries	1991–1993
Hansen et al. 2000	First survey: 533 women, 501 men Second survey: 581 women, 523 men Aged 20–35 years Denmark	1976–1978 1991–1994
Siroux et al. 2000	200 persons with asthma, 265 nonasthmatic controls Mean ages 40.1 and 42 years France	Data were not reported
Kilpelainen et al. 2001	6,503 women, 4,164 men Aged 18–25 years Finland	1995–1996
Kotaniemi et al. 2001	3,938 women, 4,067 men Aged 20–69 years Finland	1995

[§]FEV_1 = Forced expiratory volume in 1 second.

Findings			Asthma definition/comments
<u>Smoking status</u> Nonsmokers Current smokers Current with hay fever Current with atopic dermatitis	<u>OR (95% CI) compared with nonsmokers</u> 1.0 1.3 (1.05–1.6) 4.0 (2.9–5.7) 2.7 (1.6–4.4)		Physician-diagnosed asthma; adjusted for gender and age
<u>Amount smoked</u> Nonsmokers <10 cigarettes/day 10–20 cigarettes/day >20 cigarettes/day	<u>OR (95% CI) compared with nonsmokers</u> 1.0 0.81 (0.30–2.20) 1.05 (0.39–2.80) 1.7 (0.73–3.76)		Physician-diagnosed asthma; adjusted for age, area of residence, duration of residence in that area, occupation, education, indoor ventilation device use, and home coal use
<u>Smoking status</u> Nonsmokers Current smokers Former smokers	<u>Adjusted OR (95% CI) compared with nonsmokers</u> 1.0 0.58 (0.36–0.93) 0.87 (0.46–1.64)		Questions asked were: ever had asthma, age at first attack; adjusted for gender and FEV_1[§] levels
<u>Survey years</u> 1976–1978 1991–1994	<u>Asthma prevalence</u> 1.5% 4.8%	<u>Smoking prevalence</u> 62% 45%	Self-reported asthma; former smokers and never smokers were classified as nonsmokers
<u>Smoking status</u> Ever smoked Former smokers	<u>Adjusted OR (95% CI)</u> Men 1.21 (0.55–2.67) 2.20 (1.11–4.34)	Women 1.19 (0.60–2.36) 2.76 (1.19–6.42)	A positive response to having had attacks of breathlessness with a wheeze, at least 1 asthma attack, an asthma attack in the past 12 months, and a physician diagnosis or a consensus decision from a clinical review; adjusted for age, atopy, and city
Current smoking was not related to asthma			Physician-diagnosed asthma; no quantitative data were provided
<u>Smoking status</u> Nonsmokers Current smokers Former smokers	<u>OR (95% CI) compared with nonsmokers</u> 1.0 0.77 (0.59–1.01) 1.24 (0.95–1.61)		Physician-diagnosed asthma

specialist practice in Germany, Beeh and colleagues (2001) found that severe asthma, defined as a FEV_1 less than 60 percent predicted, was strongly associated with current smoking (OR = 4.8 [95 percent CI, 1.3–18.3]).

Evidence Synthesis. Although limited evidence suggests that smoking is a biologically plausible cause of asthma, the available epidemiologic evidence of an association between smoking and adult-onset asthma is inconsistent (Tables 4.16 and 4.17). A number of methodologic limitations, including different definitions of asthma, different study designs, and biases such as recall bias and healthy smoker bias, probably contribute to the inconsistent results. In contrast to studies on the causation of asthma, smoking is consistently associated with a greater severity of asthma and increased uses of emergency and hospital services. By increasing the degree of airways inflammation, smoking may worsen the inflammatory process that is considered central in the pathogenesis of asthma. The impairment of airways function caused by smoking may also increase the likelihood of more severe asthma on a clinical basis.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.

2. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyperresponsiveness.

3. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control.

Implications. Because of the large numbers of persons with asthma and an increasing prevalence of asthma worldwide, the potential role of active smoking in the causation of asthma has major public health implications. Therefore, this problem is highly relevant for further research despite methodologic challenges. Patients with asthma need to be strongly encouraged to quit smoking.

COPD. COPD is defined differently by clinicians, pathologists, and epidemiologists; each discipline uses different criteria based on physiologic impairments, pathologic abnormalities, and symptoms (Samet 1989). The hallmark of COPD is airflow obstruction based on spirometric testing, with a persistently low FEV_1 and a low ratio of FEV_1/FVC despite treatment. Clinicians often diagnose COPD when an adult cigarette smoker presents with chronic dyspnea, coughing, and consistent spirometric abnormalities.

Chronic bronchitis and emphysema with airflow obstruction are both included in the clinical syndrome of COPD. Other specific diseases associated with airflow obstruction, such as asthma, bronchiectasis, and cystic fibrosis, are specifically excluded from the clinical definition of COPD, although there may be overlapping clinical features. Chronic bronchitis and emphysema have specific definitions, although the terms are used more loosely in clinical practice. Chronic bronchitis is characterized by a chronic cough productive of sputum with airflow obstruction. Emphysema is defined as "a condition of the lung characterized by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis" (American Thoracic Society 1987, p. 225). On the basis of this definition, the diagnosis of emphysema requires an examination of gross or microscopic lung specimens or an assessment of the lungs based on computed tomography, a recently developed tool (Thurlbeck 1994).

Epidemiologic Evidence. In epidemiologic studies, the diagnosis of COPD may be derived from surveys or clinical databases. Questionnaire responses that may be used to diagnose COPD include reports of symptoms (e.g., dyspnea, coughing, or phlegm), reports of physician diagnoses (e.g., emphysema, chronic bronchitis, or COPD), or both. Spirometry is often performed in epidemiologic studies to provide objective evidence of airflow obstruction in persons with or without symptoms. Sources of data for descriptive or analytic studies of COPD include databases containing hospital discharge information or vital statistics (e.g., from death certificates). However, the quality of these data sources may vary greatly. The standard terms used for COPD in the databases include terms from the *International Classification of Diseases, 9th Revision,* such as "chronic bronchitis" (code 491), "emphysema" (code 492), and "chronic airway obstruction not elsewhere classified" (code 496) (USDHHS 1989b).

Cigarette smoking as a cause of COPD has been reviewed extensively in earlier reports of the Surgeon General (Table 4.13) (USDHHS 1984, 1989a, 1990). A considerable amount of more recent research on the relationship between COPD and cigarette smoking has focused on determining predictors of susceptibility, as

discussed previously, and on early detection. The following discussion summarizes more current key research on the epidemiology of COPD.

COPD Morbidity. COPD is a common chronic disease in the United States and a major cause of morbidity associated with limitations on physical functioning and a high utilization of medical care services (Verbrugge and Patrick 1995; Mapel et al. 2000). Approximately 10 million people in the United States have been diagnosed with COPD (Wise 1997). Verbrugge and Patrick (1995) used data collected from the National Health Interview Survey conducted from 1983–1985 to calculate the prevalence of chronic conditions in the United States and to determine their relative impact on functioning. Among adults aged 18 years and older the prevalence of COPD, which included chronic bronchitis, emphysema, and asthma, was consistently among the top 10 chronic conditions. The prevalence was highest in men and women aged 65 years and older (16.7 percent among men and 12.6 percent among women), intermediate for men and women aged 45 through 64 years (8.8 percent and 11.4 percent, respectively), and lowest for men and women aged 18 through 44 years (5.5 percent and 9.3 percent, respectively). In addition, COPD consistently ranked among the top 10 conditions in all age groups that resulted in limitations on job-related responsibilities and other activities of daily living.

More recent national data are available from the Third National Health and Nutrition Examination Survey (Mannino et al. 2000). This survey included 20,050 U.S. adults who participated from 1988–1994 and who completed an examination that included spirometry and respiratory health questions. The findings suggest that COPD occurs frequently in the United States. The authors categorized current obstructive lung disease as a report of current asthma, bronchitis, or ever having a diagnosis of emphysema. A prior but not current diagnosis of either chronic bronchitis or asthma was categorized as past obstructive lung disease. With these definitions, obstructive lung disease was found to affect 12.5 percent of current smokers, 9.4 percent of former smokers, and 5.8 percent of lifetime nonsmokers.

COPD is associated with high medical care utilization rates, including office-based physician visits and hospitalizations (Verbrugge and Patrick 1995; Sullivan et al. 2000). In the 1985 National Ambulatory Medical Care Survey, COPD was consistently among the top 10 conditions leading to a physician visit. Verbrugge and Patrick (1995) found that the largest percentage of

physician visits for COPD were among men and women aged 65 years and older (10.8 percent among men and 9.4 percent among women), intermediate for men and women aged 45 through 64 years (6.1 percent and 8.2 percent, respectively), and lowest for men and women aged 18 through 44 years (3.4 percent and 4.8 percent, respectively). In 1995, more than 16 million visits were made to physicians' offices for COPD, a 72 percent increase from 1985 (Sullivan et al. 2000). In contrast to other chronic conditions (e.g., cancer or cardiovascular disease), COPD was a less common primary cause of hospitalization in the 1984 National Hospital Discharge Survey (Verbrugge and Patrick 1995), but in 1995 it accounted for more than 500,000 hospitalizations in the United States (Sullivan et al. 2000). However, COPD often is a comorbid condition associated with other chronic conditions, including cancer and cardiovascular diseases (Ferrer et al. 1997; Mapel et al. 2000). Total estimated costs associated with COPD in 1993 were $23.9 billion, or about $1,522 per person per year, three times the per capita cost of asthma (Sullivan et al. 2000).

More recent epidemiologic investigations continue to provide strong evidence for the causal link between active smoking and COPD (Troisi et al. 1995; Forastiere et al. 1998). In the Nurses Health Study, a prospective cohort study of 74,072 women aged 34 through 68 years, the RR for self-reported, physician-diagnosed chronic bronchitis among current smokers compared with women who had never smoked was 2.85 (95 percent CI, 2.45–3.32) (Troisi et al. 1995). Forastiere and colleagues (1998), in a population-based cross-sectional survey of 1,226 women aged 55 years and older, found a marked increase in risk for self-reported, physician-diagnosed chronic bronchitis/emphysema among current smokers compared with former and lifetime nonsmokers (OR = 6.4 [95 percent CI, 3.2–12.6]).

Smoking Cessation and COPD Morbidity. Although smoking cessation slows the rate of FEV_1 decline, thus decreasing the risk for developing chronic airflow obstruction (Figure 4.1), the risk may not return to that for nonsmokers. In a population-based study of 1,391 Seventh-Day Adventists from California, which included nonsmokers and former smokers (aged 16 years or older), Berglund and colleagues (1999) found that, compared with never smoking, past smoking for 10 years was associated with a small but significant risk (OR = 1.29 [95 percent CI, 1.00–1.66]) of airflow obstruction (FEV_1/FVC less than 65 percent or FEV_1 percent predicted less than 75 percent).

The risk of self-reported physician-diagnosed chronic bronchitis returns close to that of nonsmokers, but only after 5 to 10 years of cessation (Troisi et al. 1995; Forastiere et al. 1998). In the Nurses Health Study, Troisi and colleagues (1995) found that among former smokers the incidence of chronic bronchitis among women was equal to the incidence in those who had completely abstained from smoking for five or more years. Among women aged 55 years and older from Sonoma, California, Forastiere and colleagues (1998) found that the occurrence of physician-diagnosed chronic bronchitis/emphysema was higher in former smokers who had stopped smoking for 10 years or less (OR = 4.7 [95 percent CI, 2.5–8.7]) compared with nonsmokers, but the risk returned close to that of nonsmokers after more than 10 years of cessation (OR = 1.6 [95 percent CI, 0.9–2.8]).

COPD Mortality. In 2001, COPD (excluding asthma) was the fourth leading cause of death in the United States with more than 118,000 deaths (4.9 percent of all deaths) and an overall mortality rate of 41.7 per 100,000 (Arias et al. 2003). Over the past 30 years, the age-adjusted mortality rate from COPD has been increasing. Of the 10 leading causes of death in the United States, only COPD has increased during this period (Wise 1997). Factors that contribute to the rising COPD mortality rates include decreasing mortality from other causes of death (e.g., cardiovascular diseases) and increasing mortality among women and nonwhite males (Mannino et al. 1997).

Although COPD prevalence and mortality rates since the late 1970s have been substantially higher in men than in women, the estimated percentage increases have been higher for women (Thun et al. 1995, 1997a; Mannino et al. 1997). In fact, from 1979–1988 mortality rates for men worldwide either remained stable or decreased (Brown et al. 1994). These patterns may be partially explained by differences between the prevalence of smoking and smoking behaviors in women and men that have occurred over time. During the past 20 to 30 years, the prevalence and amount of smoking among women have become increasingly similar to those of men (USDHHS 2001).

The prospective studies of the American Cancer Society (Cancer Prevention Study I [CPS-I] and Cancer Prevention Study II [CPS-II]), which were conducted in the early- to mid-1960s and in the 1980s, provide evidence for a marked increase in the risk of mortality from COPD among women (Thun et al. 1995, 1997a). In CPS-II the death rate for female current smokers (61.6 per 100,000 person-years) was three times higher than in CPS-I. The mortality RR was 12.8 for female current smokers compared with women who had never smoked. For male current smokers in CPS-II, the death rate (103.9 per 100,000 person-years) was 41 percent higher than for male current smokers in CPS-I. The mortality RR was 11.7 for male current smokers compared with men who had never smoked.

Thun and colleagues (1997b) examined mortality rates for COPD in CPS-II in relation to the number of cigarettes currently smoked at baseline. The RR for death from COPD increased with the number of cigarettes smoked per day. For female current smokers compared with women who had never smoked, the RR was 5.6 for 1 to 9 cigarettes per day, 7.9 for 10 to 19 cigarettes per day, 23.3 for 20 cigarettes per day, 22.9 for 21 to 39 cigarettes per day, and 25.2 for 40 or more cigarettes per day. The corresponding RRs for current male smokers compared with men who had never smoked were 8.8 for 1 to 9 cigarettes per day, 8.9 for 10 to 19 cigarettes per day, 10.4 for 20 cigarettes per day, 16.5 for 21 to 39 cigarettes per day, and 9.3 for 40 or more cigarettes per day.

Using CPS-I and CPS-II data on the RR of COPD mortality, Thun and colleagues (1997a,b) calculated the percentage of COPD deaths attributable to cigarette smoking. Among women in CPS-I, 85 percent of COPD deaths were attributable to smoking; this percentage increased to 92.2 percent in CPS-II. The corresponding values among men were 89.2 percent and 91.4 percent, respectively.

Mannino and colleagues (1997) analyzed mortality trends for obstructive lung disease (including asthma) among people who died in the United States from 1979–1993. Of all the deaths during this time period, 8.2 percent had obstructive lung disease listed on the death certificate, but in only 43.3 percent was the death attributed to obstructive lung disease. Over the time of the study, the age-adjusted mortality rates for obstructive lung disease were highest in white men (ranging from 98.8 to 115.5 per 100,000 per year), followed by black men (77.5 to 100.2 per 100,000), men of other races (38.1 to 58.6 per 100,000), white women (25.5 to 57.7 per 100,000), black women (14.9 to 38.5 per 100,000), and women of other races (10.9 to 20.9 per 100,000). The percentage increases in mortality rates were highest for black women (158.3 percent), followed by white women (126.3 percent), other women (91.7 percent), other men (57.8 percent), black men (29.3 percent), and lowest among white men (16.9 percent).

Smoking Cessation and COPD Mortality. The literature on the effects of smoking cessation on mortality from COPD was extensively reviewed in the 1990 Surgeon General's report, and the major conclusion relevant to mortality from that report was "With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers" (Table 4.13) (USDHHS 1990, p. 11). However, the risk of COPD mortality among former smokers, even after 20 years or more of abstinence, remains elevated compared with the risk among people who have never smoked. Moreover, within approximately the first five years of cessation, mortality rates from COPD initially increase above the rates for continuing smokers and then gradually decline with an increase in the duration of abstinence.

Evidence Synthesis. The recent literature on smoking and COPD provides further support for the conclusion of the 1984 Surgeon General's report that "cigarette smoking is the major cause of COLD in the United States for both men and women. The contribution of cigarette smoking to COLD morbidity and mortality far outweighs all other factors" (USDHHS 1984, p. 8). Whereas the risks for COPD morbidity and mortality decline with smoking cessation, they may not return to the levels of nonsmokers, probably because smoking has resulted in irreversible injury to the airways and parenchyma. A growing body of literature in recent years is providing evidence for major socioeconomic consequences of COPD associated with a marked increase in the utilization of medical care resources.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.

Implication. COPD represents a major public health problem that is increasing but could be almost completely prevented with the elimination of smoking.

Cigarette Type and Risk for Chronic Respiratory Diseases. The effect of cigarette type on respiratory symptoms and COLD was reviewed in the 1984 Surgeon General's report, by Samet (1996), and by the National Cancer Institute (NCI) Tobacco Control Monograph 13 (NCI 2001). A conclusion from the 1984 report was as follows:

Although a reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion, the risk of shortness of breath and airflow obstruction may not be reduced. Evidence is unavailable on the relative risks of developing COLD consequent to smoking cigarettes with the very low tar and nicotine yields of current and recently marketed brands (USDHHS 1984, p. 12).

Since the publication of that report, few new data are available on the relationship between cigarette type and chronic respiratory diseases (Lange et al. 1990, 1992).

Epidemiologic Evidence. Using longitudinal spirometric data obtained during five years (1976–1978 and 1981–1983) from 4,372 smokers and 3,753 nonsmokers who participated in the Copenhagen City Heart Study, Lange and colleagues (1990) examined the relationship between cigarette type (filter-tipped versus unfiltered) and lung function deterioration. Overall, there was no significant difference in FEV_1 reductions among filter-tipped cigarette smokers compared with unfiltered cigarette smokers. On average, during the time of the study the tar content of Danish unfiltered cigarettes was 35 mg per cigarette compared with 23 mg per cigarette for filter-tipped cigarettes.

Lange and colleagues (1992) also examined risks of COPD mortality associated with the type of cigarette smoked (filter-tipped versus unfiltered) and inhalation patterns in 7,703 women and 6,511 men who participated in the Copenhagen City Heart Study. The RRs for COPD-related mortality differed little between women and men based on the type of cigarette smoked. Compared with women who were nonsmokers, women who smoked unfiltered cigarettes had a RR for COPD-related mortality of 15 (95 percent CI, 3.1–65.0), and women who smoked filter-tipped cigarettes had a RR of 16 (95 percent CI, 3.6–70.0). The corresponding RRs for men were 6.4 (95 percent CI, 2.0–20.0) and 7.9 (95 percent CI, 2.3–27.0), respectively.

In four prospective cohort studies in the United Kingdom, Tang and colleagues (1995) assessed mortality in 56,225 men for smoking-induced diseases, comparing filter-tipped and unfiltered cigarettes and estimated tar yields. The mortality risk for COPD was somewhat lower for smokers of filter-tipped cigarettes, but not significantly in comparison with smokers of unfiltered cigarettes. For a tar reduction of 15 mg per cigarette, Tang and colleagues (1995) estimated that COPD mortality would drop by about 20 percent, but this estimate was quite imprecise.

Histopathologic findings have also been reported that provide insights concerning tar and nicotine yields, respiratory symptoms, and lung function levels. Auerbach and colleagues (1979) quantitated smoking-related changes in the autopsied lungs of men from a Veterans Administration hospital in New Jersey. In a rigorously studied series of autopsied lungs, these investigators showed that smokers from a period when cigarettes had comparatively high tar and nicotine yields (1955–1960) had more changes in the airways at various smoking levels compared with smokers from a later period (1970–1977). They interpreted this temporal pattern as an indication that cigarettes with lower tar and nicotine yields had fewer effects on the lungs than did higher-yield cigarettes.

A number of studies have shown that smokers of lower-yield cigarettes have comparatively lower rates of respiratory symptoms (Table 4.18). Respiratory questionnaire data collected in the late 1970s from approximately 6,000 Pennsylvania women are illustrative (Schenker et al. 1982). The brand of cigarettes currently smoked was identified and used with Federal Trade Commission tar yield information to classify the smokers according to tar exposure. A higher-tar yield was positively associated with coughing and phlegm but not with wheezing or shortness of breath. For coughing and phlegm, there were consistent exposure-response relationships with an approximate doubling of symptom frequency from the lowest to the highest exposure category. The findings of other studies are similar. For example, a large study of civil servants in the United Kingdom, the Whitehall Study, showed that the percentage of smokers reporting phlegm increased with tar yield within each stratum of cigarettes smoked per day, even the lowest (Higenbottam et al. 1980).

Not all studies show less disease associated with lower-yield cigarettes (Table 4.18). One study from Finland found that symptom levels in young smokers who were just initiating smoking did not depend greatly on tar yield (Rimpela and Teperi 1989). In this six-year follow-up study, the youth were surveyed on several occasions to determine the relationship between tar yield and symptom onset. There was little evidence of less symptom occurrence in the new smokers using low-tar cigarettes in comparison with those smoking higher-tar cigarettes. Moreover, symptoms were far more frequent in the low-tar smokers than in nonsmokers. In a randomized trial in the United Kingdom, lower-tar cigarettes were not associated with either lower symptom frequency or a higher level of ventilatory function, which was assessed by measuring the peak expository flow rate (Withey et al.

1992a,b). The investigators monitored urinary nicotine metabolites and concluded that compensation led to comparable levels across the trial period.

Respiratory morbidity also has been investigated. Follow-ups of outpatient visits by enrollees in a Kaiser Permanente group over one year showed that there was a reduced risk for pneumonia and influenza, but not for other respiratory conditions, associated with the use of low-tar and low-nicotine products compared with the use of products higher in tar and nicotine (Petitti and Friedman 1985a). However, in comparison with nonsmokers, smokers using low-tar and low-nicotine cigarettes had an increased risk for pneumonia, influenza, and COPD.

The evidence does not suggest a relationship between tar yield and lung function level. For example, in the Whitehall Study there was no cross-sectional relationship between tar yield and the FEV_1 level (Higenbottam et al. 1980). In the Normative Aging Study, a longitudinal study of U.S. veterans, tar yields of the usual brands of cigarettes smoked were not associated with a decline of FEV_1 levels (Sparrow et al. 1983), and the Tucson Study found a weak association between lung function decline and higher tar yields (Krzyzanowski et al. 1991).

In general, cohort studies assessing cigarette type and yield with COPD risks show little evidence for an association. In the CPS-I study comparing "low-" or "medium-" tar and nicotine smokers with "high-" tar and nicotine smokers, mortality from emphysema was reduced somewhat, although not significantly (Table 4.18) (Lee and Garfinkel 1981).

Evidence Synthesis. Little new evidence is available, and it does not conflict with the conclusion of the 1984 Surgeon General's report (USDHHS 1984) that "reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion" (p. 12). Limited evidence published since that report suggests that cigarette type does not influence the rate of FEV_1 decline or COPD-related mortality.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between lower machine-measured cigarette tar and a lower risk for cough and mucus hypersecretion.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in forced expiratory volume in one second decline rates.

3. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.

Implications. Although there are limited data on the relationship between cigarette type and the risk for chronic respiratory diseases, the strong benefits from smoking cessation combined with the availability of effective methods for controlling tobacco use suggest that little public health benefit will be gained by further research on the relationship between cigarette type and chronic respiratory diseases.

Diffuse Parenchymal Lung Diseases. Diffuse parenchymal lung diseases, also known as interstitial lung diseases, are a heterogeneous group of disorders associated with different types of inflammation primarily in the walls and airspaces of alveoli. Although there are more than 100 different diffuse parenchymal lung diseases, only small numbers of patients with these diseases are seen regularly by clinicians (Coultas et al. 1994), and the role of cigarette smoking has been investigated only for a few of these diseases.

Although the pathogenesis of these diseases is varied, conceptually they result from an inflammatory response in the lungs that follows the inhalation of a wide variety of particles (e.g., inorganic and organic). For some of the diseases (i.e., idiopathic pulmonary fibrosis [IPF] or sarcoidosis), emerging evidence suggests a causal role for a number of inhaled agents, but causality remains to be established. The role of cigarette smoking in the pathogenesis of diffuse parenchymal lung diseases, although not fully defined, is potentially complex and may involve altered clearance, deposition of particles, and modification of the inflammatory response. Evidence for a complex interaction between cigarette smoking and the pathogenesis of diffuse parenchymal lung diseases is based on observations that cigarette smoking is associated with an increased disease risk for some (e.g., IPF or pneumoconiosis), and a decreased risk for others (e.g., hypersensitivity pneumonitis or sarcoidosis). Available evidence suggests that modification of the inflammatory/immune response may be the mechanism for lowering the risks for hypersensitivity pneumonitis (Baron 1996) and sarcoidosis (Soliman and Twigg 1992; Baron 1996).

Idiopathic Pulmonary Fibrosis. *Epidemiologic Evidence.* Scant epidemiologic data are available on the occurrence of IPF (Coultas et al. 1994), but the available information suggests that IPF may be the most common diffuse parenchymal lung disease in the general population (Coultas et al. 1994). Until recently, etiologic investigations of this disorder had not been conducted. It is relatively uncommon, and without a lung biopsy misclassification of the diagnosis may result, making investigation of this disorder difficult. Although the term "idiopathic" means of unknown cause, during the past decade four case-control studies have been conducted to examine potential etiologic agents, including cigarette smoking (Scott et al. 1990; Iwai et al. 1994; Hubbard et al. 1996; Baumgartner et al. 1997). One case-control study of environmental exposures was conducted with 17 patients, but cigarette smoking was not examined (Mullen et al. 1998).

Overall, significant associations were found in three of the four studies. Scott and colleagues (1990) identified 40 cases of IPF seen by pulmonary physicians or tested at pulmonary function laboratories in Nottingham, England, and 106 age- and gender-matched controls were identified from patients registered with the index patient's general practitioner. In this case-control study, cigarette smoking was not significantly associated with IPF (OR = 1.11 [95 percent CI, 0.13–1.40]).

Cases of IPF seen between 1992 and 1994 at four teaching hospitals in the Trent Region, United Kingdom, were identified by Hubbard and colleagues (1996). Controls matched by age, gender, and community were identified from patients registered with the same general practitioner. Information on smoking and other exposures was obtained from 218 patients and 569 controls who returned a mailed questionnaire; 165 cases and 408 controls completed telephone interviews for verification. Having ever smoked was significantly associated with IPF (OR = 1.57 [95 percent CI, 1.01–2.43]).

Iwai and colleagues (1994) identified 86 patients with IPF evaluated by two research committees in Japan. Two controls for each patient were matched for age, gender, and residential area: a person selected from voters' lists and a hospital patient with a non-IPF respiratory disease. Compared with healthy controls, IPF patients were significantly more likely to smoke (OR = 2.94 [95 percent CI, 1.37–6.30]).

Baumgartner and colleagues (1997) conducted a multicenter case-control study in the United States that included 16 institutions in 15 states. A total of 248 patients had been diagnosed with IPF between 1989 and 1993; and 491 community controls matched for age, gender, and geographic location were identified using random-digit telephone dialing. Standardized telephone interviews were used to obtain risk factor information from cases and controls. Ever smoking

Table 4.18   Studies on the association between cigarette tar yields and chronic respiratory diseases

Study	Design/population	Variable studied
Dean et al. 1978	Sample of 12,736 men and women Aged 37–67 years Living in England, Scotland, and Wales in 1972	Filter-tipped or unfiltered cigarettes
Hawthorne and Fry 1978	Prospective cohort study 18,786 people attending a multiphasic screening examination Followed from 1965–1977 in West Central Scotland	Filter-tipped or unfiltered cigarettes
Higenbottam et al. 1980	Cross-sectional study 18,000 male civil servants surveyed from 1968–1975 United Kingdom	Cigarette habit and tar yield
Lee and Garfinkel 1981	Prospective cohort study 12-year follow-up of CPS-I[†] of over 1 million men and women from 1960–1972	Tar yield: low (0–10 mg/cigarette) vs. high (29 mg/cigarette)
Schenker et al. 1982	Cross-sectional study 5,686 adult women who completed a standardized respiratory disease questionnaire	Data were not reported
Sparrow et al. 1983	Cohort study 1,355 men (383 current, 555 former, and 417 never smokers) from an aging study from 1969–1974 in Boston, Massachusetts	Cigarette habit and tar yield
Alderson et al. 1985	Case-control study 12,693 hospital inpatients Followed from 1977–1982	Always filter-tipped or unfiltered cigarettes
Petitti and Friedman 1985a	Prospective cohort study 16,270 current, regular cigarette smokers and 42,113 persons who never used any form of tobacco Followed from 1979–1983	Low yield

*NS = Not significant.
[†]American Cancer Society Cancer Prevention Study I.
[‡]RR = Relative risk.
[§]OR = Odds ratio.
 CI = Confidence interval.

Outcome	Findings
Respiratory symptoms	Morning coughs in men and women and a shortness of breath in women were lower for filter-tipped cigarette smokers; estimates were adjusted for age, social class, number of cigarettes/day, inhalation, and occupation
Prevalence of respiratory symptoms	Among current cigarette smokers of filter-tipped compared with unfiltered cigarettes, men had $x^2 = 1.0$ for chronic bronchitis (NS*), 5.7 (p <0.05) for shortness of breath, 9.3 (p <0.01) for wheezing, and 5.6 (p <0.05) for phlegm; women had $x^2 = 7.7$ (p <0.01), 5.9 (p <0.05), 11.8 (p <0.001), and 5.0 (p <0.05), respectively; estimates were adjusted for age
Lung function and respiratory symptoms	Low-tar smokers had lower phlegm production, although airflow obstruction was not affected; low-tar smokers of 20 cigarettes/day had the same phlegm production as high-tar smokers
Emphysema	For smokers of low-tar vs. high-tar cigarettes, RR[‡] = 0.78 for men and 0.59 for women; no significant differences between low- and high-tar yields
Several respiratory symptoms	Higher cigarette tar content was an independent risk factor for chronic coughs (p = 0.005) and chronic phlegm (p = 0.077); OR[§] for high-tar cigarette smokers (average = 22 mg/cigarette) = 2.01 for chronic coughs and OR = 1.59 for chronic phlegm relative to low-tar cigarette smokers (average = 7 mg/cigarette); the effect of cigarette tar was linear and independent of the number of cigarettes/day
Lung function (by spirometry)	Tar yield did not significantly influence baseline levels of forced vital capacity or forced expiratory volume in 1 second, after controlling for age, height, and the number of cigarettes/day
Chronic bronchitis	For smokers of filter-tipped vs. unfiltered cigarettes, RR for men = 0.25 and for women = 0.75, adjusted for the number of cigarettes/day
All respiratory diseases	RR = 0.97 (95% CI , 0.84–1.13) per 5.0 mg increase in tar yield among current, regular cigarette smokers for all diseases of the respiratory system

Table 4.18 Continued

Study	Design/population	Variable studied
Rimpela and Teperi 1989	Longitudinal study 2,266 men and women from Finland, born between July 20 and July 31, 1966	Low yield
Brown et al. 1991	Population-based cohort study 2,801 men and women aged 40–59 years from the Scottish Heart Health Study conducted between 1985 and 1986 who were current smokers and knew their brands of cigarettes	Cigarette tar yield: Low = 12 mg/cigarette Middle = 13–14 mg/cigarette High = 15 mg/cigarette
Krzyanowski et al. 1991	Prospective cohort study 690 smokers from a sample of households in Tucson, Arizona Followed from 1981–1988	Tar, nicotine, and carbon monoxide yields
Lange et al. 1992	Prospective cohort study 6,511 men and 7,703 women selected randomly after age stratification from the general population in Copenhagen Followed for 13 years, from 1976–1989	Filter-tipped and unfiltered cigarettes
Withey et al. 1992a,b	Randomized intervention trial in 21 local authority districts in England; male middle-tar smokers aged 18–44 years; 7,029 smokers selected from 265,016 who were sent questionnaires; 643 controls; assigned 1 of 3 different types of cigarettes for 6 months Followed from 1985–1989	Middle-tar smokers (>12 mg/cigarette) were assigned to test low-tar/middle-nicotine cigarettes with 9.5 mg tar/1.16 mg of nicotine, middle-tar/middle-nicotine cigarettes with 13.8 mg tar/1.24 mg nicotine, or low-tar/low-nicotine cigarettes with 9.3 mg tar/1.04 mg nicotine
Tang et al. 1995	4 cohorts of 56,255 men studied between 1967 and 1982 from the British United Provident Association Study (London), Whitehall Study (London), Paisley-Renfrew Study (Scotland), and U.K. Heart Disease Prevention Project (England and Wales)	Tar yields of manufactured cigarettes

Outcome	Findings
Respiratory symptoms (especially cough and phlegm)	Number of cigarettes/day was associated with morning cough, cough during day or night, and morning phlegm, on a significant or nearly significant level ($p = 0.047–0.075$), while no dependent variable was significantly related to phlegm during the day or night; tar yields played no role in the prediction of symptoms
Chronic coughs and chronic phlegm	Rates of chronic cough and phlegm were greater for women who smoked higher-tar cigarettes (low-tar vs. high-tar: $p <0.001$) but not for men; higher tar content was a significant risk factor for women after controlling for daily number of cigarettes smoked, number of years smoked, and social class ($p <0.05$); no RR was provided
Respiratory symptoms, pulmonary function	After adjusting for the intensity and duration of smoking and depth of inhalation, there were no effects of tar or nicotine on chronic phlegm, cough, or dyspnea; pulmonary function was estimated to decline more rapidly with increasing yields
Chronic obstructive pulmonary disease (COPD)-related mortality	Among current cigarette smokers, RR for men who smoked filter-tipped cigarettes = 1.2 (95% CI, 0.7–2.0) compared with men who smoked unfiltered cigarettes; women = 1.3 (95% CI, 0.6–1.6)
Respiratory symptoms	There were no differences in respiratory symptoms after switching to different types of cigarettes; urine nicotine metabolites analyses showed that smokers adjusted their smoking so that throughout the trial, their nicotine inhalation differed little from their pretrial nicotine intakes when they were smoking their usual cigarettes
COPD-related mortality	Among current cigarette smokers with a 15 mg decrease in the tar yield/cigarette, RR = 0.78 (95% CI, 0.40–1.48)

was significantly associated with IPF (OR = 1.6 [95 percent CI, 1.1–2.4]), but there was no dose-response relationship with pack-years of smoking. Moreover, there was no increased risk in current smokers (OR = 1.06 [95 percent CI, 0.6–1.8]). However, among former smokers there was an inverse trend in risk with time since cessation (OR = 3.5 [95 percent CI, 1.1–11.9] for cessation of less than 2.5 years, OR = 2.3 [95 percent CI, 1.3–4.2] for cessation of 2.5 to 10 years, OR = 1.9 [95 percent CI, 1.1–3.2] for cessation of 10 to 25 years, and OR = 1.3 [95 percent CI, 0.7–2.3] for cessation of 25 or more years).

Evidence Synthesis. Inflammation is thought to have a central role in the pathogenesis of IPF.

Smoking, which increases lung inflammation, could plausibly increase the risk for IPF. Several studies show an association between ever smoking and IPF; however, the data are limited and further studies are needed.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and idiopathic pulmonary fibrosis.

Implication. Further research will be needed to determine whether there is a causal relationship between active smoking and pulmonary fibrosis.

Conclusions

Acute Respiratory Illnesses

1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.

3. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.

Chronic Respiratory Diseases

4. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants.

5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy.

6. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood.

7. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.

8. The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence.

9. The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood.

10. The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function.

11. The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked.

12. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.

13. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.

14. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.

15. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.

16. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.

18. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyper-responsiveness.

19. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control.

20. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.

21. The evidence is suggestive but not sufficient to infer a causal relationship between lower machine-measured cigarette tar and a lower risk for cough and mucus hypersecretion.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in forced expiratory volume in one second decline rates.

23. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.

24. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and idiopathic pulmonary fibrosis.

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Chapter 5
Reproductive Effects

Introduction

Smoking harms many aspects of reproduction. An estimated 6 million women become pregnant each year in the United States, and more than 11,000 give birth each day (Ventura et al. 2000; Martin et al. 2002). Studies have shown that women who smoke are at an increased risk for a delay in becoming pregnant and for both primary and secondary infertility. Research has also shown that women who smoke during pregnancy risk complications, premature birth, low birth weight (LBW) infants, stillbirth, and infant mortality. LBW is a leading cause of infant deaths (Martin et al. 2002). Despite increased knowledge of the adverse health effects of smoking during pregnancy, only 18 to 25 percent of women quit smoking once they become pregnant. Data also suggest that a substantial number of pregnant women and girls continue to smoke (estimates range from 12 to 22 percent) (U.S. Department of Health and Human Services [USDHHS] 2001). This chapter reviews the evidence for a relationship between smoking and adverse reproductive effects. In particular, it examines the associations between smoking and fertility, smoking and pregnancy complications, and the health of children born to smokers.

Conclusions of Previous Surgeon General's Reports

Numerous previous reports of the Surgeon General on smoking and health have examined the effects of active smoking on the reproductive capabilities and outcomes for both men and women (Table 5.1). The 1964 Surgeon General's report (U.S. Department of Health, Education, and Welfare [USDHEW] 1964) identified an association between smoking during pregnancy and LBW (infants weighing <2,500 grams [g] at birth) that has been further explored in subsequent reports. The 1969 Surgeon General's report (USDHEW 1969) presented evidence on smoking during pregnancy and preterm delivery (<37 weeks completed gestation), spontaneous abortion, stillbirths, and neonatal mortality. The 1978 Surgeon General's report (USDHEW 1978) introduced new findings concerning smoking and pregnancy complications including placental abruption, placenta previa, and the premature rupture of membranes. The 1980 report on the health consequences of smoking for women (USDHHS 1980) extended previous findings on birth weight, retarded fetal growth, benefits of smoking cessation early in pregnancy, pregnancy complications, effects of smoking on the placenta, and mortality including sudden infant death syndrome (SIDS). This report also introduced new information on smoking risks and fertility, congenital malformations, and longer-term morbidity. The 1989 report (USDHHS 1989) evaluated new data and continued to find (1) a relationship between maternal smoking during pregnancy and lower birth weights, (2) higher rates of fetal and perinatal mortality associated with maternal smoking during pregnancy, (3) mixed findings on the relationship of maternal smoking to congenital malformations, (4) a higher risk of infertility among women and possibly men related to smoking, and (5) conflicting findings with regard to maternal smoking and longer-term physical development in the infant and child. The 1990 report on the health benefits of cessation (USDHHS 1990) noted that LBW could be reduced by 26 to 42 percent if smoking during pregnancy were eliminated. The 2001 report described findings on birth weight, infertility, ectopic pregnancy, spontaneous abortion, pregnancy complications, and SIDS (USDHHS 2001). That report also addressed smoking and breastfeeding, a topic not considered in this report. In prior reports, causal conclusions have been reached for a number of adverse reproductive outcomes (Table 5.1).

Table 5.1   Conclusions from previous Surgeon General's reports concerning smoking as a cause of reproductive effects

Disease and statement	Surgeon General's report
Low birth weight	
"Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight." (p. 39)	1964
"New data are presented which confirm the finding that maternal smoking during pregnancy is associated with low birth weight in infants. . . ." (p. 5)	1969
"Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birthweight and an increased incidence of prematurity, defined by weight alone." (p. 13)	1971
"Among all women in the United States, cigarette smokers are nearly twice as likely to deliver low-birth-weight infants as are non-smokers." (p. 121)	1973
"A dose-response relationship exists between smoking and the incidence of low birth weight, preterm delivery, perinatal mortality, abruptio placentae, placenta previa, bleeding during pregnancy, and prolonged and premature rupture of the membranes." (p. 17)	1978
"There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight. . . .Birth weight is affected by maternal smoking independently of other determinants of birth weight. The more the mother smokes, the greater the baby's birth-weight reduction." (p. 1-21)	1979
"Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable nonsmoking women." (p. 10)	1980
"There is a dose-response relationship between maternal smoking and reduced birth weight; the more the woman smokes during pregnancy, the greater the reduction in birth weight." (p. 10)	1980
"If a woman gives up smoking early during pregnancy, her risk of delivering a low-birth-weight baby approaches that of a nonsmoker." (p. 10)	1980
"Women who stop smoking before pregnancy or during the first 3 to 4 months of pregnancy reduce their risk of having a low birthweight baby to that of women who never smoked." (p. i)	1990
"Infants born to women who smoke during pregnancy have a lower average birth weight. . .than infants born to women who do not smoke." (p. 307)	2001

Table 5.1   Continued

Disease and statement	Surgeon General's report
Small for gestational age	
". . .maternal smoking is associated with an increased incidence of prematurity defined by weight alone." (p. 5)	1969
"Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate. . . ." (p. 1-21)	1979
"Maternal smoking during pregnancy exerts a direct growth-retarding effect on the fetus; this effect does not appear to be mediated by reduced maternal appetite, eating or weight gain." (p. 11)	1980
"Although there is little effect of maternal smoking on mean gestation, the proportion of fetal deaths and live births that occur before term increases directly with maternal smoking level. Up to 14 percent of all preterm deliveries in the United States may be attributable to maternal smoking." (p. 11)	1980
"Infants born to women who smoke during pregnancy. . .are more likely to be small for gestational age than are infants born to women who do not smoke." (p. 307)	2001
Infertility	
"Studies in women and men suggest that cigarette smoking may impair fertility." (p. 12)	1980
". . .the data suggest that impairment of fertility measured as delay in time to conception is related to smoking near the time of attempting to conceive and that smoking cessation prior to conception returns fertility to that of never smokers." (p. 375)	1990
"Women who smoke have increased risks for conception delay and for both primary and secondary infertility." (p. 307)	2001
Ectopic pregnancy	
"Women who smoke may have a modest increase in risks for ectopic pregnancy." (p. 307)	2001
Spontaneous abortion	
". . .it appears that maternal smoking during pregnancy may be associated with an increased incidence of spontaneous abortion, stillbirth, and neonatal death and that this relationship may be most marked in the presence of other risk factors." (p. 5)	1969
"There is insufficient evidence to support a comparable statement for abortions [as for fetal deaths and stillbirths]." (p. 13)	1971

Table 5.1   Continued

Disease and statement	Surgeon General's report
"Perinatal mortality increases significantly with smoking as well as with other risk factors such as maternal age, parity, socioeconomic status, previous pregnancy history, and hemoglobin level." (p. 17)	1978
"The risk of spontaneous abortion, fetal death, and neonatal death increases directly with increasing levels of maternal smoking during pregnancy; interaction of maternal smoking with other factors which increase perinatal mortality may result in an even greater risk." (p. 11)	1980
"Cigarette smoking is now considered to be a probable cause of unsuccessful pregnancies. . . ." (p. 20)	1989
"Women who smoke may have a modest increase in risks for. . .spontaneous abortion." (p. 307)	2001
Pregnancy complications	
"Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes." (p. 1-22)	1979
"Increasing levels of maternal smoking result in a highly significant increase in the risk of abruptio placentae, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery—all of which carry high risks of perinatal loss." (p. 11)	1980
"The incidence of preeclampsia is decreased among women who smoke during pregnancy; however, if preeclampsia develops in a smoking woman, the risk of perinatal mortality is markedly increased compared to preeclamptic nonsmokers." (p. 11)	1980
"Smoking during pregnancy is associated with increased risks for preterm premature rupture of membranes, abruptio placentae, and placenta previa, and with a modest increase in risk for preterm delivery." (p. 307)	2001
"Women who smoke during pregnancy have a decreased risk for preeclampsia." (p. 307)	2001
Fetal deaths and stillbirths	
"There is strong evidence to support the view that smoking mothers have a significantly greater number of unsuccessful pregnancies due to stillbirth and neonatal death as compared to nonsmoking mothers." (p. 13)	1971
"A strong, probably causal association between cigarette smoking and higher late fetal and infant mortality among smokers' infants is supported by the. . .evidence." (p. 134)	1973

Table 5.1   Continued

Disease and statement	Surgeon General's report
"A strong, probably causal, association exists between cigarette smoking and higher late fetal and infant mortality among smokers' infants." (p. 17)	1978
"When adjustments are made for age-parity differences in mothers, their socio-economic status, and previous pregnancy histories, the risk of perinatal mortality attributable to smoking is highly significant, independent of these factors, and is dose-related." (p. 1-22)	1979
"The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy." (p. 307)	2001
Infant mortality	
"Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes. . . .Smoking by pregnant women contributes to the risk of their infants being victims of the 'sudden infant death syndrome'. . . .Maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant." (p. 1-22)	1979
"Excess deaths of smokers' infants are found mainly in the coded cause categories of 'unknown' and 'anoxia' for fetal deaths, and the categories of 'prematurity alone' and 'respiratory difficulty' for neonatal deaths. . . ." (p. 11)	1980
"An infant's risk of developing the 'sudden infant death syndrome' is increased by maternal smoking during pregnancy." (p. 11)	1980
"Cigarette smoking is now considered to be a probable cause of. . .increased infant mortality. . . ." (p. 20)	1989
Congenital malformations	
". . .no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformation at the present time." (p. 137)	1973
"The accumulated evidence does not support a conclusion that maternal smoking increases the incidence of congenital malformations." (p. 1-22)	1979
"There are insufficient data to support a judgement on whether maternal and/or paternal cigarette smoking increases the risk of congenital malformations." (p. 11)	1980
"Smoking does not appear to affect the overall risk for congenital malformations." (p. 307)	2001

Table 5.1   Continued

Disease and statement	Surgeon General's report
Impairment of children's development	
"According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11." (p. 1-21)	1979
"Maternal smoking during pregnancy may adversely affect the child's long-term growth, intellectual development, and behavioral characteristics." (p. 11)	1980
Low sperm quality	
"The available information suggests that current smoking is related to low sperm density. However, these data are limited." (p. 405)	1990

Sources: U.S. Department of Health, Education, and Welfare 1964, 1969, 1971, 1973, 1978, 1979; U.S. Department of Health and Human Services 1980, 1989, 1990, 2001.

Biologic Basis

The biologic basis of smoking and reproductive effects is complicated by how exposure is defined for reproductive effects, and is perhaps best discussed using a methodologic framework. When researchers examine the effects of smoking on reproductive outcomes, measuring exposure to smoking and adjusting for possible confounding are two important methodologic concerns. The critical exposure periods during gestation are brief for some adverse reproductive outcomes that have possible causal associations with active smoking. For example, when examining the relationship between smoking and congenital malformations, relevant data include exposure to tobacco smoke during the early part of pregnancy or during organogenesis. Similarly, for studying fetal growth restrictions, knowledge of smoking habits during the third trimester—the time when most of the growth in the fetus occurs—is of critical importance. However, in many studies the average amount smoked during pregnancy has been used as the exposure measure without collecting or reporting information sorted by the month of pregnancy or by the trimester.

For pregnancy outcomes, several potential confounding factors should be considered along with tobacco use, such as social class and racial and ethnic group. Among women of a lower social standing, not only are rates of smoking higher but rates of adverse pregnancy outcomes are also higher. Whereas lower social standing is thus a potential confounding variable, it may also be part of a common causal pathway serving as one of the determinants of exposure to smoking. Most recent studies do take potential confounders into account, and within the body of relevant literature, confounding has been adequately considered in the aggregate. However, for studies of some outcomes, such as those that examine associations of active smoking during pregnancy with child outcomes (i.e., physical, neurologic, and cognitive development), fully accounting for all potential confounders in the postpartum period is not feasible. The appropriateness of accounting for confounders will be discussed in each of the three sections that follow.

Another challenging issue that should be addressed is the mechanistic role of smoking in the causal pathway of adverse reproductive outcomes. For the role of smoking in preterm deliveries, for example, prenatal cigarette exposure might (1) increase the risk for pregnancy complications leading to a preterm

delivery (e.g., the premature rupture of membranes), (2) decrease immune system functioning leading to an increased susceptibility to infections, or (3) act more directly through mechanisms not yet understood. Many studies do not capture data in a way that facilitates an adequate dissection of the underlying pathway. For example, few studies stratify analyses by the presence of pregnancy complications, and most such studies do not account for infections, as this purported risk factor for a preterm delivery has emerged only recently.

This methodologic challenge is further illustrated by SIDS, smoking during pregnancy, and the role of birth weight in the causal pathway. Because prenatal smoking results in lower birth weights and LBW is also a risk factor for SIDS, most studies account for birth weight, and some studies even limit the analyses to infants born weighing at least 2,500 g. It is unclear, however, that this analytic strategy is the most appropriate if the total contribution of smoking to the risk of SIDS is of interest. Only a few studies have examined the association between smoking and SIDS by stratifying the sample by birth weight.

Studies reviewed for this chapter were selected from a MEDLINE literature search from the mid-1960s to 2000, with some earlier studies identified through bibliographies. Title and abstract search terms included "smoking," and outcomes of interest such as "pregnancy," "fertility," "pregnancy complications," "birth weight," "preterm delivery," "cognitive development," "congenital malformations," "infant mortality," and "SIDS." For some searches (e.g., pregnancy complications), specific disorders were used as a search term (e.g., placenta previa). "Smoking" was also used as a Medical Subject Headings term, and review articles were consulted as additional sources for references.

As some of the topics presented in this chapter have been extensively investigated and the evidence found to support causality (e.g., smoking and birth weight), this chapter focuses on more recent studies and emerging areas such as male erectile dysfunction. When possible, recent studies were reviewed as the patterns of smoking among women of childbearing age and pregnant women have changed over the past few decades. In addition, the topic of smoking and cervical cancer is discussed in Chapter 2.

Fertility

Epidemiologic Evidence

Smoking and Sperm Quality

Cigarette smoking among men can affect spermatogenesis and sperm quality through hormonal and toxic influences. In a review of the literature on male reproduction and smoking, Vine (1996) noted that the cytotoxic effects of exposures to tobacco smoke may reduce the numbers and function of sperm, or may affect male reproductive hormone levels and lead to impairment of spermatogenesis. Although the results of studies supporting the latter mechanism are mixed, several studies have found that levels of testosterone, estradiol, estrone, androstenedione, and follicle-stimulating hormone are increased among smokers compared with nonsmokers (Barrett-Connor and Khaw 1987; Simon et al. 1992; Field et al. 1994; Vine 1996), while other studies have found decreases among smokers compared with nonsmokers or no differences between the two groups (Andersen et al. 1984; Barrett-Connor and Khaw 1987; Klaiber and Broverman 1988;

Simon et al. 1992). Small sample sizes may partially explain the conflicting findings (Vine 1996) as larger studies tend to find increased levels of male reproductive hormones in smokers compared with nonsmokers (Simon et al. 1992; Field et al. 1994). Toxins found in tobacco smoke, such as cadmium, nicotine, lead, and radioactive alpha-particle emitting elements (internal emitters in particular), may be directly toxic as they circulate in the blood and reach the testes (Mattison 1982; Ravenholt 1982; Mattison et al. 1989; Oldereid et al. 1989).

In the following discussion, the studies examined associations between sperm production and male smoking and had larger sample sizes as well as some consideration of potential confounders. However, many of the studies on sperm quality included men seeking treatments for infertility, and the findings may have restricted generalizability. Also most do not adequately consider potential confounders such as abstinence, occupational exposures (e.g., teratogens and toxins in the workplace), or health behaviors (e.g., caffeine, alcohol, or drug use). Studies on smoking and

sperm quality have examined measures such as ejaculate volume and sperm output, density, viability, motility, and morphology (Vogel et al. 1979; Evans et al. 1981; Godfrey 1981; Andersen et al. 1984; Handelsman et al. 1984; Kulikauskas et al. 1985; Dikshit et al. 1987; Saaranen et al. 1987; Marshburn et al. 1989; Oldereid et al. 1989; Close et al. 1990; Holzki et al. 1991; Lewin et al. 1991; Chia et al. 1994) (Table 5.2). Handelsman and colleagues (1984) studied 119 healthy volunteer sperm donors and examined a variety of physical, demographic, and health behavioral factors and sperm quality. Although it is not clear how the category of smokers was defined, when compared with nonsmokers this group had a significantly reduced total sperm output (316 million versus 181 million sperm), motility (72 million versus 67 million sperm), motile sperm (235 million versus 127 million sperm), and total oval sperm (251 million versus 120 million sperm). These values were unadjusted for other factors. Marshburn and colleagues (1989) studied 445 men and reported a significantly reduced sperm volume for smokers compared with nonsmokers but no differences in sperm density, sperm motility, or the presence of abnormalities or dead sperm. The authors, however, warned against the confounding effect of coffee drinking in this and other studies. Chia and colleagues (1994) studied 618 men receiving treatment for infertility and reported means for volume, density, motility, and morphology adjusted for age, medical history, occupational exposure to cigarette smoke, and testicular size. Current smokers had a lower sperm density, a lower proportion with normal morphology, and a higher proportion with head defects than nonsmokers (lifetime nonsmokers and former smokers). Most studies have not found dose-response relationships with the amount smoked, and a number of studies found no difference in sperm quality between smokers and nonsmokers (Saaranen et al. 1987; Oldereid et al. 1989; Close et al. 1990; Holzki et al. 1991; Lewin et al. 1991). One large study found no differences between those exposed to tobacco smoke and chewing and those not exposed to tobacco smoke and chewing (Dikshit et al. 1987).

A meta-analysis of 20 different study populations conducted by Vine and colleagues (1994) found that sample size was a major contributor to apparent inconsistencies among the study findings. Overall, the weighted estimate of reduction in sperm density among smokers compared with nonsmokers was 13 percent (95 percent confidence interval [CI], 8.0–21.0) adjusted for population source, minimum number of cigarettes smoked by smokers, number of specimens analyzed, and whether laboratory staff were blinded

to the status of the participants (Vine et al. 1994). This estimate is somewhat lower than that of an earlier review of 10 studies, which found a reduction in smokers compared with nonsmokers to be 22 percent.

In summary, studies on the association between smoking and sperm quality have produced conflicting findings. Many studies have small sample sizes comprised of men who may have problems with infertility unrelated to smoking. And despite comments about similarities between smokers and nonsmokers, few included adjustments for potential confounders such as sexual abstinence, occupational exposures, and health practices of participants (e.g., consumption of alcohol, caffeine, or drugs). Nonetheless, the evidence suggests that smokers may have decreased semen volume and sperm number and increased abnormal forms, although any clinical relevance of these findings is not clear.

Smoking and Fertility in Women

Numerous studies have shown that smoking results in reduced fertility and fecundity for couples with one or both partners who smoke (Table 5.3). Fertility might be reduced by active smoking through numerous mechanisms. Animal studies suggest that prenatal exposure to polycyclic aromatic hydrocarbons has a destructive effect on oocytes and may affect the release of gonadotropins, corpora lutea formation, gamete interaction, and implantation. Studies in rats and humans also have shown that postfertilization cleavage is delayed in smokers (Mattison et al. 1989; Hughes et al. 1992; Rowlands et al. 1992). In the rat, nicotine delays implantation of the fertilized ovum, but whether this delay affects fertility remains to be determined. Smoking also has been shown to affect menstrual function by shortening cycles and increasing anovulation, which may also contribute to subfecundity and infertility (Windham et al. 1999).

The literature uses a number of different indicators to measure fertility and fecundity. Infertility in the United States is defined as the inability to conceive for 12 months; the World Health Organization uses failure to conceive for 24 months or more. Primary infertility refers to women who have not had prior pregnancies while secondary infertility concerns women who have been pregnant before. Unfortunately, the literature on smoking and fertility among women does not consistently employ these standard measures.

Laurent and colleagues (1992) studied primary infertility in 2,714 cases and controls. Primary infertility was associated with smoking more than one pack per day compared with nonsmokers (odds ratio

[OR] = 1.36 [95 percent CI, 1.14–1.61]) and starting to smoke before 18 years of age compared with nonsmokers (OR = 1.30 [95 percent CI, 1.0–1.68]). These estimates were adjusted for education, age, race, and history of ovarian disease. Joffe and Li (1994) examined the time to first pregnancy among 3,132 women. After adjusting for age, education, and smoking status of the father in a Cox survival model, women who smoked before conception were less likely to become pregnant than nonsmokers; the risk ratio for time to pregnancy for women who smoked was 0.89 (95 percent CI, 0.83–0.97). Alderete and colleagues (1995) studied 1,341 primiparas and reported that women who smoked, regardless of whether they drank coffee, had about one-half the fertility (OR = 0.5 to 0.6 for conception times of 6 and 12 months) of nonsmokers who did not drink coffee.

As early as the 1960s, an association between smoking and decreased fertility was observed. In a sample of 2,016 women in Tennessee, women who smoked had a 46 percent higher rate of infertility than women who did not smoke (Tokuhata 1968). In a large prospective family planning study of more than 17,000 women, which included 6,199 episodes of contraceptive stoppage for the purpose of becoming pregnant, Howe and colleagues (1985) demonstrated a dose-response relationship between the amount of current smoking and reduced fertility that was based on pregnancy rates five years after terminating contraception. Women who smoked more than 20 cigarettes per day had their fertility reduced by 22 percent compared with lifetime nonsmokers and former smokers. Lighter smokers (<15 cigarettes per day) did not show demonstrable reductions in fertility. Although this study did not adjust for potential confounders, reduced fertility in smokers did not vary significantly by social class. Suonio and colleagues (1990) demonstrated a dose-response relationship between any current smoking and a delay to conception for short (6-month) and long (18-month) periods of time. In this sample of 2,198 mothers interviewed at 20 weeks of gestation, with adjustments for several confounders (age, prior pregnancies, prior terminations and spontaneous abortions, alcohol consumption, occupation of the mother, employment, smoking status and alcohol consumption of the father), the OR of conception delay for smokers (>four cigarettes per day) compared with nonsmokers at six months was 1.6. Conception delays continued for smokers (any smoking) compared with nonsmokers at 12 and 18 months after discontinuing contraception. Women who smoked more than four cigarettes per day had a 2.1 OR for conception delay

at 18 months compared with nonsmokers. Dose-response relationships were demonstrated for lighter and heavier smokers for most outcomes (Suonio et al. 1990).

In a large multicountry study, Bolumar and colleagues (1996) examined the association between smoking and time to pregnancy that exceeded nine and one-half months in two large samples: (1) a population-based sample of women aged 25 through 44 years and (2) a sample of pregnant women recruited from prenatal clinics. Each sample had more than 4,000 couples. The OR was 1.7 (95 percent CI, 1.3–2.1) for a longer time to pregnancy for women smoking 11 or more cigarettes per day compared with nonsmokers in the population sample. For current pregnancy in the pregnant sample, the OR was also 1.7 (95 percent CI, 1.3–2.3), demonstrating a dose-response relationship for this outcome. Women who smoked 1–10 cigarettes per day had an OR of 1.4 in the population sample (95 percent CI, 1.1–1.7) and also in the pregnant sample (95 percent CI, 1.0–1.8). In the population-based sample, associations were also examined for the most recent pregnancies. For the most recent wait time, women who smoked 11 cigarettes or more per day compared with nonsmokers had an OR of 1.6 (95 percent CI, 1.3–2.1). ORs in this study were adjusted for age, coital frequency, education, oral contraceptive use, and coffee consumption (Bolumar et al. 1996). Curtis and colleagues (1997) reported a decreased fecundability (the monthly probability of conception), measured by time to pregnancy after discontinuing contraception, among smokers compared with nonsmokers. The fecundability ratio of smokers was 0.90 (95 percent CI, 0.81–0.95), and a dose-response relationship was observed for heavier smokers. Fecundability ratios for those smoking 11–20 cigarettes and more than 20 cigarettes per day were 0.87 (95 percent CI, 0.77–0.99) and 0.74 (95 percent CI, 0.59–0.92), respectively. Curtis and colleagues (1997) also reported associations with spousal smoking habits. Compared with both partners who were nonsmokers, when both the woman and her spouse smoked the fecundability ratio was 0.77 (0.68–0.86). In their study of 678 pregnant women, Baird and Wilcox (1985) reported that smokers had 3.4 times the risk of taking more than one year to conceive than nonsmokers, and heavy smokers showed an even greater reduced fertility than light smokers. In a review of 13 studies on this topic, Hughes and Brennan (1996) reported that all but one study found a reduced fecundity among smokers compared with nonsmokers.

Table 5.2   Studies on the association between smoking and sperm quality

Study	Study period	Population	Definition of smoking
Vogel et al. 1979	NR*	474 men	Smokers and nonsmokers (242 nonsmokers and 232 smokers)
Evans et al. 1981	NR	86 men	Number of cigarettes/day (0, <15, ±20, ±25, >30) (43 smokers of 1 cigarette/day and 43 nonsmokers)
Godfrey 1981		344 men	• Nonsmokers • Smokers: <20 and 20 cigarettes/day
Andersen et al. 1984	1977–1981	233 men and 250 women referred to an infertility clinic	Smokers: >10 cigarettes/day
Handelsman et al. 1984	NR	119 healthy men presenting for screening as potential sperm donors	Smokers: Current and former
Kulikauskas et al. 1985	NR	253 men aged 19–32 years	• Smokers: 4 cigarettes/day for at least the last 5 years • Nonsmokers had never smoked or had not smoked for at least 5 years
Barrett-Connor and Khaw 1987	1972–1974 1985–1986	590 men aged 30–79 years without a history of cardio-vascular disease	Never/former/current smokers were classified at time of inter-view: • 176 never smokers • 304 former smokers • 110 current smokers (<10, 11–20, >20 cigarettes/day)
Dikshit et al. 1987	July 1985– September 1986	626 male partners aged 20–32 years of couples undergoing idiopathic infertility	• Nonusers: no tobacco use in any form • Smokers: >10 cigarettes/day • Tobacco chewers: >10 helpings/day (288 nonusers, 219 smokers, and 119 tobacco chewers)

*NR = Data were not reported.

Key results

- Smoking may be correlated with gonadal function and with particular central nervous system functions influenced by gonadal hormones
- Smokers had less gonadal hormone stimulation than nonsmokers
- Differences were observed only in smokers who started smoking at 15 years of age or younger (early smokers), compared with late smokers who were older than 15 years of age when they began

- An examination of morphologic abnormalities in sperm samples revealed that smokers had a significantly greater percentage of abnormal forms than nonsmokers
- There was no clear quantitative association between the degree of abnormality and the number of cigarettes smoked
- Sperm abnormalities in cigarette smokers may reflect genetic damage as a consequence of cigarette smoke

- Sperm morphology did not differ significantly among the three groups
- No differences in sperm motility
- No significant differences in sperm counts

- Male smokers had significantly higher serum testosterone levels and lower semen volumes, while luteinizing hormone, follicle stimulating hormone, and sperm density, motility, and morphology did not differ between smokers and nonsmokers
- Cigarette smoking may increase central dopaminergic tonus and reduce serum prolactin levels, but the biologic significance of this finding to reproductive functions is unknown

- Smoking was associated with a highly significant reduction in sperm output and motility
- Sperm density and output as well as the equivalent parameters for motile and morphologically normal sperm were lower in smokers than in nonsmokers
- Semen volume or the percentage of atypical forms did not differ between the two groups

- Spermatozoa from smokers possessed significantly decreased density and motility compared with nonsmokers
- Individual sperm counts indicated more than twice as many smokers as nonsmokers had a sperm density of $<40 \times 10^6$ sperm/mL, considered to be the lower limit of the normal range
- Morphologic abnormalities appeared to be more prevalent among smokers, but did not differ significantly

- Current cigarette smokers had significantly higher mean endogenous androstenedione, estrone, and estradiol levels compared with nonsmokers
- Among smokers, a dose-response relationship was apparent for these hormones, with mean levels increasing with increased cigarette use

- Results failed to demonstrate a significant influence of tobacco use (smoking or chewing) on seminal parameters
- Although there was a reduction in volume, sperm density, and total count among tobacco users, the differences were statistically insignificant
- Tobacco use was not associated with impaired sperm quality in males selected from an idiopathically hypofertile population

Table 5.2   Continued

Study	Study period	Population	Definition of smoking
Saaranen et al. 1987	NR	190 men of reproductive age with no previous history of infertility	• Nonsmokers • Occasional smokers (1–15 cigarettes/day) • Regular smokers (16 cigarettes/day)
Dai et al. 1988	1980–1986	• Longitudinal study, 121 men from the Multiple Risk Factor Intervention Trial (MRFIT) • Case-control study, 163 MRFIT men who developed coronary heart disease, and 163 matched controls	Smokers averaged 34 cigarettes/day
Marshburn et al. 1989	1978–1982	445 men	None, <20 cigarettes/day, and 20 cigarettes/day
Oldereid et al. 1989	NR	350 men aged 20–58 years under fertility investigation	• Moderate smokers: 1–14 cigarettes/day • Heavy smokers: 15–40 cigarettes/day (203 smokers, 147 nonsmokers)
Close et al. 1990	NR	164 men from infertile couples referred to a urologic fertility clinic	• Number of packs/day • Nonsmokers included former smokers
Holzki et al. 1991	1984–1987	90 men retrospectively selected from an infertility clinic	• Nonsmokers had never smoked • Smokers: >10 cigarettes/day (50 smokers, 40 nonsmokers)
Lewin et al. 1991	November 1986–February 1988	675 men aged <45 years under infertility investigation	Smokers: >10 cigarettes/day (293 smokers, 382 nonsmokers)

Key results

- Sperm output was normal in both smokers and nonsmokers, but semen volume was smaller in heavy smokers than in nonsmokers
- Percentage change in sperm motility during 24 hours was different in men with different smoking habits: initially, sperm motility was better in heavy smokers than in those who smoked <16 cigarettes/day; the motility decreased more rapidly for heavy smokers than for nonsmokers, and the rapid decrease in the survival spermatozoa in smokers may be harmful with respect to fertility

- Serum total and free testosterone concentrations were positively correlated with cigarette smoking among the longitudinal sample and controls but not for the baseline serum from the coronary heart disease cases
- There was no association between either serum estradiol or estrone concentrations and cigarette smoking in this population

- Individuals who drank >4 cups of coffee/day and smoked   20 cigarettes/day had a lower proportion of motile spermatozoa and a higher proportion of dead cells compared with nonsmokers who did not drink coffee
- The effects of smoking on seminal volume, and of coffee drinking on sperm density, did not appear to be dose-dependent

- There were no significant differences in any aspect of sperm quality including DNA distribution among nonsmokers, moderate smokers, and heavy smokers
- Using conventional parameters, the study did not show that smoking has deleterious effects on sperm quality

- Current cigarette smokers, marijuana users, and heavy alcohol users showed greater numbers of leukocytes in the seminal fluid than did nonusers
- Cigarette smokers had lower sperm penetration assay scores than nonsmokers (median: 2.5 vs. 8.0, respectively)
- Compared with nonusers of cigarettes, users of marijuana or alcohol showed no decrease in sperm counts or motility, or in the percentage of oval sperm

- Smokers had sperm volumes significantly smaller than nonsmokers of the same age
- No additional effects on sperm parameters were found
- Cigarette smoking revealed no detrimental effect on spermatogenesis

- An overall reduction of sperm concentrations was seen in smokers compared with nonsmokers in relation to the effects of the number of cigarettes/day and number of pack-years (the number of years of smoking multiplied by the number of packs smoked per day) calculated to measure the cumulative effects of smoking
- No differences were observed in sperm motility and sperm penetration assay
- In men <45 years of age with sperm analyses showing motility >30%, concentration >10 x 10^6/mL, and normal morphology, smoking was not detrimental to fertility

Table 5.2   Continued

Study	Study period	Population	Definition of smoking
Chia et al. 1994	January 1991–June 1992	618 men undergoing infertility screening	• Nonsmokers had never smoked a cigarette or had quit for more than a year • Current smokers

Not all studies have reported positive associations between smoking and reduced fertility. A prospective study of fertility conducted by de Mouzon and colleagues (1988) with 1,887 couples found that reduced fertility associated with smoking was no longer statistically significant once possible confounders (method of birth control, attempting to conceive, oral contraceptive use as the most recent method, social class, prior deliveries, and year) were included in the analyses. Specifically comparing smokers with nonsmokers, cigarette smoking by the woman produced a 0.86 rate of relative fertility (95 percent CI, 0.63–1.19) and by the man a rate of 0.99 (95 percent CI, 0.85–1.14) after accounting for oral contraceptive methods, previous deliveries, social class, and prior attempts to conceive.

An increasing number of studies have used couples seeking treatment for infertility. These studies have consistently shown that treatment success is affected by smoking. Several studies documented that the success of in vitro fertilization (IVF) is significantly reduced among smokers compared with nonsmokers (Elenbogen et al. 1991; Pattinson et al. 1991; Hughes et al. 1992; Rosevear et al. 1992; Rowlands et al. 1992; Van Voorhis et al. 1996; El-Nemr et al. 1998), but other studies have not shown this reduction (Trapp et al. 1986; Sharara et al. 1994; Sterzik et al. 1996). Joesbury and colleagues (1998) examined the association of smoking by both partners with the likelihood of pregnancy within 498 consecutive IVF treatment cycles. Although female smoking had no association, male smoking was associated with a reduction in the probability of achieving a 12-week pregnancy. This study observed that age did modify the effect of smoking. For every one-year increase in age, there was a 2.4 percent reduction in the probability that the man's partner would achieve a 12-week pregnancy (Joesbury et al. 1998). The authors suggest that pre-zygotic genetic damage is the mechanism causing these reductions in a successful pregnancy.

Evidence Synthesis

Although mechanisms for an effect of smoking on sperm quality have been proposed, study findings are inconsistent for an association between active smoking and sperm quality. Some studies have shown positive associations, with a few demonstrating dose-response relationships with the amount smoked; others find no association. Many of the studies have potential flaws related to participant selection and confounding.

The evidence for a positive association between active smoking and subfertility and subfecundity in women consistently shows that active cigarette smoking reduces fecundity and increases the risk of primary infertility. The number of studies is substantial and various study designs and outcome measures have been used. Several studies demonstrated a dose-response relationship with the number of cigarettes smoked. Although the evidence is less consistent in

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Key results

- Smokers had a significantly poorer sperm density, a lower percentage of sperm with normal morphology, and a higher percentage of headpiece spermatozoa defects compared with nonsmokers
- Cigarette smoking appeared to affect sperm density and spermatozoa morphology, especially the headpiece
- A dose-response relationship between cigarette smoking and spermatogenesis is suggested based on calculated cigarette-years (the number of years of smoking multiplied by the number of cigarettes smoked per day): 0, 1–199, 200
- Sperm density (10^6/mL) shows a decreasing trend as cigarette-years increase. Differences are significant (p <0.0001) even after using ANCOVA to adjust for medical history, occupational exposure, age, and testicular volumes

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studies examining the impact of smoking on the success of IVF, these studies may be limited by inadequate adjustment for fertility-related confounders. Moreover, animal and human studies are beginning to provide an understanding of the mechanisms by which cigarette smoke or its components affect fertilization in females, pointing to the plausibility of this association. The evidence reviewed shows consistency, dose-response relationships, and appropriate temporality, and partially characterizes the mechanistic basis. Based on the evidence through 2000, the 2001 Surgeon General's report concluded that "women who smoke have increased risks for conception delay and for primary and secondary infertility" (USDHHS 2001, p. 307).

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality.

2. The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women.

Implications

Regarding smoking and sperm quality, future studies should also include more samples of men not seeking treatment for infertility, larger study populations, and the information to adjust for potential confounding factors such as occupational exposures (e.g., teratogens and toxins in the workplace) and health behaviors (e.g., caffeine, alcohol, or drug use). Women intending to become pregnant should be warned that their smoking reduces fertility; health care workers should be aware of the causal association of smoking by women with reduced fertility.

Table 5.3   Studies on the association between smoking and fertility in women

Study	Study period	Population	Definition of smoking
Tokuhata 1968	NR*	2,016 women from a death registry	• Number of cigarettes smoked • Tobacco habits data included chewing tobacco and using snuff
Baird and Wilcox 1985	1983	678 pregnant women who had stopped using birth control in order to get pregnant	• Smokers: 1 cigarette/day during at least the first month after stopping birth control • Nonsmokers: all others
Howe et al. 1985	1968–1974	17,032 white married women, aged 25–39 years, from the Oxford Family Planning Association contraceptive study	• Never smoked • Former smokers • Current smokers stratified by cigarettes/day (1–5, 6–10, 11–15, 16–20, 21)
Trapp et al. 1986	1984–1985	114 patients who underwent IVF†	Smokers or nonsmokers
de Mouzon et al. 1988	1977–1982	1,887 couples	• Nonsmokers did not smoke • Smokers: 1 cigarette/day
Suonio et al. 1990	1983	2,198 mothers 20 weeks pregnant	• Nonsmokers • Light smokers (1–4 cigarettes/day) • Heavy smokers (>4 cigarettes/day)
Elenbogen et al. 1991	NR	41 women aged <37 years suffering from mechanical infertility	• Nonsmokers • Smokers: >15 cigarettes/day

*NR = Data were not reported.
†IVF = In vitro fertilization.
‡OR = Odds ratio.

Key results

- Cigarette smokers had increased risks of infertility, reduced frequency of pregnancies, and an increased risk of fetal losses
- Risks of infertility and fetal losses were higher in those who developed breast and genitalia cancer, but were not further increased by smoking
- In contrast, the risks were lower in those with noncancerous diseases, but were elevated by smoking
- The husband's smoking history was independent of the association between the wife's smoking and reproductive histories

- Smokers were 3.4 times more likely to have taken more than a year to conceive compared with nonsmokers
- Fertility of smokers was estimated to be 72% of that for nonsmokers
- Heavy smokers experienced lower fertility rates than light smokers (57% and 75% of the pregnancy rate of nonsmokers, respectively)
- Fertility was not affected by the husband's smoking

- There was an inverse relationship between the age at stopping contraception and fertility, in both nulliparous and parous women, but the effect was greater in nulliparous women
- There was a dose-response relationship between smoking and decreased fertility: more cigarettes/day were associated with decreased relative fertility rates

- There were no significant differences in IVF outcomes (fertilization and pregnancy rates) between smokers and nonsmokers
- The rhodanide (SCN) concentrations in serum and follicular fluid were higher in smokers than in nonsmokers
- The influence of smoking on IVF is difficult to ascertain; IVF methods need to improve

- Cigarette smoking by both spouses was related to decreased fertility when considered independently, but the association did not remain significant when confounding variables were controlled
- The relationship between tobacco and subfertility is not clear, and if it exists, is very low
- The effects of tobacco on fertility found by different studies may be explained by behavioral factors related to tobacco use

- A significant deleterious effect of smoking on fecundity was observed, which increased with longer delays in conception
- The OR[‡] shifted from 1.1 at 6 months to 3.2 at 18 months for those who smoked 1–4 cigarettes/day; and from 1.6 to 2.0 for smokers of >4 cigarettes/day
- Among those who became successfully pregnant in 12 months, both maternal and paternal smoking increased the risk of conception delay (OR = 1.5 and 1.3, respectively), and the effect was potentiated by advancing age (OR = 2.3 and 1.6, respectively)

- Follicular fluid levels of estradiol were significantly lower in smokers than in nonsmokers
- Fertilization rates were lower for smokers (40.9 vs. 61.7%)
- Cigarette smoking had a detrimental effect on IVF and embryo transfer

Table 5.3   Continued

Study	Study period	Population	Definition of smoking
Pattinson et al. 1991	March 1984– March 1989	447 couples seeking IVF[†]	Both partners were asked if they smoked and if so, how many cigarettes/day
Hughes et al. 1992	March 1990–May 1991	222 couples undergoing consecutive IVF and embryo transfer	Women were classified as nonsmokers, smokers of 1–14 cigarettes/day, and smokers of 15 cigarettes/day
Laurent et al. 1992	December 1980–April 1983	2,714 randomly selected women aged 20–54 years; 483 had primary infertility and 2,231 served as controls	Smokers began smoking cigarettes before or during the period of unprotected inter- course (for the infertile cases) or before the first conception (for the controls)
Rosevear et al. 1992	1989–1991	45 women with tubal and other complica- tions of infertility	Smoking was determined by concentration levels of nicotine metabolite cotinine (less or more than 20 ng/mL) in ovarian follicular fluid
Rowlands et al. 1992	NR	Couples who received IVF	Smoking histories for both partners were recorded
Joffe and Li 1994	1958–1991	11,407 persons: 3,132 female and 2,576 male cohort members who had borne or fathered at least 1 live birth	Current smoking habits of the cohort member and partner, and the smoking habit of the cohort member for 12 months before conception of each ascertained pregnancy
Sharara et al. 1994	January 1991– December 1992	210 women from a general infertile population with 102 undergoing IVF	• Nonsmokers had never smoked cigarettes • Current cigarette smokers • Former smokers not currently smoking were excluded

[†]IVF = In vitro fertilization.
[§]CI = Confidence interval.

Key results

- There were no significant differences between smokers and nonsmokers in peak estradiol levels, the number of eggs retrieved, or fertilization or implantation rates
- The incidence of spontaneous abortion was higher in smokers (42%) than in nonsmokers (19%); consequently, the delivery rate per IVF cycle was significantly lower in smokers (11 of 124, 9%) than nonsmokers (40 of 236, 17%)
- There was no effect when only the husband was a smoker

- There were no differences in ovarian stimulation, peak estradiol levels, or the number of oocytes retrieved
- Heavy smokers had higher fertilization rates than nonsmokers (79.3 vs. 61.3%)
- The rate of embryo cleavage was retarded in a dose-dependent fashion: in smokers of 1–14 cigarettes/day, the likelihood of transferring an embryo at >4-cell stage was 0.87 (95% CI[§], 0.56–1.4); and in smokers of 15 cigarettes/day, the likelihood was 0.52 (95% CI, 0.31–0.88)
- No significant differences were noted in clinical outcomes following embryo transfer

- Smoking 1 pack/day (OR = 1.36) and starting to smoke (OR = 1.3) were significantly associated with increased infertility
- Smoking did not significantly increase the time required to conceive among infertile women
- Women should stop smoking when they are attempting to become pregnant

- Smoking (57%) is associated with reduced fertilization of eggs to about two-thirds of the normal rate for nonsmokers (75%)
- The median fertilization rates for high vs. low cotinine groups were 57% and 75%, respectively
- Analysis of individual fertilization rates gave medians of 75% (range 0–100) for the cotinine-undetectable group, and 57% (0–100) for the cotinine-detectable group (p <0.05, Kruskal Wallis)
- Women should be advised to stop or reduce smoking generally, especially before IVF

- There was a significant difference in fertilization rates among couples who were: nonsmokers, female only smokers, male only smokers, and both smokers
- Reduced numbers of mature oocytes and reduced pre-ovulatory estradiol concentrations were seen in the partners of men who smoked, but the differences were not significant

- Both the time to pregnancy and clinical subfertility were associated with smoking habits and educational levels of both partners
- A multivariate analysis showed that paternal smoking failed to enter the model if educational variables were also included (p >0.05 did not meet the criteria for inclusion)
- Maternal smoking affects fertility, but earlier reports of an apparent effect of paternal smoking may be due to confounding with socioeconomic status

- Smokers had an increased incidence of diminished ovarian reserves (12.31%) compared with age-matched nonsmoking controls (4.83%)
- Smokers with normal ovarian reserves had ovarian responses and pregnancy rates equivalent to nonsmoking controls
- A diminished ovarian reserve may be a principal mechanism reducing fecundity among women who smoke cigarettes

Table 5.3   Continued

Study	Study period	Population	Definition of smoking
Alderete et al. 1995	1959–1966	1,341 women who were primigravidas	• Smokers: 1 cigarette/day after discontinuing contraception • Nonsmokers: gravidas who had never smoked • To assess dose responses, light = 1–9 cigarettes/day, moderate = 10–19, heavy = 20
Bolumar et al. 1996	August 1991–February 1993	• Women aged 25–44 years randomly selected; the unit of analysis was the couple • Women at least 20 weeks pregnant recruited during prenatal visits (unit of analysis was a pregnancy) • More than 4,000 couples in each sample	• Cigarettes/day (1–10, 11) • For male partners, dichotomous data on smoking (yes/no) were available
Sterzik et al. 1996	NR	197 women aged 23–39 years from an IVF† program	• Nonsmokers: cotinine concentrations <20 ng/mL • Passive smokers : cotinine concentrations >20 ng/mL and <50 ng/mL • Active smokers: cotinine concentrations >50 ng/mL (68 nonsmokers, 26 passive smokers, 103 active smokers)
Van Voorhis et al. 1996	January 1989–July 1994	499 women treated at an assisted reproductive techniques program	• Smoking was determined by asking if women ever smoked and if yes, number of pack-years (number of packs of cigarettes smoked per day multiplied by the number of years the woman smoked) was ascertained • Nonsmokers (had never smoked) • Former smokers (had quit before their cycle) • Current (smoked during their assisted reproductive cycle)

†IVF = In vitro fertilization.

 Exposed to someone else's tobacco smoke.

Key results

- Smokers had about one-half the fertility (OR = 0.5–0.6) of nonsmokers and noncoffee drinkers for times to conception of 6 and 12 months, regardless of whether they drank coffee
- Nonsmoking coffee drinkers did not have decreased fertility compared with nonsmokers who did not drink coffee (adjusted OR = 1.0–1.2)
- Coffee drinking did not further increase the risk of delayed conception among smokers over the risk posed by smoking (OR = 0.6–0.8)

- Female smoking was associated with subfecundity both with the first pregnancy (OR = 1.7) and during the most recent waiting time to pregnancy (OR = 1.6)
- No significant association was found with male smoking

- There were no significant differences in fertilization and pregnancy rates among nonsmokers, passive smokers, and active smokers
- The serum estradiol levels were decreased significantly in women who smoked when compared with nonsmokers and passive smokers; decreased serum estradiol concentrations were not associated with adverse effects on fertilization and pregnancy rates in smokers
- There was no clinically detectable impairment of fertilization potential attributable to female smoking, and other factors have a greater influence on IVF outcomes

- Current and former smokers had reduced gonadotropin-stimulated ovarian function compared with nonsmokers
- Increased tobacco exposures were associated with decreased serum estradiol concentrations, decreased number of retrieved oocytes, and fewer embryos obtained
- Women who smoked during their treatment cycle had a 50% reduction in implantation and ongoing pregnancy rates compared with never smokers
- Cigarette smoking was associated with prolonged and dose-dependent adverse effects on ovarian function

Table 5.3   Continued

Study	Study period	Population	Definition of smoking
Curtis et al. 1997	1991–1992	2,607 planned pregnancies over the previous 30 years	• Nonsmokers did not smoke (former smokers who had quit smoking as of the year they started trying to conceive were treated as nonsmokers, except in analyses requiring former smokers to be examined separately) • Smoking was stratified by cigarettes/day (0, 1–5, 6–10, 11–20, >20) and pack-years (0, 0–5, >5–10, >10) • Data were also collected on ever smoked, current smoking habits, number of years smoked; and for those who quit, the year of cessation
El-Nemr et al. 1998	9-month period in 1995	173 women undergoing IVF[†]-embryo transfer cycle at a fertility center	• 108 nonsmokers, 65 smokers at the time of the interview • Cigarettes/day
Joesbury et al. 1998	January 1994– December 1995	385 couples, 498 IVF treatment cycles	• Nonsmokers included never and former smokers • Current smokers
Hull et al. 2000	April 1991– December 1992	14,893 pregnant women	• Cigarettes/day • Smokers were active, passive, or both

[†]IVF = In vitro fertilization.

Key results

- Cigarette smoking among women and men was associated with decreased fecundability (fecundability ratio 0.90 and 0.88, respectively)
- Caffeine consumption among women was not associated with decreased fecundability, even in higher amounts
- Alcohol use among women and men was not associated with fecundability

- Cigarette smoking in women appeared to significantly reduce their ovarian reserve and lead to poor responses to ovarian stimulation at an earlier age
- Women who smoked had a higher mean basal follicle stimulating hormone concentration and required a higher mean dosage of gonadotropins for ovarian stimulation than nonsmokers
- Compared with nonsmokers, smokers had a lower mean number of oocytes, and higher rates of abandoned cycles and total fertilization failure
- The difference in the clinical pregnancy rate per cycle, 16.9% for smokers vs. 21.3% for nonsmokers, was not statistically significant

- Male smoking interacted with age and was associated with a 2.4% decrease in the likelihood of achieving a 12-week pregnancy with every 1-year increase in age
- Ovarian reserves diminished with increasing age more significantly for female smokers than for nonsmokers
- The study failed to show that there was an elevated incidence of pregnancy loss among female smokers

- Active smoking by women was significantly associated with failure to conceive at >6 months (OR = 1.23 [95% CI, 0.98–1.49]) and at >12 months (OR = 1.54 [95% CI, 1.19–2.01]) after adjusting for confounding factors
- Compared with women who did not smoke, female passive smokers had significantly delayed conception of >6 months (OR = 1.17 [95% CI, 1.02–1.37]) and >12 months (OR = 1.14 [95% CI, 0.92–1.42]), after adjusting for confounding factors
- Active smoking by the men was significantly associated with failure to conceive within 6 months, after adjusting for confounding factors including the women's smoking. However, active smoking by men was not significantly associated with failure to conceive within 6 months
- Heavy smoking by men was independently associated with delayed conception, and delays lengthened with an increasing number of cigarettes smoked

Pregnancy and Pregnancy Outcomes

Epidemiologic Evidence

Smoking Patterns Among Women During Childbearing Years

National data for the United States indicate that somewhere between 13 percent (National Center for Health Statistics, reported in Guyer et al. 1999) and 17 percent (Substance Abuse and Mental Health Services Administration 2001) of pregnant women smoke. For 1998, the 2001 Surgeon General's report gives a figure of 12.9 percent based on birth certificate data (USDHHS 2001). The prevalence of pregnant women who smoked in 2001 was 12 percent, and the prevalence of teenage mothers aged 15 through 19 years who smoked during pregnancy was 17.5 percent in 2001 (Martin et al. 2002). The proportion of women who smoke during pregnancy has declined over the last 10 years; in 1990, 18 percent of women reported prenatal smoking (Guyer et al. 2000). At the same time, smoking among teenage mothers was increasing. In 1994, 16.7 percent of teenage mothers smoked during pregnancy, rising to 17.5 percent in 2001 (Martin et al. 2002). Since somewhere between 18 and 25 percent of women quit smoking once they become pregnant, the proportion of women who smoke around the time of pregnancy is greater than these numbers suggest (Lumley 1987; O'Campo et al. 1995).

Most information on smoking during pregnancy, including that obtained for studies on reproductive effects, comes from self-reports by the pregnant woman. In the United States, smoking during pregnancy is now widely viewed as unacceptable—that is, women are considered responsible for exposing the fetus to tobacco metabolites, and a number of researchers have noted that underreporting of smoking during pregnancy is common. High rates of underreporting have been reported in intervention trials. In a randomized trial from public health maternity clinics, Windsor and colleagues (1993) found a deception rate of 28 percent for self-reports provided at the end of pregnancy using salivary cotinine as a comparison. Underreporting can be a result of the social stigma associated with smoking or the typical change in patterns of smoking during pregnancy. Most women who smoke before pregnancy either quit or reduce their levels of smoking during pregnancy (O'Campo et al. 1995). Thus, if women reduce smoking levels as the pregnancy progresses, they may report the lowest smoking level rather than the greatest, or an average level over the course of their pregnancy. This underreporting, however, is likely to move any positive associations toward a null relationship as this type of misclassification will result in classifying heavy smokers as light smokers and classifying some true smokers as nonsmokers. Researchers have tried to address this problem by incorporating biochemical measures of tobacco exposure into their studies. Three studies showed that cotinine levels in blood collected along with self-reports during the prenatal period were more highly correlated with birth weight than were self-reported smoking levels (Haddow et al. 1987; English et al. 1994; Peacock et al. 1998).

Smoking and Ectopic Pregnancy

Ectopic pregnancy, a rare yet serious complication, occurs when implantation of the fertilized ovum takes place outside of the uterus, often in the fallopian tubes. The etiology of ectopic pregnancy is not fully known but involves the motility and patency of the fallopian tubes. Exposure to nicotine in rhesus monkeys has been shown to decrease tubal motility. Reduced motility may result in the fertilized ovum remaining in the tubes for a longer time which, in turn, may increase the chance of tubal implantation and ectopic pregnancy (Mattison et al. 1989). Cigarette smoking also has been associated with pelvic inflammatory disease, a strong risk factor for tubal pregnancy (Marchbanks et al. 1990). It is unclear whether this association is due to confounding factors such as more sex partners among smokers compared with nonsmokers, or to a direct biologic effect through suppressed immune function in smokers (Holt 1987).

Several studies report an increased risk of ectopic pregnancy among active smokers (Matsunaga and Shiota 1980; Handler et al. 1989; Coste et al. 1991; Kalandidi et al. 1991; Stergachis et al. 1991; Tuomivaara and Ronnberg 1991) (Table 5.4). ORs for active smokers compared with nonsmokers in these studies ranged from 1.3 to 2.5. Dose-response relationships have been reported in some studies (Handler et al. 1989; Coste et al. 1991) but not others (Phillips et al. 1992). Confounding is a potential source of bias when

examining maternal smoking and ectopic pregnancy, although most studies adjusted for some potential confounders (e.g., prior problems relating to fertility involving the fallopian tubes or prior infections). The association with smoking does not appear to represent confounding alone.

Smoking and Spontaneous Abortion

Fetal loss or spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation; some studies define spontaneous abortion as occurring before 28 weeks. Spontaneous abortions are extremely difficult to study, as most early fetal losses are underreported and unrecognized. As many as 50 percent of all pregnancies end in miscarriage, and 20 to 40 percent of all pregnancy losses may occur too early to be recognized or confirmed (Wilcox et al. 1988; Eskenazi et al. 1995a). Furthermore, the etiology of spontaneous abortions is multifactorial and not fully understood. Some early miscarriages result from chromosomal abnormalities in the developing embryo; others are related to factors associated with maternal age, the pregnancy, or exposures (e.g., occupational, alcohol consumption, or fever). There is evidence that smoking has a role in promoting spontaneous abortions, and various mechanisms have been proposed. Exposure to nicotine in sea urchins prevents the cortical granule reaction, which eliminates the entry of additional sperm into the egg. If this same process operates in humans, it may be a mechanism by which abnormalities in the developing embryo result in spontaneous abortions (Longo and Anderson 1970; Mattison et al. 1989). Several tobacco components and metabolites are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, carbon monoxide, and polycyclic aromatic hydrocarbons (Lambers and Clark 1996; Werler 1997).

Several studies have reported an increased risk of spontaneous abortion among smokers compared with nonsmokers; the reported ORs range from 1.2 to 3.4 (Kline et al. 1977; Stein et al. 1981; Armstrong et al. 1992; Dominguez-Rojas et al. 1994) (Table 5.5). Various potential confounding factors have been considered in these studies (USDHHS 2001). Dose-response relationships also have been reported (Stein et al. 1981; Armstrong et al. 1992). Armstrong and colleagues (1992) examined three strata of cigarette smoking and compared rates of early fetal loss among smokers and nonsmokers. ORs and CIs for spontaneous abortions for women smoking 1 to 9, 10 to 19, and 20 or more

cigarettes compared with nonsmokers were 1.07 (95 percent CI, 0.97–1.18), 1.22 (95 percent CI, 1.13–1.32), and 1.68 (95 percent CI, 1.57–1.79), respectively. Most studies of smoking have not provided an opportunity to explore the basis for a spontaneous abortion. In a study of 2,305 karyotyped cases of miscarriage that separated chromosomally normal from abnormal fetuses, Kline and colleagues (1995) found a higher risk of aborting a chromosomally normal fetus among heavier smokers (>14 cigarettes per day) compared with nonsmokers (OR = 1.3 [95 percent CI, 1.1–1.7]). Data from a study of women undergoing IVF indicate that smokers have a higher rate of spontaneous abortions compared with nonsmokers, 42 percent versus 19 percent, respectively (Pattinson et al. 1991).

Some studies have found no association between smoking and spontaneous abortions (Sandahl 1989). In a review of 13 U.S. and European studies, DiFranza and Lew (1995) reported fairly consistent findings across studies despite differences in design, sample selection, and adjustments for confounding. Pooled relative risks (RRs) and ORs were 1.2 (95 percent CI, 1.19–1.3) for cohort studies and 1.32 (95 percent CI, 1.18–1.48) for case-control studies for smokers compared with nonsmokers.

Smoking and Pregnancy Complications

Placenta Previa

Placenta previa occurs when the maturing placenta is close to the cervical os or completely obstructs the os. The etiology of placenta previa is still largely unknown. Some researchers claim that placental enlargement among smokers increases the chance that the placenta implants near or at the cervical os. However, others have found that placentas in smokers and nonsmokers are similar in size, so differences in placental size may be due to factors other than smoking (Zhang and Fried 1992). Zhang and Fried (1992) also note that a detection bias may lead to the greater ascertainment of placenta previa among smokers and will consequently inflate this association in many studies.

Placenta previa consistently has been found to be more frequent in smokers compared with nonsmokers; ORs range from 1.3 to 4.4 with most estimates around 2.3 (Kramer et al. 1991; Williams et al. 1991b; Zhang and Fried 1992; Handler et al. 1994; Chelmow et al. 1996) (Table 5.6). A few studies have examined dose-response associations based on the number of cigarettes smoked per day; one reported a significant dose-dependent relationship (Monica and Lilja 1995)

Table 5.4   Studies on the association between maternal smoking and ectopic pregnancy

Study	Study period	Population	Definition of smoking
Matsunaga and Shiota 1980	January 1962– December 1974	3,614 human embryos derived from artificial termination of pregnancy	Data were not reported
Daling et al. 1987	1979–1981	340 women: 170 with primary infertility and 170 matched controls	Smoking history included number of cigarettes/day, age at smoking initiation, and age at cessation if they had quit
Handler et al. 1989	1983–1987	4,921 women: 634 with ectopic pregnancy, and 4,287 controls who delivered a single live-born infant	• Maternal smoking was recorded as a dichotomous variable (yes/no), and as a continuous variable (number of cigarettes/day) • Four levels of smoking were considered: <10 cigarettes/day, 10–19, 20–29, and 30
Coste et al. 1991	During 1998	Women aged 15–44 years attending maternity hospitals	Smokers were classified by the number of cigarettes/day at the time of conception
Kalandidi et al. 1991	1986–1987	203 women: 70 with ectopic pregnancy and 133 controls	Never, former, and current smokers
Stergachis et al. 1991	October 1981– September 1986	1,001 women: 274 who were hospitalized for tubal pregnancy and 727 controls	• Never smoked cigarettes • Ever smoked • Current and former smokers
Tuomivaara and Ronnberg 1991	1977–1981	929 infertile couples examined and treated for complications	Smoking or not smoking

*Pack years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
†CI = Confidence interval.
‡Primary infertility due to tubal conditions. The focus of this study is on women with primary infertility (those who have never conceived despite unprotected intercourse for at least one year), diagnosed by the patient's physician and attributed to a tubal condition on the basis of an abnormal hysterosalpingogram or a tubal abnormality identified during surgery.
§RR = Relative risk.
 OR = Odds ratio.

Key results

- A number of maternal characteristics including smoking and drinking were significantly associated with either ectopic or myomatous pregnancy
- Ectopic pregnancy was significantly associated with lowered parity, previous ectopic pregnancy, and maternal smoking and drinking

- Among current smokers, women who had more than 5 pack-years* of exposure had 4.2 (95% CI[†], 1.8–10.2) times the risk of tubal infertility[‡] than women who had never smoked
- Among women who used both an intrauterine device and smoked, the RR[§] for tubal infertility was 6.7 (95% CI, 1.4–32.2)
- There is a possibility that both smoking and tubal infertility are related to factors not addressed in the study, such as exposure to sexually transmitted infections that can cause tubal damage

- Women who reported smoking during pregnancy had a greater than twofold risk of ectopic pregnancy (OR = 2.5 [95% CI, 1.9–3.2]) compared with women who had never smoked
- The estimated RR rose from 1.4 (95% CI, 0.8–2.5) for a woman smoking <10 cigarettes/day to 5.0 (95% CI, 2.9–8.7) at 30 cigarettes/day
- The dose-response relationship supports the argument that smoking may be a causal factor in ectopic pregnancy

- Maternal cigarette smoking was associated with an increased risk of ectopic pregnancy (OR = 1.3–2.49)
- The partner's smoking was not associated with ectopic pregnancy

- Tobacco smoking significantly increased the risk of an ectopic pregnancy, RR = 2.35 (95% CI, 1.19–4.67)

- The RR of tubal pregnancy associated with ever having smoked cigarettes was 1.3 (95% CI, 1.0–1.8)
- Those who smoked at the time of conception had a 40% increase in the risk of tubal pregnancy compared with never smokers (95% CI, 1.0–2.0)
- Results support earlier reports of a greater risk of tubal pregnancy associated with current or recent maternal smoking

- Previous ectopic pregnancy, an industrial occupation, and smoking reduced fecundity and increased the risk of ectopic pregnancy
- The strongest risk of ectopic pregnancy was associated with a previous tubal pregnancy (9.9-fold risk)
- Although current smokers had an increased risk of infertility and ectopic pregnancy, smoking was not a significant indicator in the stepwise logistic analysis, so it could be of secondary importance

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Table 5.4   Continued

Study	Study period	Population	Definition of smoking
Phillips et al. 1992	July 1986–April 1987	170 pregnant women: 69 with tubal ectopic pregnancy and 101 controls	• Current smokers (number of cigarettes/day smoked during the month of conception, and the total number of years of smoking) • Not currently smoking • Former smokers (smoked before the month of conception)

while others were only suggestive (Handler et al. 1994; Chelmow et al. 1996). Most recent studies adjusted for potential confounders including age, parity, prior caesarean sections, and prior pregnancy terminations.

Placental Abruption

A placental abruption occurs when the normally implanted placenta prematurely separates from the wall of the uterus, and it is associated with high rates of preterm deliveries, stillbirths, and early infant deaths. The etiology of this rare pregnancy complication is not fully known, but risk factors are trauma, multiple births, uterine tumors, advanced maternal age, hypertensive disorders, history of uterine scarring, and prior history of placental abruption (Ananth et al. 1996). Active smoking during pregnancy results in decreased intervillous placental blood flow (Lambers and Clark 1996). Smoking has been proposed as a link to placental abruptions through vasoconstriction and underperfusion around the site of placental implantation, leading to necrosis and hemorrhage (Lehtovirta and Forss 1978).

Most studies have found an increased risk of placental abruption associated with active smoking during pregnancy (Voigt et al. 1990; Williams et al. 1991a; Raymond and Mills 1993; Spinillo et al. 1994a) (Table 5.7). Studies have reported adjusted ORs ranging from 1.4 to 2.4; some report a dose-response relationship, with risks increasing for heavy smokers compared with light smokers (Ananth et al. 1996).

Preeclampsia and Eclampsia

Preeclampsia is a hypertensive disorder developed during pregnancy with proteinuria and edema. The more severe form, eclampsia, includes one or more seizures and/or coma. Preeclampsia is a severe disorder in pregnancy that is associated with maternal mortality, intrauterine growth retardation (IUGR), and preterm birth. Smoking has been negatively associated with hypertensive disorders during pregnancy, although the underlying mechanism is uncertain (Salafia and Sheverick 1999).

Studies on smoking during pregnancy consistently find reduced rates of preeclampsia among smokers compared with nonsmokers (Marcoux et al. 1989; Eskenazi et al. 1991; Klonoff-Cohen et al. 1993; Spinillo et al. 1994b; Sibai et al. 1995; Cnattingius et al. 1997) (Table 5.8). ORs for smokers range from 0.45 to 0.71. Some studies have reported a dose-response relationship, with the lowest rates of preeclampsia among heavier smokers compared with light smokers and nonsmokers (Marcoux et al. 1989).

Preterm Premature Rupture of Membranes

The rupture of the amniotic sac before the onset of labor is called a premature rupture of membranes (PROM). When PROM occurs before 37 weeks of gestation, it is referred to as preterm PROM. PROM is multifaceted in its etiology, possibly involving multiple steps before the membranes rupture (French and McGregor 1996). Potential determinants of PROM include infections, inflammation, physical stress, disturbance of collagen metabolism, and health behaviors such as nutrition and smoking. Cigarette smoke components may increase the risk of PROM through several mechanisms, including disruption of the cytokine system, impairment of immune function in the reproductive tract, and promotion of inflammatory mechanisms (French and McGregor 1996). It also is possible that impaired nutrition, specifically the reduction of

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Key results

- When current smokers were compared with never smokers and former smokers, the adjusted OR for smoking associated with ectopic pregnancy was 2.4 (95% CI, 1.2–5.1)
- Cigarette smoking may be associated independently with ectopic pregnancy, and smoking cessation before the month of conception may reduce this risk

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available nutrients and cellular amino acid uptake, is involved in PROM (French and McGregor 1996). However, confirmation of any one of these pathways from smoking to PROM awaits future studies. It is likely that preterm PROM and non-preterm PROM have somewhat different etiologies (French and McGregor 1996).

Preterm PROM has been studied in relation to smoking during pregnancy (Harger et al. 1990; Williams et al. 1992; Spinillo et al. 1994d), with most studies finding an elevated risk (Table 5.9). Adjusted ORs for smokers range from 1.6 to 2.1, and dose-response relationships of risk with daily smoking levels have been investigated but with mixed results (Williams et al. 1992; Spinillo et al. 1994d). Studies that have shown no increased risk for smokers generally had small sample sizes and inadequate consideration of potential confounding (Harger et al. 1990).

Shortened Gestation

A shortened gestational period can be measured in two ways: by the number of days or weeks of pregnancy and by a preterm delivery, defined as less than 37 weeks of completed gestation. One major mechanism whereby active smoking leads to a shortened gestation is through pregnancy complications. Smoking during pregnancy increases the risk for and exacerbates several pregnancy complications such as PROM, infections, placenta previa, and placental abruption, which in turn are associated with shortened gestations. When a shortened gestation is measured in continuous days, differences between smokers and nonsmokers are on the order of two to three days.

A shortened gestation attributable to smoking, measured by a preterm delivery, has been reported in numerous studies. In a meta-analysis of 20 prospective studies, Shah and Bracken (2000) reported an overall adjusted OR for a preterm delivery of 1.27 (95 percent CI, 1.21–1.33) for smokers compared with nonsmokers. Not all of the 20 studies reported a significantly elevated risk for smokers compared with nonsmokers, and very few accounted for complications such as PROM, infections, placenta previa, or others. Shiono and colleagues (1986b) studied preterm delivery risks for light and heavy smokers, stratifying their sample by the presence of pregnancy complications (PROM, placenta previa, or placental abruption) and no complications. These authors reported that the risk of a preterm delivery was elevated both among the subsamples with complications and within the sample with no pregnancy complications, suggesting that prenatal smoking may act to increase rates of preterm deliveries by causing complications and also by a more direct pathway.

Birth Weight and Intrauterine Growth Retardation

Key outcomes in relation to maternal smoking during pregnancy include birth weight, LBW, and IUGR. Infants with LBW, defined as weighing less than 2,500 g at birth, have a higher risk of subsequent infant morbidity, mortality, and longer-term childhood and adult adverse consequences. IUGR, as the name implies, is reduced fetal physical growth during gestation. One indicator of IUGR, small for gestational age, is often defined as the lowest 10 percent of birth weights (or sometimes the lowest 5 percent) for any gestational age. A number of possible mechanisms leading to reductions in birth weight and fetal growth as a result of smoking have been suggested.

Table 5.5   Studies on the association between maternal smoking and spontaneous abortion

Study	Study period	Population	Definition of smoking
Kline et al. 1977	April 1974– August 1976	894 women aged 18–40 years, who were admitted to public services for spontaneous abortions (574 cases and 320 controls)	• Nonsmokers did not smoke during pregnancy • Smokers smoked during pregnancy (0–19 cigarettes/ day or 20 cigarettes/day)
Stein et al. 1981	6 years	4,088 women: 2,748 with spontaneous abortion, and 1,340 controls who carried their pregnancies to 28 weeks or more	• Never smokers • Current smokers • Former smokers
Sandahl 1989	Data were not reported	2,747 pregnant women who consulted a hospital: 610 with spontaneous abortion, 800 with induced abortion, and 1,337 deliveries	Two different definitions of smoking: (1) smokers and nonsmokers, (2) smoked >10 cigarettes/day, and nonsmokers
Armstrong et al. 1992	1982–1984	56,000 women who had a delivery or a spontaneous abortion in a hospital	Number of cigarettes/day
Dominguez-Rojas et al. 1994	January 1989– June 1991	711 female hospital workers aged 20–41 years	• Nonsmokers • Smokers: 1–10 cigarettes/day and >10 cigarettes/day
Kline et al. 1995	1974–1986	6,609 women: 2,376 with spontaneous abortion and 4,233 controls	• Never smoked • Former smokers • Current smokers (1–13 cigarettes/day) • Current smokers (14 cigarettes/day)

*OR = Odds ratio.

Key results

- Women who had aborted spontaneously reported smoking during pregnancy more often (OR* = 1.8) than those who delivered after 28 weeks of gestation
- Findings suggest that the association between spontaneous abortion and smoking status is lower in women with a history of two or more spontaneous abortions than in women without previous multiple abortions
- This trend should be confirmed through independent data before making interpretations

- There was a dose-response relationship between an increased risk of spontaneous abortion and the number of cigarettes/day
- The OR of spontaneous abortion increased by 46% for the first 10 cigarettes smoked and 61% for the first 20 cigarettes smoked
- The OR of spontaneous abortion for a woman who smoked 1 pack/day and who drank alcohol daily was 4.08 times more than for an abstinent nonsmoker
- Findings suggest that smoking during pregnancy but not before conception is associated with spontaneous abortion

- There was no significant effect of smoking on miscarriage; the only trend was that smokers had a slightly reduced OR for miscarriage
- In late miscarriages (week 20 or later), there is a tendency for an OR above 1, but this finding is based on a small number of pregnancies and is not statistically significant

- The OR for spontaneous abortion increased by a factor of 1.2 for each 10 cigarettes/day
- Alcohol consumption was also associated with an elevated risk for spontaneous abortion; the OR increased by a factor of 1.26 for each drink/day
- The association between coffee consumption and spontaneous abortion was weaker but statistically significant; the OR increased by a factor of 1.1 for each cup/day

- Tobacco and caffeine were clear risk factors for spontaneous abortion
- There was a dose-response relationship between maternal smoking and spontaneous abortion: the adjusted OR for 11 cigarettes/day was 3.35 (95% confidence interval, 1.65–6.92)

- Cigarette smoking during pregnancy was associated with chromosomally normal spontaneous abortions
- Both former and current smoking were associated inversely with trisomic loss in women under 30 years of age and positively in older women

Table 5.6   Studies on the association between maternal smoking and placenta previa

Study	Study period	Population	Definition of smoking
Kramer et al. 1991	1984–1987	3,020 singleton births: 598 with placenta previa and 2,422 controls	• Smokers: mothers who smoked at any time during pregnancy • Nonsmokers: mothers who did not smoke at any time during pregnancy
Williams et al. 1991b	August 1977–March 1980	12,420 mothers: 69 with placenta previa and 12,351 controls	• Smokers ever smoked during first or second trimester • Three levels of cigarette smoking: nonsmokers, smokers of 1–9 cigarettes/day, and smokers of 10 cigarettes/day • Three levels of smoking duration: never smokers, smokers for 1–5 years, and smokers for 6 years
Zhang and Fried 1992	1988–1989	4,646 women from birth certificate data from 1 state: 766 women with placenta previa and 3,880 controls	• Smoking during pregnancy • Average number of cigarettes/day
Handler et al. 1994	1988–1990	3,036 women: 304 with placenta previa and 2,732 controls	• Maternal smoking was recorded as a dichotomous variable (yes/no), and as a continuous variable (number of cigarettes/day) • Women who had quit smoking were included in the "smoking yes" category
Monica and Lilja 1995	1973–1990	1,825,998 infants from a birth registry	Women were classified by cigarette smoking during pregnancy as nonsmokers, smokers of <10 cigarettes/day, and smokers of 10 cigarettes/day
Chelmow et al. 1996	July 1992–March 1994	128 pregnant women: 32 with placenta previa and 96 controls	• Never, former, and present smokers • Light smokers: <1 pack/day • Heavy smokers: 1 pack/day

*OR = Odds ratio.
†CI = Confidence interval.

Key results

- Maternal smoking approximately doubled the risk of placenta previa after adjusting for maternal age (OR* = 2.1 [95% CI†, 1.7–2.5])
- The association between maternal smoking and placenta previa did not alter when other confounding variables were adjusted for including marital status, parity, gravidity, previous cesarean section, and both previous spontaneous abortions and elective abortions

- Women who smoked during the first two trimesters of pregnancy had a 90% increase in risk for placenta previa (OR = 1.9 [95% CI, 1.2–3.0]) than women who did not smoke during pregnancy
- Compared with never smokers, women who smoked throughout pregnancy had a threefold increase in risk for placenta previa (OR = 3.1 [95% CI, 1.2–8.1])
- The duration of smoking was not an independent risk factor for placenta previa when smoking during pregnancy was considered

- Although maternal smoking during pregnancy might affect placenta previa, the magnitude was substantially smaller than previously reported
- After potential confounders such as maternal age, race, gravidity, parity, and previous pregnancy terminations were controlled for, the OR was 1.29 (95% CI, 1.05–1.58) with slight dose-response gradients

- A dose-response relationship between smoking cigarettes and placenta previa was observed independently of other known risk factors
- Pregnant women who smoked >20 cigarettes/day were more than two times more likely to experience placenta previa compared with nonsmokers (OR = 2.3 [95% CI, 1.5–3.5])
- Pregnant women who used cocaine were 1.4 times (95% CI, 0.8–2.4) as likely to experience placenta previa as nonusers

- Maternal smoking was an independent risk factor for placenta previa. The OR for placenta previa and maternal smoking compared with women without placenta previa was 1.53 (95% CI, 1.4–1.67) for all smokers
- The effect of smoking on the risk of having placenta previa increased with increasing parity but did not differ in the maternal age groups
- A dose-response relationship between the number of cigarettes/day during pregnancy and the risk of placenta previa was indicated

- Current cigarette smoking was associated with a 2.6- to 4.4-fold increased risk of placenta previa
- A dose-response relationship was suggested: compared with never smokers, the OR for light smokers was 2.2 (95% CI, 0.87–7.83) and for heavy smokers 4.0 (95% CI, 0.69–93.1)

Table 5.7   Studies on the association between maternal smoking and placental abruption

Study	Study period	Population	Definition of smoking
Lehtovirta and Forss 1978	NR*	12 healthy women aged 19–31 years, 35–40 weeks pregnant	All participants had smoked cigarettes before but not during pregnancy
Voigt et al. 1990	1984–1986	3,412 singleton births: 1,089 with abruptio placentae and 2,323 controls	Smokers smoked at any time during pregnancy
Williams et al. 1991a	1977–1980	1,400 women: 143 with abruptio placentae and 1,257 controls	NR
Raymond and Mills 1993	1974–1977	30,681 singleton pregnancies at 28 weeks of gestation	• Smokers or nonsmokers unless otherwise noted • Categorized by packs/day (0, <0.5, 1, 1.5) • Heavy smokers (1 pack/day)
Spinillo et al. 1994a	1985–1991	781 women: 55 with abruptio placentae, and 726 controls who delivered between 24 and 36 weeks of gestation	• Nonsmokers • Former • <10 cigarettes/day • 10 cigarettes/day
Ananth et al. 1996	January 1986–December 1992	61,667 women seeking antenatal care from hospitals	Smokers had smoked during pregnancy

*NR = Data were not reported.
†RR = Relative risk.
‡CI = Confidence interval.
§OR = Odds ratio.

Key results

- Smoking caused an acute reduction in intervillous blood flow of the human placenta in near-term pregnancy
- Repeated decreases in intervillous blood flow could explain growth retardation of the fetus and other pregnancy-related complications in women who smoke
- A possible effect of nicotine was also seen in accelerated heart rate and elevated blood pressure during smoking

- Smoking was associated with placental abruption (RR[†] = 1.6 [95% CI[‡], 1.3–1.8])
- The association with small for gestational age (SGA) status was identical for smokers and nonsmokers
- The increase in SGA infants among women whose pregnancies were complicated by abruption was not explained by maternal smoking

- Lifestyle factors associated with abruptio placentae in univariate analyses include maternal cigarette smoking, marijuana use, and alcohol consumption during pregnancy
- Although the association of cigarette smoking during pregnancy was of borderline significance (OR[§] = 1.5 [95% CI, 1.0–2.2]), the risk of abruption rose with increased levels of smoking

- Each pack of cigarettes smoked/day increased the risk of placental abruption by 40% (OR = 1.39 [95% CI, 1.09–1.79])
- If abruption occurred, the perinatal mortality rate was substantially higher in offspring of women who smoked 1 pack/day than in offspring of nonsmokers (RR = 2.53 [95% CI, 1.14–5.61])
- Heavier smoking increased the risk of both abruption and perinatal death

- Abruptio placentae was associated with a low number of antenatal visits, smoking during pregnancy, hypertension, intravenous drug abuse, and a history of recent abdominal trauma
- Since abruption is highly associated with low gestational age, and smoking is a primary risk factor for preterm delivery, the increased rate of preterm deliveries among smokers may in part account for the correlation between smoking and abruptio placentae

- Smokers had a RR of 2.05 for abruption and 1.36 for placenta previa compared with nonsmokers (RR = 1.0)
- Cigarette smoking was not associated with uterine bleeding of unknown etiology

Table 5.8   Studies on the association between maternal smoking and preeclampsia

Study	Study period	Population	Definition of smoking
Marcoux et al. 1989	1984–1986	928 women: 172 with preeclampsia, 251 with gestational hypertension, and 505 controls	• Never smokers had never smoked • Former smokers stopped smoking at any time before pregnancy • Smokers smoked 1 cigarette/day at the beginning of the pregnancy
Eskenazi et al. 1991	1984–1985	271 pregnant women: 139 women with preeclampsia and 132 controls with no hypertensive pregnancy disorder	Smoking habits were classified as yes/no
Klonoff-Cohen et al. 1993	January 1984–December 1986	225 women aged 15–35 years: 110 nulliparous women with preeclampsia and 115 healthy nulliparous women	Smoking was determined by (1) lifetime smoking history (ever smoked/never smoked); and (2) smoking during pregnancy (smoked/did not smoke)
Spinillo et al. 1994b	1990–1992	585 pregnant women who had prenatal care and delivered at a hospital	• Never smoked • Smoked <10 cigarettes/day • Smoked 10 cigarettes/day
Sibai et al. 1995	Data were not reported.	2,947 healthy women with a single fetus	• Never smoked or had not smoked for >1 year • Quit at the start of pregnancy • Continued smoking
Cnattingius et al. 1997	1987–1993	317,652 women aged 15–34 years who had had a single birth	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: 10 cigarettes/day

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.

Key results

- Compared with women who had never smoked, women who were smokers at the onset of pregnancy had a reduced risk of preeclampsia (RR* = 0.51 [95% CI†, 0.34–0.77])
- The protective effect of smoking on preeclampsia was stronger for women who continued to smoke after 20 weeks of pregnancy
- While smoking tended to reduce the risk of gestational hypertension, the effect was less evident than that of preeclampsia

- Smoking had a protective effect on preeclampsia (adjusted OR‡ = 0.45 [95% CI, 0.18–1.1]) in both multi-parous and nulliparous women
- High body mass, working during pregnancy, and a family history of hypertension were significant risk factors for preeclampsia

- Smoking during pregnancy was not associated with preeclampsia (OR = 0.71 [95% CI, 0.33–1.5]) after adjusting for confounding variables
- There was no evidence of a dose-response relationship with a reduced risk for heavy smokers (nonsmokers = 0 packs/day, light smokers = <1/2 pack/day, heavy smokers = >1/2 pack/day)
- To identify dose-response relationships, smokers were divided into the following categories: 0 packs, <1/2 pack/day, and 1/2 pack/day; adjusted ORs = 0.65 (95% CI, 0.27–1.55) for light smokers and 0.88 (95% CI, 0.23–3.28) for heavy smokers, compared with nonsmokers; these ORs reflect a slight inverse trend where heavy smokers had a lower reduction in risk than light smokers

- Smoking during pregnancy was a significant protective factor against the occurrence of preeclampsia (adjusted OR = 0.5 [95% CI, 0.28–0.8])
- A history of preeclampsia in previous pregnancies, low educational level, a body mass index >24, and maternal blood group AB were factors independently associated with increased risks of preeclampsia
- The study confirms that smoking during pregnancy reduces the risk of preeclampsia; however, the harmful consequences of smoking on pregnancy outcomes far outweigh this risk reduction

- There was a significant inverse relationship between cigarette smoking and preeclampsia when smoking history was dichotomized between current or recent smokers, and those who had never smoked or had quit at least a year earlier
- Findings indicate that cigarette smoking during pregnancy is associated with a reduced incidence of preeclampsia
- The highest incidence of preeclampsia was among women who had never smoked (5.9%), and the lowest incidence was among those who had quit at the start of pregnancy (2.7%)

- Maternal smoking was associated with significantly reduced risks of mild and severe preeclampsia (RR = 0.6 and 0.5, respectively)
- In pregnancies with severe preeclampsia, smoking 10 cigarettes/day was associated with increased rates of perinatal mortality (from 24–36 per 1,000), abruptio placentae (from 31–67 per 1,000), and small for gestational age (SGA) infants (from 28–68%)
- Smokers in whom preeclampsia develops have very high risks of perinatal mortality, abruptio placentae, and SGA infants

Table 5.9   Studies on the association between maternal smoking and premature rupture of membranes

Study	Study period	Population	Definition of smoking
Harger et al. 1990	1982–1983	594 women: 341 women with PROM* and 253 controls	• Cigarette smoking only • Nonsmokers • Stopped before pregnancy • Stopped during pregnancy • Current smokers
Williams et al. 1992	August 1977– March 1980	3,047 mothers who delivered at 1 hospital: 307 with PROM, 488 preterm non-PROM mothers, and 2,252 controls	Average number of cigarettes/day
Spinillo et al. 1994d	1988–1992	405 pregnant women: 138 diagnosed with idiopathic premature membrane rupture and 267 controls	Data were not reported

*PROM = Premature rupture of membranes.
†OR = Odds ratio.

On the basis of animal studies, it appears that nicotine acts on the respiratory and central nervous systems of the fetus and concentrates in maternal and fetal blood, amniotic fluid, and breast milk (Lambers and Clark 1996). The physiologic effects of tobacco on fetal growth may result from the vasoconstrictive effects of nicotine on the uterine and umbilical arteries and an increase in carboxyhemoglobin, leading to reduced oxygenation of the fetus (Lambers and Clark 1996; Werler 1997). Nicotine may have a direct toxic effect on the fetal cardiovascular system resulting in reduced blood flow (Bruner and Forouzan 1991). Abstaining from smoking for 48 hours during the third trimester increased the available oxygen to the fetus by 8 percent (Davies et al. 1979). Cadmium from cigarette smoke accumulates in the placenta and leads to morphologic and functional impairment (Sikorski et al. 1988). The fetus is likely exposed to the cadmium because this element has been detected in cord blood (Chatterjee et al. 1988).

Some researchers have argued against a nutritional effect of smoking on reduced fetal weight and size; smoking mothers have been found to eat more than nonsmoking mothers, and an increased energy intake does not prevent IUGR (Muscati et al. 1996).

Furthermore, tricep and subscapular skinfold measurements of infants of smokers were found to be normal and/or similar to those of infants of nonsmoking mothers (Harrison et al. 1983). In fact, infants of smokers lose lean body mass and not adipose tissue, which is consistent with the hypothesis that maternal nutrition is not a mediator of this effect. Hypoxia has been suggested as mediating part of this process (Harrison et al. 1983).

The primary mechanism by which birth weights are reduced among infants of smokers compared with those of nonsmokers is through fetal growth restriction. Birth weight and LBW, however, were often examined for research purposes, as both are available and reliably reported for nearly all infants. Accurate determination of IUGR, however, requires an estimate of the gestational age of the infant, which is subject to greater uncertainty and misreporting.

Reported birth weight differences between infants of smokers and infants of nonsmokers are surprisingly consistent across studies and populations (Simpson 1957; Butler et al. 1972; D'Souza et al. 1981; Sexton and Hebel 1984; Backe 1993; Bardy et al. 1993; Wilcox 1993; Ellard et al. 1996) (Table 5.10). On average, women who smoke throughout their pregnancies

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Key results

- Current smoking, antepartum vaginal bleeding in more than one trimester, and previous preterm delivery were independent risk factors for preterm PROM
- The OR[†] for current smoking was 2.1 (95% CI[‡], 1.4–3.1)
- Smoking cessation by pregnant women may reduce the risk of preterm PROM

- The RR[§] of preterm PROM for women who reported ever having smoked during pregnancy compared with nonsmokers was 1.6 (95% CI, 1.1–2.4)
- No gradient between the number of cigarettes/day and the risk of preterm PROM was observed
- Women who smoked during pregnancy had an increased risk of preterm non-PROM (adjusted OR = 2.1 [95% CI, 1.4–3.1])

- Previous preterm deliveries, preeclampsia, low social class, maternal smoking, high body mass index, 1st and 2nd–3rd trimester hemorrhages, maternal anemia, and incompetent cervix were significant risk factors for preterm PROM
- Cigarette smoking and reproductive history were significant risk factors for both early (<32 weeks) and late (32 weeks) PROM

[‡]CI = Confidence interval.
[§]RR = Relative risk.

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have infants who weigh about 200 g less than infants of women who do not smoke during pregnancy. Women who quit smoking early in their pregnancy have infants with similar weights to infants of non-smokers (USDHHS 1990). Thus, the evidence on birth weights after smoking cessation by the mother supports the hypothesis that smoking contributes to lighter infants. Numerous studies also document the association between active smoking during pregnancy and LBW (Hopkins et al. 1990; McDonald et al. 1992; Mainous and Hueston 1994). Only a few studies have not found an association between lower birth weights among smoking compared with nonsmoking mothers, and numerous studies have demonstrated a dose-response relationship with the number of cigarettes smoked and the degree of reduction in birth weights. Studies with biochemically measured smoking exposures (e.g., cotinine levels) also have confirmed, in an even stronger dose-response pattern than that seen from self-reported data, the relationship between pre-natal smoking and birth weight (Haddow et al. 1987; Bardy et al. 1993; Li et al. 1993; Eskenazi et al. 1995b; Peacock et al. 1998).

The greatest risk of subsequent mortality and morbidity is among infants born with very low birth weight (VLBW), or weight at birth of less than 1,500 g. VLBW occurs in approximately 3 percent or fewer births; thus, very few studies have a large enough sample size to be able to break out VLBW infants to examine the association with smoking. Hopkins and colleagues (1990) examined the association between smoking and VLBW for births in Ohio for 1989 and reported elevated risks (adjusted OR = 1.4 and population attributable risk = 8.4 percent) among smokers compared with nonsmokers. More recent reviews, however, suggest that the effect of smoking during pregnancy on birth weight is primarily on infants who weigh around 2,500 g and that smoking does not substantially increase the risk of VLBW (Shiono and Behrman 1995; Strobino 1999). Further studies are needed to determine whether and how smoking during pregnancy is related to VLBW births.

The association between smoking and IUGR also has been demonstrated in a number of studies (Cnattingius 1989; Ferraz et al. 1990; Wen et al. 1990; McDonald et al. 1992; Backe 1993; Bakketeig et al. 1993; Lieberman et al. 1994; Spinillo et al. 1994c) (Table 5.10).

Table 5.10 Studies on the association between maternal smoking, birth weight, and intrauterine growth retardation

Study	Study period	Population	Definition of smoking
Simpson 1957	1953–1955	7,499 obstetric patients from 3 hospitals	• Nonsmokers did not smoke • Light smokers: 1–10 cigarettes/day • Heavy smokers: >10 cigarettes/day
Butler et al. 1972	March 1958–May 1958	16,994 singleton births occurring in 1 week, and 7,000 late fetal and neonatal deaths occurring during the following 3 months	• Nonsmokers did not smoke • Smokers: four groups based on the average number of cigarettes smoked (1–4, 5–9, 10–19, 20–30)
D'Souza et al. 1981	NR*	452 mothers aged 19–35 years, who attended antenatal clinics and had normal singleton pregnancies	• Nonsmokers did not smoke • Light to moderate smokers: 1–14 cigarettes/day • Heavy smokers: 15 cigarettes/day
Sexton and Hebel 1984	2½ years	935 women aged 14–42 years: 463 receiving smoking cessation interventions and 472 controls	Women were classified by the number of cigarettes/day (0, 1–5, 6–10, 11–20, >20)
Martin and Bracken 1986	May 1980–March 1982	3,891 antenatal patients	Tobacco smoke exposure: none, passive (exposed to someone else's cigarette for at least 2 hours/day), direct, and passive and direct
Haddow et al. 1987	July 1980–June 1983	4,211 women between 15 and 21 weeks of gestation	Smokers were classified by reported daily cigarette use and serum cotinine levels

*NR = Data were not reported.
†RR = Relative risk.
‡CI = Confidence interval.

Key results

- Incidence of premature births was twice as great for smokers as for nonsmokers
- Prematurity rates increased with the number of cigarettes/day; the highest rates were for heavy smokers and the lowest were for nonsmokers

- Mortality rates for late fetal plus neonatal deaths, according to the average number of cigarettes/day, showed that the death rate was lowest for nonsmokers, intermediate for those smoking 1 to 4 cigarettes/day, and highest among those smoking >4 cigarettes/day
- Smoking habits established at the end of the fourth month of pregnancy had an effect on perinatal mortality independent of maternal prepregnancy smoking habits
- Similarly, the effect on birth weight of smoking before pregnancy became nonsignificant after taking into account the average number of cigarettes smoked regularly after the fourth month

- Heavy smokers gained significantly less weight than nonsmokers, but there was no significant difference in skinfold thickness
- Babies born to smokers weighed less, had smaller head circumferences, and were shorter than those born to nonsmokers, but skinfold thickness was similar

- The treatment group infants had a mean birth weight 92 g heavier and were 0.6 cm longer than the control infants
- There were no significant differences between the two groups in head circumferences, gestational age, or Apgar scores
- Findings suggest that some fetal growth retardation can be overcome by smoking cessation assistance to pregnant women

- The RR[†] of low birth weight for passive exposures to smoke compared with unexposed women was 2.17 (95% CI[‡], 1.05–4.5)
- Those passively exposed to smoke delivered infants 24 g lighter on average
- The risk of low birth weight at term attributable to direct cigarette smoking was 3.54 (95% CI, 1.62–7.71)

- Both cotinine levels and smoking history were significantly associated with reduced birth weight, but cotinine correlated significantly better
- Women who smoked >25 cigarettes/day had infants 289 g lighter than nonsmokers
- Women with high serum cotinine levels (>284 ng/mL) had infants who were 441 g lighter than infants of women with the lowest cotinine levels (<24 ng/mL)

Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Cnattingius 1989	1983–1985	280,809 live births to women aged 15–44 years	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: 10 cigarettes/day
Alameda County Low Birth Weight Study Group 1990	NR	311 black and 220 white singleton infants of normal birth weight selected randomly	Cigarette smoking during pregnancy: did not smoke at all, only at the beginning of the pregnancy, off and on throughout, and regularly throughout
Ferraz et al. 1990	September 1984–February 1986	3,406 singleton infants: 429 preterm, 422 with intrauterine growth retardation, and 2,555 controls with normal birth weights and gestational ages	NR
Fox et al. 1990	NR	714 children whose mothers smoked at the beginning of pregnancy	• Women who smoked throughout the pregnancy • Quitters (women who reported 0 cigarettes/day at the eighth month contact)
Hopkins et al. 1990	January 1989–June 1989	74,139 singleton infants: 62,732 white infants and 11,407 black infants	• Light smokers: <0.5 pack/day • Moderate smokers: 0.5–1 pack/day • Heavy smokers: >1 pack/day
Wen et al. 1990	January 1983–January 1988	15,539 births from women who received prenatal care and who delivered at 1 hospital	Cigarette use during the pregnancy before the first visit
McDonald et al. 1992	NR	40,445 single pregnancies from a survey	Women were classified as nonsmokers, smoked <10 cigarettes/day, 10–19 cigarettes/day, or 20 cigarettes/day

§OR = Odds ratio.
SGA = Small for gestational age.

Key results

- A significant interaction between maternal age and moderate or heavy smoking was observed for the risk of having a SGA infant
- The RR of SGA for heavy smokers vs. nonsmokers was 1.9 in the youngest age group and 3.4 in the oldest age group

- The RR of low birth weight in black smokers compared with black nonsmokers was 3.6; in white smokers it was 3.0
- The RR of term low birth weight (intrauterine growth retardation) was 4.5 in black smokers and 5.1 in white smokers
- Quitting smoking in the first 3 months of pregnancy was associated with a lower RR for low birth weight for black and white babies

- Smoking, a heavy workload during pregnancy, <5 or >10 antenatal visits, and any gestational or intrapartum complications were associated with higher risks of preterm and intrauterine growth-retarded births
- For preterm cases, the adjusted OR[§] associated with smoking during pregnancy was 1.5 (95% CI, 1.2–2.0)
- For intrauterine growth retardation, the adjusted OR for smoking during pregnancy was 1.5 (95% CI, 1.1–2.0)

- By 3 years of age, the children of women who had quit smoking during pregnancy were taller and heavier than those of women who had smoked throughout the pregnancy
- Differences in weight but not in height were partly accounted for by the postpartum maternal smoking status
- Results suggest that deficits associated with maternal smoking are not overcome by 3 years of age, and some of the observed anthropometric deficits may be extensions of deficits in fetal growth

- Infants born to smokers were more than twice as likely to have low birth weight as infants born to non-smokers
- The risk of low birth weight increased by the level of exposure: adjusted ORs = 1.8, 2.2, and 2.4 for light, moderate, and heavy smokers, respectively
- For both blacks and whites, risks were directly proportionate to smoking levels

- Smoking lowered birth weights by decreasing fetal growth and by lowering gestational age at delivery
- The effect was significantly greater as maternal age increased: smoking was associated with a fivefold increased risk of growth retardation in women aged >35 years, but less than a twofold risk in women aged <17 years
- Smoking reduced birth weights by 134 g in younger women, and by 301 g in women aged >35 years

- The risk of low birth weight for gestational age (LBWGA) increased substantially with smoking: for every 10 cigarettes/day, the risk of LBWGA increased by a factor of 1.51 (95% CI, 1.44–1.57)
- Smoking accounted for 39% of LBWGA cases, 35% of low birth weights, and 11% of preterm births
- Risk was reduced for women who decreased their smoking and who smoked before but not during the first trimester

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Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Werler et al. 1992	1976–1990	2,657 infants from a surveillance program on birth defects: 76 with gastroschisis and 2,581 controls	Smoking was determined by the number of cigarettes/day during pregnancy
Backe 1993	1988–1989	1,908 women in 1 county who delivered during a 1-year period	The number of cigarettes/day (0, 1–5, 6–10, 11–20, >20)
Bakketeig et al. 1993	January 1986–March 1988	5,722 pregnant women	Smokers: women who at first visit reported daily smoking at the time of conception
Bardy et al. 1993	February 1991–March 1991	1,237 pregnancies and newborns representing all live birth pregnancies during 1 week in 1 country	• Nonsmokers: had not smoked • Quitters: smoked during the first trimester and then quit • Smokers: smoked during the entire pregnancy
Cnattingius et al. 1993	1983–1988	538,829 women with singleton births	• Nonsmokers: nondaily smokers • Smokers: 1–9 cigarettes/day and 10 cigarettes/day
Li et al. 1993	1986–1991	1,277 women <32 weeks pregnant at the first prenatal visit to a clinic	Smokers: at her first prenatal visit reported at least one puff from a cigarette in the last 7 days, and/or had a baseline or follow-up cotinine level of >30 ng/mL
Wilcox 1993	1980–1984	260,000 white singleton births in 1 state	• Nonsmokers: mothers who reported no smoking during pregnancy • Smokers: mothers who reported smoking 1 pack of cigarettes/day • Smokers of <1 pack were excluded

SGA = Small for gestational age.

Key results

- Cigarette smoking was not associated with gastroschisis
- Age-adjusted RRs for smoking and coffee intake were close to 1.0
- There was a strong inverse relationship between maternal age and gastroschisis, with a 16-fold increased risk for the youngest mothers

- Smokers experienced a mean birth weight impairment of 182 g (adjusted for parity and age)
- There was a dose-response effect of the number of cigarettes/day on birth weight at the first visit
- The RR for SGA newborns of smokers <25 years of age was not significant, whereas women aged 35 years had a RR of 3.8

- Mothers who smoked cigarettes around the time of conception nearly doubled their risk of SGA births
- If the mother smoked and had a previous low birth weight delivery, the RR rose to nearly 5.5
- Low prepregnancy weight and smoking together increased the risk of a SGA birth fourfold

- Tobacco exposure was associated with shorter gestational age, reduced birth weight, and shorter crown-heel length of newborns: exposed newborns were on average 188 g lighter and 10 mm shorter than unexposed newborns
- Maternal cotinine concentrations explained the neonatal findings better than the reported smoking habits
- There was a quantitative dose-response relationship with tobacco exposure, and a decrease in gestational age at birth and in the size of the neonate

- Among multiparous women, smoking increased the ORs for low birth weight and preterm delivery by 2.4 and 1.6, respectively; the corresponding increases for nulliparous women were 1.7 and 1.1, respectively
- With advancing maternal age, there was a smoking-related relative increase in the ORs for SGA births
- The age effect on the relative increase of low birth weight, preterm delivery, and SGA births was greater among nulliparous women than among multiparous women

- Infants born to women who had quit smoking had the highest mean birth weight, followed by infants born to women who had reduced their smoking, and women who did not change their smoking behavior
- Although smoking cessation increased infant gestational age at delivery by 1 week, reducing smoking had no effect
- Cotinine-validated smoking reduction rates were positively associated with an increase in infant birth weight

- Infants of mothers who smoked 1 pack of cigarettes/day were on average 320 g lighter than unexposed infants (3,180 g compared with 3,500 g)
- Perinatal mortality for infants of smokers was 14.5 per 1,000 compared with 10.4 per 1,000 for infants of nonsmokers
- The RR was not uniform across birth weights: among infants less than 3 kg, weight-specific mortality rates were lower for exposed vs. unexposed infants; among heavier infants, the risk was reversed, with mortality higher for exposed infants
- When standardized weight-specific mortality rates are compared, the pattern becomes more consistent, with exposed infants showing a higher risk of mortality across all relative birth weights

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Table 5.10   Continued

Study	Study period	Population	Definition of smoking
Lieberman et al. 1994	August 1977–March 1980	11,177 women with singleton pregnancies from a hospital-based cohort	Women were classified as nonsmokers, smoked throughout pregnancy, smoked during the first trimester only, smoked during the first and second trimesters only, and smoked during the second and third trimesters or during the third trimester only
Mainous and Hueston 1994	1988	4,876 women who gave birth	• Nonsmokers did not smoke cigarettes at all during the year before birth • Smokers: (1) those who stopped smoking during the first trimester of pregnancy, (2) those who continued smoking beyond the first trimester of pregnancy
Spinillo et al. 1994c	1988–1992	1,041 pregnancies: 347 with fetal growth retardation and 694 controls	Maternal smoking was classified as none, 1–10 cigarettes/day, 11–20 cigarettes/day, and >20 cigarettes/day
Eskenazi et al. 1995b	1964–1967	3,529 pregnant women around 27 weeks of gestation	• Smokers: current smokers at the time of interview • Nonsmokers: never smoked or had quit before the pregnancy

SGA = Small for gestational age.

Key results

- Women who began smoking during the second or third trimester had an elevated risk of SGA births (OR = 1.83 [95% CI, 1.25–2.67]) similar to that of women who had smoked throughout pregnancy (OR = 2.2 [95% CI, 1.9–2.54])
- Risks for SGA births increased with the number of cigarettes smoked during the third trimester

- Women who did not smoke during pregnancy were less likely to give birth prematurely (5.9 vs. 8.2%) or to give birth to a low birth weight baby (5.5 vs. 8.9%) than women who smoked at some time during the year before birth
- Compared with those who smoked beyond the first trimester, those who quit smoking within the first trimester had reductions in the proportion of preterm deliveries (6.7 vs. 9.1%) and low birth weight infants (7.9 vs. 9.6%)

- Fetal growth retardation was associated with maternal smoking (OR = 2.87 [95% CI, 2.17–3.8])
- Smoking-related risks of fetal growth retardation were increased in the case of a male fetus, nulliparity, maternal age <20 years, a history of first trimester hemorrhage, and low prepregnancy weight

- Compared with infants of unexposed nonsmokers, infants of exposed nonsmokers weighed 45 g less on average
- Infants of smokers weighed on average 78, 191, and 233 g less for the first, second, and third cotinine tertiles, respectively
- Birth weight decreased 1 g for every increase in nanogram per milliliter of cotinine

Table 5.10   Continued

Study	Study period	Population	Definition of smoking
Ellard et al. 1996	NR	3,038 mothers who gave birth to live singleton babies after 28 weeks of gestation	• Smoking was determined by self-reported daily cigarette use (0, 1–12, >12), and urinary nicotine metabolites/creatinine ratios (0, 0.01–11.0, >11.0 μg/mg) • Proven nonsmokers: reported nonsmoking status was confirmed by negative urine tests • Proven smokers: reported smoking was confirmed by positive urine test results
Muscati et al. 1996	1979–1989	1,339 pregnant women	• Nonsmokers: did not report smoking at any time during pregnancy, or had stopped by 10 weeks of pregnancy • Smokers: 1 cigarette/day throughout entire pregnancy
Peacock et al. 1998	August 1982– March 1984	1,254 white women seeking antenatal care from a hospital	Number of cigarettes/day

SGA = Small for gestational age.

The RRs range from 1.5 to 2.5 for smokers compared with nonsmokers. Several studies demonstrated dose-response relationships of risk with the amount smoked, with the highest smoking categories showing RRs of 5.0 to 9.9 (Wen et al. 1990; Bakketeig et al. 1993; Lieberman et al. 1994; Spinillo et al. 1994c). Most studies adjusted for numerous potential confounding factors and still reported strong associations and dose-response relationships with daily smoking levels. These associations with active smoking by the mother may be underestimated as a substantial proportion of women in the nonsmoking control groups are exposed to secondhand cigarette smoke. Exposure to secondhand smoke also reduces birth weight, and removing the group of passively exposed women from the control group increases RRs (Martin and Bracken 1986). One study examining the contributions of smoking, energy intake, weight gain, and fetal growth reported that the effect of smoking was independent of energy intake (which was higher in smokers) and weight gain (which was lower in smokers) (Muscati et al. 1996). Thus, this finding supports a direct effect of smoking

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Key results

- Adjusted birth weight deficits of babies born to active smokers averaged 226 g (95% CI, 194–258 g)
- Dose-dependent effects were only apparent when nicotine intake was based on urinary nicotine metabolites/creatinine ratios than on self-reports
- Maternal weight gain during pregnancy was substantially reduced in smokers
- Placental weight gain was unaffected by smoking

- Smoking was independently associated with a higher energy intake but a lower maternal weight gain (-2.16 kg) and infant birth weight (-205 g)
- The important negative effect of smoking on fetal growth retardation cannot be adequately mitigated by simply increasing energy intake
- The estimated percentage of SGA infants attributable to smoking was 30.8%

- Among smokers, cotinine levels were more closely related to birth weight than the number of cigarettes smoked, indicating that cotinine is a better predictor of birth weight than the reported number of cigarettes smoked
- Among nonsmokers, the association between cotinine levels and birth weight was not statistically significant after adjusting for confounding factors
- The difference in mean birth weights between nonsmokers in the lower and upper quintiles of cotinine was 0.2%
- Any effect of maternal passive smoking was small compared with the effects of maternal active smoking on birth weight

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on the growth of the fetus rather than an indirect effect through nutritional intake among smokers.

Evidence Synthesis

The evidence addresses smoking during pregnancy and diverse outcomes. For some of the outcomes, causal conclusions have been previously reached. Most studies on the relationship between smoking and ectopic pregnancy have demonstrated a positive association, with several demonstrating a dose-response relationship between risk and amount smoked. However, the number of studies is still limited, and uncontrolled confounding remains as an alternative explanation to a causal association. Biologic mechanisms include a possible indirect causal pathway through an increased risk for a pelvic infection in smokers, a delayed fertilization process, and reduced tubal motility in association with exposures to nicotine.

Despite methodologic challenges in studying spontaneous abortions, most studies on the association between active smoking and spontaneous pregnancy loss have reported increased risks for smokers compared with nonsmokers, and some studies demonstrate dose-response relationships. Animal models have indicated plausible mechanisms that may underlie the association.

Most studies demonstrate an increased risk for maternal smoking and preterm PROM, placenta previa, and placental abruption. These findings have been consistently observed across time and across many study populations in multiple countries. Also, biologic evidence supports the contribution of active smoking to these particular pregnancy conditions.

Many studies show an increased risk of preterm delivery among smokers compared with nonsmokers even though the overall risk of preterm delivery may be small, with ORs on the order of 1.2 or 1.3. One major mechanism by which smoking is related to preterm delivery is through an increase in the risks of pregnancy and/or fetal complications that result in a spontaneous abortion or a medically indicated early delivery.

Many studies have consistently demonstrated a positive association between maternal smoking during pregnancy and reduced birth weight, and several have demonstrated dose-response relationships with the amount smoked. For smoking throughout pregnancy the effect is large, and successful cessation of smoking before the third trimester eliminates much of the reduction caused by maternal smoking. Some mechanisms by which smoking reduces birth weight have been established. They act in large part through reduced fetal growth, but the association between smoking and birth weight also results from early delivery, often from pregnancy complications. The biologic evidence supporting this causal effect is strong and includes fetal hypoxia from increased carboxyhemoglobin; reduced blood flow to the uterus, placenta, and fetus; and direct effects of nicotine and other compounds in tobacco smoke on the placenta and fetus.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

3. The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption.

4. The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia.

5. The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation.

6. The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight.

Implications

The evidence reviewed in this chapter suggests that smoking is associated with ectopic pregnancy and spontaneous abortion. As both ectopic pregnancy and infertility are on the rise, reducing smoking among women intending to become pregnant is warranted. More studies are needed that are designed to prospectively assess very early losses and to examine the association of smoking around the time of conception with types of spontaneous abortions.

The evidence of an association of smoking during pregnancy and adverse pregnancy complications, such as preterm PROM, placenta previa, and placental abruption, is sufficient to warrant promoting smoking cessation among women before they become pregnant and during pregnancy. Werler (1997) noted that as much as 10 percent of abnormal placentation could be avoided if smoking during pregnancy were eliminated. The decreased risk of preeclampsia among smokers compared with nonsmokers does not outweigh the adverse outcomes that can result from prenatal smoking.

The occurrence of LBW could be reduced by an estimated 20 percent, and fetal growth restriction by 30 percent, if all women were nonsmokers during pregnancy (Alameda County Low Birth Weight Study Group 1990; Cnattingius et al. 1993; Li et al. 1993; Muscati et al. 1996). The impact of smoking on these outcomes can be lessened if women quit before their third trimester; thus, there is a need for widespread implementation of effective smoking cessation interventions targeting all women of childbearing age as well as those already pregnant.

Congenital Malformations, Infant Mortality, and Child Physical and Cognitive Development

Epidemiologic Evidence

Congenital Malformations

Because of the direct fetal effects observed from exposure to tobacco smoke, and the chemically complex nature of cigarette smoke, researchers have assessed the association between prenatal exposure and congenital malformations. Researchers have examined these associations with malformations as an overall group and with single malformations separately. The etiologies of the multiple congenital malformations vary widely, making the discussion of the contribution of prenatal smoking to an increased risk of birth defects difficult overall.

Most studies investigating associations between maternal smoking during pregnancy and all congenital malformations together have not found an association (Hemminki et al. 1983; Shiono et al. 1986b; Malloy et al. 1989; Seidman et al. 1990; Van den Eeden et al. 1990) (Table 5.11). One study reported an increased risk only among heavy smokers (Kelsey et al. 1978), with an adjusted RR of 1.6 (p = 0.03) for women smoking 21 or more cigarettes per day during pregnancy compared with nonsmokers.

Down syndrome has been consistently shown not to be associated with maternal smoking in pregnancy (Hook and Cross 1985; Cuckle et al. 1990a; Van den Eeden et al. 1990; Källén 1997a). Neural tube defects are not elevated among smokers compared with nonsmokers (Malloy et al. 1989; Wasserman et al. 1996; Källén 1998). However, Källén (1998) demonstrated a significant protective effect for neural tube defects among smokers compared with nonsmokers in the 1.2 million births studied (OR = 0.75 [95 percent CI, 0.61–0.91]).

Li and colleagues (1996) reported an association between maternal smoking and urinary tract anomalies among light smokers (<1,000 cigarettes smoked during pregnancy) compared with nonsmokers; the anomalies occurred mainly in female infants. The OR for light smokers versus nonsmokers was 3.7 (95 percent CI, 1.7–8.6); among mothers of female infants, comparing light smokers with nonsmokers yielded an OR of 6.1 (95 percent CI, 2.0–18.4). This study reported a lower risk for heavy smokers compared with non-smokers (OR = 1.4 [95 percent CI, 0.6–3.3]). As an

explanation for this dose-dependent response, Li and colleagues (1996) suggest that heavier smokers may be more likely than light smokers to abort malformed fetuses. Malloy and colleagues (1989) and McDonald and colleagues (1992) found little association between smoking and genitourinary defects at birth.

Gastroschisis is a defect of the abdominal wall closely related to the defect omphalocele thought to result from vascular interruption (Hoyme et al. 1983). Findings on the association between gastroschisis and smoking have been conflicting. Smaller studies show a positive association (Haddow et al. 1993), whereas most larger studies and those controlling for confounders show no association (Werler et al. 1992; Torfs et al. 1994).

The association of fetal limb defects and smoking also has been studied. One study looked at the risk of limb defects from maternal and paternal smoking and found contradictory results (Wasserman et al. 1996). Risk was elevated only with heavy paternal smoking (OR = 2.0 [95 percent CI, 1.3–3.6]) compared with neither parent smoking. Maternal smoking, even heavy maternal smoking, did not elevate the risk of limb defects; nor did having both parents smoke or having passive exposures at home or at work. Because there is no evident biologic explanation for this particular pattern of association, paternal smoking in the absence of maternal smoking may be a proxy for other factors contributing to this risk. This study also reported that the risk of conotruncal heart defects was elevated when both parents smoked (OR = 1.9 [95 percent CI, 1.2–3.1]) (Wasserman et al. 1996).

The most convincing evidence supports an association between smoking and oral clefts (Saxen 1974; Khoury et al. 1987; Hwang et al. 1995; Shaw et al. 1996; Källén 1997b; Wyszynski et al. 1997), yet not all studies report an association (Shiono et al. 1986a; Malloy et al. 1989; Werler et al. 1990). Studies have examined the association with smoking for all oral cleft defects and for the categories of a cleft lip with or without a cleft palate, and cleft palate alone. Even when subgroups are examined, studies produce contradictory findings. One meta-analysis of 11 studies of oral clefts that compared mothers who smoked during the first trimester with mothers who did not smoke reported an overall OR of 1.29 (95 percent CI, 1.18–1.42) for a

Table 5.11 Studies on the association between maternal smoking and congenital malformations

Study	Study period	Population	Definition of smoking
Saxen 1974	1967–1971	599 cases of oral clefts reported to a register of congenital malformations	Smoking during pregnancy: >5 cigarettes/day
Kelsey et al. 1978	1974–1976	4,338 infants: 1,370 with congenital malformations and 2,968 normal controls	The number of cigarettes/day during pregnancy
Hemminki et al. 1983	1967–1977	3,300 children from a register of congenital malformations	• Smoking habits were described in 10 categories in the question-naire • Different categories of smokers were created separately for the analysis
Hook and Cross 1985	1980–1981	300 mothers: 100 with Down syndrome children, 100 with children with other defects, and 100 with children with no defects	• Nonsmokers (those who never smoked) • Former smokers at the time of conception • Current smokers
Shiono et al. 1986a	1974–1977 (birth defects study) 1959–1966 (perinatal study)	33,434 live births in a birth defects study, and 53,512 live births in a perinatal project	The number of cigarettes or packs/day
Khoury et al. 1987	1987	251 infants from a birth defects reporting system: 27 with cleft lip, 26 with cleft palate, and 198 with other sentinel defects	Asking respondents whether they smoked at any time during pregnancy and if yes, how many cigarettes/day (1–5, 6–10, 11–20, >20)
Malloy et al. 1989	1980–1983	288,067 singleton births recorded in birth defects registry	• Nonsmokers: did not smoke • Smokers: <1 pack/day or 1 pack/day

*RR = Relative risk.
†CI = Confidence interval.
‡OR = Odds ratio.

Key results

- Smoking during pregnancy was significantly more frequent among mothers of children with clefts than among controls
- Other factors associated with oral clefts in children included parental age, socioeconomic status, threatened abortion (bleeding and/or pains during pregnancy), pelvic x-ray examinations before pregnancy, emotional factors, and birth weight

- Women who smoked >20 cigarettes/day during pregnancy had a RR* of about 1.6 for congenital malformations in offspring compared with women who smoked 20 cigarettes/day during pregnancy
- There was no significant increase in risk among women who reported smoking 20 cigarettes/day compared with women who did not smoke during pregnancy
- The higher risk in heavy smokers could be a result of confounding factors or response bias, so further research is needed to determine a causal relationship between maternal smoking and congenital malformations

- The associations between maternal smoking and congenital malformations were statistically nonsignificant; there was a slight increase with the number of cigarettes smoked, suggesting a minor effect
- Women who smoked >10 cigarettes/day had a higher frequency of spontaneous abortions than any other group of women

- The RR for the association of cigarette smoking around the time of conception with Down syndrome was 0.58 (90% CI†, 0.34–0.98) in the case-defect control group, and 0.56 (90% CI, 0.33–0.95) in the case-normal control group
- The negative association may be attributable to a selective effect of smoking on survival, on the fertilizability of >21 gametes before conception, or on survival of >21 conceptuses after fertilization

- Since associations found in a single study could be the result of chance, deficiencies in study design, or peculiarities of the population studied, data from another study were used to check for consistencies of the associations initially found
- The associations of specific congenital malformations with smoking during pregnancy were suggested in the birth defects study, but the results could not be confirmed by the results from the perinatal study
- Smoking is unlikely to be responsible for a large increase in malformations at birth

- Mothers of infants with oral clefts smoked more during pregnancy than mothers of infants with other defects
- The OR‡ for cleft lip with or without cleft palate was 2.56, and the OR for cleft palate was 2.39
- There was a dose-response relationship between the daily amount smoked and the risk of clefting

- Infants of women who smoked were not at a greater risk for congenital malformations than infants of women who did not smoke
- Maternal smoking appears to be a risk factor for gastrointestinal malformations, but other congenital malformations occur less frequently in infants of smokers compared with nonsmokers

Table 5.11 Continued

Study	Study period	Population	Definition of smoking
Cuckle et al. 1990a,b	NR[§]	462 pregnant women	• Smoking was determined by cotinine concentrations in maternal serum samples • Maximum likelihood analysis was used to determine cotinine cut-off levels for separating smokers from nonsmokers
Van den Eeden et al. 1990	1984–1986	7,784 mothers with singleton live births: 3,284 with a congenital malformation and 4,500 controls without malformations	NR
Haddow et al. 1993	January 1980– April 1989	62,103 consecutive second trimester singleton pregnancies	Smokers or nonsmokers
Torfs et al. 1994	March 1988– August 1990	330 mothers: 110 mothers of infants with gastroschisis and 220 age-matched mothers of normal infants	<1 pack/day and >1 pack/day
Hwang et al. 1995	1984–1992	467 infants: 69 with cleft palate, 114 with cleft lip with or without cleft palate, and 284 controls with noncleft birth defects	Records on whether and how many cigarettes were smoked during pregnancy
Li et al. 1996	1990–1991	487 infants: 118 cases and 369 controls	Light smokers: 1–1,000 cigarettes during pregnancy

[§]NR = Data were not reported.

Key results

- In pregnancies with and without Down syndrome, the 25th, median, and 75th centiles of AFP (alpha-feto protein) and DHEAS (dehydroepiandrosterone) were higher in smokers than in nonsmokers, whereas those for uE$_3$ (unconjugated estriol), hCG (human chorionic gonadotrophin), and progesterone were lower
- When screening for Down syndrome using maternal age, AFP, uE$_3$, and hCG, allowance could be made for smoking by deriving separate medians for smokers and nonsmokers to calculate MoM values (multiple of the median value in unaffected pregnancies of the same gestation)

- When all malformations were considered together, there was no association with maternal smoking
- Maternal smoking was associated with increased risks for a number of specific malformations, including microcephalus (RR = 2.0 [95% CI, 1.0–4.0]), cleft defects (RR = 1.4 [95% CI, 1.0–2.0]), and clubfoot (RR = 1.4 [95% CI, 1.0–2.0])
- No association was found with Down syndrome or any other malformation

- Pregnant women who smoked cigarettes had at 2.1 times greater odds of having an infant with gastroschisis than nonsmokers (95% CI, 0.9–4.8)
- Smoking data from this study combined with smoking data from two other studies showed an OR of 1.6 (95% CI, 1.2–2.2)

- There was a significant association of gastroschisis with a history of maternal smoking and with the use of either a recreational drug, alcohol, or tobacco during the trimester preceding pregnancy
- During the preconceptional trimester, the OR for the risk of having an infant with gastroschisis for smokers of <1 pack/day was 1.4 (95% CI, 0.78–2.5) and 1.77 (95% CI, 0.93–3.39) for smokers of 1 pack/day

- A gene-environment interaction between infant genotype and maternal smoking was associated with birth defects among those with or without a family history of birth defects
- Infants carrying the C2 allele who were exposed to maternal smoking of <10 cigarettes/day showed a 6.16-fold increase in risks for cleft palate only (95% CI, 1.09–34.7), while similar infants whose mothers smoked 10 cigarettes/day showed an 8.69-fold higher risk (95% CI, 1.57–47.8)

- Maternal smoking during pregnancy was associated with a twofold increased risk of congenital urinary tract anomalies in the offspring
- The risk was higher among light smokers (OR = 3.7 [95% CI, 1.7–8.6]) than among heavy smokers (OR = 1.4 [95% CI, 0.6–3.3])
- The increased risk of congenital urinary tract anomalies associated with light smoking but not with heavy smoking was more apparent among female than male offspring

Table 5.11 Continued

Study	Study period	Population	Definition of smoking
Shaw et al. 1996	January 1987– December 1989	1,465 infants: 731 with orofacial clefts and 734 nonmalformed controls	• Active smoking: number of cigarettes/day by the mother during the 4 months after date of conception • Passive smoking: whether anyone else inside the mother's home smoked daily during the 4 months after conception, or whether she regularly frequented places where others smoked • Paternal smoking was determined by how many cigarettes the infant's natural father smoked during the 3 months before through 3 months after conception
Wasserman et al. 1996	1987–1988	1,130 infants: 207 with conotruncal heart defects, 264 with neural tube defects, 178 with limb deficiencies, and 481 controls	• Active smoking: number of cigarettes/day by the mother during the 4 months after date of conception • Passive smoking: whether anyone else inside the mother's home smoked daily during the 4 months after conception, or whether she regularly frequented places where others smoked • Paternal smoking was determined by how many cigarettes the infant's natural father smoked during the 3 months before through 3 months after conception
Källén 1997a	1983–1993	1,321 infants with Down syndrome	• None • <10 cigarettes/day • 10 cigarettes/day
Källén 1997b	1983–1992	1,834 infants with oral clefts selected from a birth registry and a congenital malformation registry	• None • <10 cigarettes/day • 10 cigarettes/day

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Key results

- The risks associated with maternal smoking were most elevated for isolated cleft lip with or without cleft palate (OR = 2.1 [95% CI, 1.3–3.6]) and for isolated cleft palate (OR = 2.2 [95% CI, 1.1–4.5]) when mothers smoked >20 cigarettes/day
- Clefting risks were even greater for infants with the transforming growth factor alpha (TGF-) allele whose mothers smoked >20 cigarettes/day
- Risk of orofacial clefting in infants may be influenced by maternal smoke exposure alone, as well as in combination with the presence of the uncommon TGF- allele (gene-environment interaction)
- Paternal smoking was not associated with clefting, and passive exposures were associated with a slightly increased risk

- Moderately elevated risks were observed for conotruncal heart defects (OR = 1.9 [95% CI, 1.24–3.1]) and limb deficiencies (OR = 1.7 [95% CI, 0.96–2.9]) with both parents smoking
- There were no increased risks for congenital abnormalities associated with maternal smoking in the absence of paternal smoking, although an increased risk associated with paternal smoking in the absence of maternal smoking was observed for limb deficiencies
- Risks associated with paternal smoking for conotruncal defects differed among racial and ethnic groups

- No association between maternal smoking and all cases of Down syndrome was found (OR = 0.98 [95% CI, 0.86–1.11]), but heterogeneity over strata existed
- A decreased OR (0.91 [95% CI, 0.72–1.15]) for any maternal smoking was indicated among primiparous women but not among multiparous women
- Findings indicate that no direct effect of smoking on Down syndrome risk exists, but the association observed in primiparous women is attributable to covarying factors

- A statistically significant association between maternal smoking during pregnancy and oral clefts was found
- The OR for maternal smoking among cases of cleft lip with or without a cleft palate was 1.16 (95% CI, 1.02–1.32)
- For cases of cleft palate alone, the OR was 1.29 (95% CI, 1.08–1.54)

Table 5.11   Continued

Study	Study period	Population	Definition of smoking
Wyszynski et al. 1997	1966–1996	Meta-analysis of 11 studies	NR
Källén 1998	1983–1993	621 infants with neural tube defects	• None • <10 cigarettes/day • 10 cigarettes/day

cleft lip with or without a cleft palate, and 1.32 (1.10–1.62) for a cleft palate (Wyszynski et al. 1997). Recent studies have examined genetic and environmental interactions in relation to oral clefts. Two studies (Hwang et al. 1995; Shaw et al. 1996) reported that infants who were heterozygous or homozygous for transforming growth factor alpha allele and were exposed to smoking during pregnancy had significantly increased risks for a cleft palate of 7.0 (95 percent CI, 1.18–28) (Hwang et al. 1995) and 4.0 (95 percent CI, 1.7–9.2) (Shaw et al. 1996). Risks for a cleft lip with or without a cleft palate were lower, about twofold, and were only significant in one study where smoking alone significantly elevated the risks of both outcomes (OR = 1.6) (Shaw et al. 1996). In the other study, smoking alone was not associated with either category of oral clefts (Hwang et al. 1995).

Infant Mortality and Stillbirths

Stillbirths (fetal death after 28 weeks) and infant deaths (death within the first year of life) have been examined in relation to smoking in numerous studies. These outcomes have declined significantly in the United States in recent years, as infant mortality has declined from 13 deaths per 1,000 births in 1980 to 7 deaths per 1,000 in 1998 (Guyer et al. 1999). Much of this improvement before and after 1980 has been from advances in medical interventions for the very smallest and sickest infants. Numerous studies have demonstrated associations between active maternal smoking and stillbirths (Meyer and Tonascia 1977; Kiely et al. 1986; Cnattingius 1992; Little and Weinberg 1993; Raymond et al. 1994) and neonatal and perinatal mortality (Comstock and Lundin 1967; Rush and Kass 1972; Cnattingius et al. 1988; Malloy et al. 1988; Schramm 1997). Even in the face of modern neonatal intensive care, numerous studies have demonstrated increased

risks for neonatal mortality (death of a live-born infant within 28 days) (Cnattingius et al. 1988; Malloy et al. 1988; Schramm 1997), with reported ORs for infants of smokers around 1.2 compared with infants of nonsmokers.

SIDS—or sudden, unexplained, unexpected death before one year of age—has been investigated in relation to fetal exposures to maternal smoking and the exposure of the infant to smoking by the mother and others during the postpartum period. Although social and behavioral risk factors for SIDS have been identified, the biologic mechanism is still unknown. Concerning smoking and SIDS, one proposed mechanism is chronic hypoxia—via elevated levels of carbon monoxide or reduced placental perfusion—affecting factors such as the normal development of the central nervous system (Bulterys et al. 1990). In animal studies designed to investigate neurotoxic effects, nicotine was found to target neurotransmitter receptors in the fetal brain, leading to reduced cell proliferation and, consequently, altered synaptic activity. The cholinergic and catecholaminergic systems and neurotransmitter pathways are affected acutely and, possibly, over the long term. Alterations in the peripheral autonomic pathways may lead to increased susceptibility to hypoxia-induced brain damage and SIDS (Slotkin 1998). In a study of newborns, the auditory arousal threshold for babies whose mothers smoked during pregnancy was greater than for those whose mothers did not smoke (Franco et al. 1999). Stick and colleagues (1996) observed the respiratory function of newborns in the hospital and reported lower function in infants of smokers compared with nonsmokers. This observation suggests a fetal effect of smoking that continues beyond the postpartum period.

Key results

- There was a small increased risk among mothers who smoked during the first trimester of the pregnancy of having a child with either a cleft lip with or without a cleft palate (OR = 1.29 [95% CI, 1.18–1.42]), or with a cleft palate alone (OR = 1.32 [95% CI, 1.10–1.62])

- A highly significant effect of maternal smoking on the incidence of neural tube defects was found (adjusted OR = 0.75 [95% CI, 0.61–0.91])
- A protective dose-response effect of smoking was indicated but was not statistically significant

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The death rate attributable to SIDS has declined by more than half over the last two decades; the SIDS rate in 1979 was 151.1 per 100,000 live births, and in 1998 the rate was 64 per 100,000 live births (Guyer et al. 1999). SIDS has decreased dramatically because of interventions such as the "Back to Sleep" campaign implemented in the 1990s. The diagnosis of SIDS, preferably by conducting an autopsy to exclude other causes, makes it a difficult outcome to study. Moreover, studies that examine maternal smoking during pregnancy may not be able to account for levels of postpartum smoking. In such studies (Malloy et al. 1992), the risk estimates for maternal smoking may be underestimated, since many women who quit or reduce the amount they smoke during pregnancy resume or increase their prepregnancy smoking levels after giving birth (Floyd et al. 1993; O'Campo et al. 1995).

Most studies have demonstrated that an increased risk of SIDS is associated with maternal smoking during pregnancy (Bergman and Wiesner 1976; Malloy et al. 1988; Kraus et al. 1989; McGlashan 1989; Bulterys et al. 1990; Haglund and Cnattinguis 1990; Mitchell et al. 1991; Schoendorf and Kiely 1992; MacDorman et al. 1997); adjusted ORs for mothers who smoked compared with nonsmokers ranged from 1.4 to 3.0 (Table 5.12). Some studies reported a dose-response relationship, comparing mothers who smoked 1 to 9 cigarettes with those who smoked 10 or more cigarettes per day (Haglund and Cnattinguis 1990; MacDorman et al. 1997). However, because very few smokers smoke only during pregnancy and not after delivery, it is nearly impossible to identify the risks associated only with prenatal exposure. Recent studies have begun to examine differences in the risk for SIDS between infants of women who smoke only after giving birth and infants of women who smoke both during pregnancy and after delivery (Mitchell et al. 1991; Schoendorf and Kiely 1992; Klonoff-Cohen

1997). These studies suggest that both prenatal and postpartum exposures to tobacco smoke increase the risk of SIDS. For infants exposed to tobacco only during the postpartum period, ORs were 2.4 (95 percent CI, 1.49–3.83) for blacks and 2.2 (95 percent CI, 1.29–3.78) for whites. For infants exposed during pregnancy and after delivery, ORs were 2.9 (95 percent CI, 2.12–4.07) for blacks and 4.07 (95 percent CI, 3.03–5.48) for whites (Schoendorf and Kiely 1992).

In a study containing more information about passive exposure to tobacco smoke, Klonoff-Cohen (1997) reported a dose-response relationship for postpartum smoking exposures even after adjusting for prenatal smoking levels of the mother. With one person smoking in the infant's room, the OR for SIDS was 3.67 (95 percent CI, 1.66–8.13); two to four persons smoking in the infant's room yielded an OR of 20.91 (95 percent CI, 4.02–108.7). These ORs should be interpreted cautiously given the wide CIs. A dose-response relationship was also demonstrated in this study for the number of cigarettes per day that the infant was exposed to during the postpartum period.

Child Physical and Cognitive Development

Strong associations between maternal smoking during pregnancy and adverse outcomes such as lowered birth weight and IUGR have prompted researchers to investigate the longer-term consequences of smoking during pregnancy on the physical growth and cognitive development of infants, children, and young adults. These studies are difficult to conduct, in part because of the need to consider multiple potential confounding factors that can intervene between pregnancy and the outcome of interest (e.g., family or environmental circumstances). Of particular concern is the effect of a continued exposure to passive smoking in the household on the developing infant or child.

Table 5.12   Studies on the association between maternal smoking and infant mortality

Study	Study period	Population	Definition of smoking
Comstock and Lundin 1967	1953–1963	1,113 infants: 448 live-born infants, 234 still-births, and 431 deaths	Mothers were classified as non-smokers and smokers (smokers included those who abstained during pregnancy)
Rush and Kass 1972	1961–1962	3,276 pregnant women	Smoked at least 1 cigarette daily
Bergman and Wiesner 1976	January 1970–February 1974	142 families: 56 who lost babies to SIDS* and 86 control families	• Smoking habits of both parents were ascertained during and after pregnancy • Maternal cigarette use was classified as none, <10, 10–19, or 20 cigarettes/day
Meyer and Tonascia 1977	1960–1961	51,490 singletons in 10 hospitals	None, <1 pack, or 1 pack/day
Cnattingius et al. 1988	1983–1985	281,808 births to mothers aged 15–44 years	• Nonsmokers (nondaily smokers) • 1–9 cigarettes/day • 10 cigarettes/day
Malloy et al. 1988	1979–1983	305,730 white live-born singletons, including 2,720 infant deaths	Maternal smoking status during pregnancy was classified as nonsmokers, smoked <1 pack/day or 1 pack/day

*SIDS = Sudden infant death syndrome.
†RR = Relative risk.
‡OR = Odds ratio.

Key results

- Maternal smoking during pregnancy was associated with an increased risk of death for the child
- Findings indicate that some characteristics associated with smoking must be responsible for increased neonatal mortality rates rather than smoking per se
- Many of the increased hazards for children of smoking mothers appeared to be associated with decreased birth weight

- Compared with all other groups, African American smokers had a perinatal mortality rate almost double that of white smokers, white nonsmokers, and African American nonsmokers
- African American smokers had an 86% excess mortality rate over African American nonsmokers; white smokers had an excess mortality rate of 11% compared with white nonsmokers
- African American smokers and African American women had infants of lower birth weight; African American women also had shorter gestation periods

- A higher proportion of mothers who lost their children to SIDS had smoked both during pregnancy (61 vs. 42%) and after their babies were born (59 vs. 37%) compared with mothers who did not smoke
- SIDS mothers smoked a significantly greater number of cigarettes than controls
- Exposure of infants to cigarette smoke (passive smoking) appears to enhance the risk of SIDS for reasons not known

- Increases in smoking levels were associated with increases in the frequency of early fetal death and of neonatal deaths due to premature delivery
- These deaths were associated with smoking-related increases in the incidence of bleeding during pregnancy, abruptio placentae, placenta previa, and premature rupture of membranes

- Smokers aged <35 years had a RR[†] of late fetal deaths ranging from 1.1 to 1.6, while the risk doubled if the mothers were aged 35 years and smoked
- Late fetal death rates would be reduced by 11% and early neonatal mortality by 5% if smoking could be eliminated from the pregnant population
- Smoking may be the most important preventable risk factor for late fetal deaths

- The association of smoking was higher with postneonatal deaths than with neonatal deaths (adjusted OR[‡] = 1.61 vs. 1.17)
- The association with smoking varied by cause of death and was particularly high for respiratory diseases (OR = 3.4) and SIDS (OR = 1.9)
- Findings indicate that respiratory deaths and SIDS deaths may be related to the effects on the infant of passive exposure to tobacco smoke after birth

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
Kraus et al. 1989	1959–1966	2,132 infants: 202 cases of SIDS* and 1,930 controls who survived the first year of life	• Nonsmokers • >10 cigarettes/day
McGlashan 1989	1980–1986	49,435 live infants	Maternal smoking classified as 0, <10 cigarettes/day, 11–20 cigarettes/day, and >20 cigarettes/day for each of the three categories: whether the mother was normally a smoker, whether she smoked during pregnancy, and whether she smoked during the baby's first year of life
Bulterys et al. 1990	1959–1966	2,123 infants: 193 cases of SIDS and 1,930 controls	Women were classified by the number of cigarettes/day during pregnancy (0, <10, or 10)
Haglund and Cnattingius 1990	1983–1985	279,938 infants surviving the first week of life	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: 10 cigarettes/day
Mitchell et al. 1991	November 1987–October 1988	631 infants: 128 cases of SIDS and 503 controls	Maternal smoking was assessed by (1) obstetric records, where any amount of smoking was recorded as "yes," and (2) parental interview that recorded whether the mother had smoked cigarettes in the last 2 weeks and if "yes," the number of cigarettes/day
Cnattingius et al. 1992	1983–1987	173,715 nulliparous Nordic women aged 20 years who delivered singletons	• No smoking • 1–9 cigarettes/day • >9 cigarettes/day

*SIDS = Sudden infant death syndrome.
§CI = Confidence interval.

Key results

- Maternal smoking, maternal aemia during pregnancy, and lack of early prenatal care were all positively associated with SIDS
- A positive trend in SIDS risks with increasing numbers of cigarettes smoked during pregnancy remained after adjusting for birth weights
- The unadjusted OR for maternal cigarette smoking during pregnancy was 1.6 (95% CI[§], 1.1–2.5) for >10 cigarettes/day vs. nonsmoking; cigarette smoking was stratified under different categories for different analyses

- Cigarette smoking by parents leading to passive exposures of the baby carried a high RR of SIDS (RR = 3.0)
- If the mother was a habitual smoker, the risk of SIDS was very high (RR = 2.98); the risk was also very high if the mother smoked during pregnancy (RR = 3.32)
- A dose-response relationship between cigarette smoking and increases in the risk of SIDS is suggested

- Infants born to mothers who smoked 10 cigarettes/day and who were anemic during pregnancy were at a higher risk of SIDS than infants born to mothers who did not smoke and were not anemic (OR = 4.0 [95% CI, 2.1–7.4])
- Smoking 10 cigarettes/day vs. none increased the risk of SIDS by 70% among women with hematocrits >30%, but the risk increased threefold among women with hematocrits <30%
- A low hematocrit was not a risk factor for SIDS among nonsmokers, but became an important predictor among heavy smokers

- Maternal smoking was strongly related to SIDS even while controlling for other risk factors
- Smoking 9 cigarettes/day doubled the risk of SIDS, and smoking 10 cigarettes/day tripled the risk of SIDS, compared with nonsmokers
- Early SIDS: 7 to 67 days; late SIDS: 68 to 145 days. Logistic regression of the difference between early and late SIDS (based only on SIDS cases) showed that moderate maternal smoking was strongly associated with an increased risk of early SIDS (RR = 1.7 [95% CI, 1.2–2.1])

- Three risk factors were significantly associated with SIDS: maternal smoking, prone sleeping position of baby, and breastfeeding
- The ORs associated with maternal cigarette smoking, compared with no maternal smoking, were as follows: 1–9 cigarettes/day, OR = 1.87 (95% CI, 0.98–3.54); 10–19 cigarettes/day, OR = 2.64 (95% CI, 1.47–4.74); 20 cigarettes/day, OR = 5.06 (95% CI, 2.86–8.95)
- These three risk factors may account for an estimated 79% of SIDS deaths

- Women who were nonsmokers and those who had cohabited with the infant's father had the lowest rates of late fetal and early neonatal deaths
- Delayed childbearing among nulliparous women with uncomplicated pregnancies was associated with increased risks of poor pregnancy outcomes

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
Malloy et al. 1992	1980–1985	2,271 infants: 757 cases of SIDS* and 1,514 living controls	Packs of cigarettes/day
Schoendorf and Kiely 1992	1988	10,000 births and 6,000 infant deaths from a national maternal and infant health survey	• Nonexposed group: infants whose mothers did not report cigarette smoking either during pregnancy or at the time of the survey • Passive exposure group: infants whose mothers reported smoking at the time of the survey but not during pregnancy • Combined exposure group: infants whose mothers reported smoking at the time of the survey and during pregnancy
Little and Weinberg 1993	1980	4,667 births: 2,832 live-born infants and 1,835 stillbirths	Daily cigarette smoking during pregnancy (none, 1–19, 20–29, 30)
Raymond et al. 1994	1983–1989	638,242 pregnancies >28 weeks of gestation in Nordic citizens aged >20 years	Women were nonsmokers, smoked 1–9 cigarettes/day, and 10 cigarettes/day
Klonoff-Cohen et al. 1995	1989–1992	400 parents of infants: 200 whose infants died of SIDS and 200 controls who delivered healthy infants	Smoking status of both parents and other live-in adults during pregnancy and after childbirth was ascertained to determine a child's exposure to tobacco smoke
Stick et al. 1996	Data were not reported	500 healthy infants of mothers participating in a cohort study	Mothers were never smokers, smoked <10 cigarettes/day, and 10 cigarettes/day

*SIDS = Sudden infant death syndrome.
*t*PTEF/*t*E = Time to peak tidal expiratory flow as a proportion of expiratory time.

Key results

- In the Missouri study population, there was evidence of a dose-response relationship between smoking during pregnancy and the incidence of SIDS*
- Data from the National Institute of Child Health and Human Development did not support a dose-response relationship
- Neither data set supported a relationship between the age of occurrence of SIDS and smoking during pregnancy
- The benefits of promoting smoking reduction as a means of reducing the occurrence of SIDS remains to be determined

- Infants who died of SIDS were more likely to be exposed to maternal cigarette smoke than were surviving infants
- After adjusting for demographic risk factors, the OR for SIDS among normal birth weight infants was approximately 2 for passive exposure and 3 for combined exposures for both black and white infants
- The results suggest that both intrauterine and passive tobacco smoke exposures are associated with an increased risk of SIDS, and are further inducements to encourage smoking cessation among pregnant women and families with children

- Factors for mothers that appeared to increase the risks of a stillbirth were age 35 years, black race, smoking up to 29 cigarettes daily, first delivery, and high body mass
- Smoking 1–29 cigarettes was associated with an increased risk of stillbirth, but smoking 30 cigarettes/day appeared to be protective
- One possible explanation for the protective effect of heavy smoking could be that heavily exposed and susceptible fetuses die earlier and are lost before 28 weeks

- Older women (aged 35 years), smokers, and nulliparous women had elevated risks of stillbirths
- There was a dose-response relationship between smoking and the risk of stillbirth, with the risk increasing with the number of cigarettes/day (1–9 cigarettes: OR = 1.2 [95% CI, 1.02–1.4]; 10 cigarettes: OR = 1.6 [95% CI, 1.4–1.8])
- The association between smoking and stillbirths is explained entirely by the higher incidence of growth retardation and placental complications in smokers

- Infants who died from SIDS were significantly more likely to be exposed to passive smoke from the mother (OR = 2.28), father (OR = 3.46), or other live-in adults (OR = 2.18) than were control infants
- A dose-response relationship was observed indicating an increase in the risk of SIDS associated with an increase in the child's exposure to tobacco smoke in the first year of life
- Breastfeeding was protective against SIDS among nonsmokers (OR = 0.37) but not smokers (OR = 1.38)

- In utero smoke exposure, a family history of asthma, and maternal hypertension during pregnancy were associated with reduced respiratory function after birth
- There was a significant dose-response relationship of maternal smoking on *t*PTEF/*t*E; infants of mothers who smoked 10 cigarettes/day had the lowest mean *t*PTEF/*t*E, and infants of nonsmoking mothers had the highest

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
MacDorman et al. 1997	United States: 1990–1991 Sweden: 1983–1992	Linked birth and death records for more than 1 million infants	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: 10 cigarettes/day
Schramm 1997	1978–1990	176,843 women	Women were asked if they used tobacco during pregnancy (yes/no) and the number of cigarettes/day (0, <1 pack, 1 pack)

*SIDS = Sudden infant death syndrome.

Although rates of reducing and quitting smoking during pregnancy are substantial, many women (approximately 70 percent) resume smoking once their infant is delivered (USDHHS 2001). Overpeck and Moss (1991) studied maternal smoking during pregnancy and the exposure to secondhand smoke of children aged five years and younger by mothers and other household members, and found that only 1.2 percent of children were exposed to tobacco smoke prenatally but not postpartum. Thus, a comparison group of infants who had been exposed to smoking during pregnancy but not after delivery is rarely available, making it difficult to attribute any observed effects to prenatal smoking alone.

The mechanisms by which maternal smoking during pregnancy may lead to compromised physical and cognitive development are not clear. However, regarding cognitive development, effects of smoking, and nicotine in particular, on central nervous system development have been proposed. Alterations in the peripheral autonomic pathways, mentioned earlier, may lead to an increased susceptibility to hypoxia-induced short-term and long-term brain damage (Slotkin 1998).

Several studies have examined the association between prenatal maternal smoking and subsequent physical growth of the infant or child, with mixed findings (Goldstein 1971; Rantakallio 1983; Barr et al. 1984; Fogelman and Manor 1988; Eskenazi and Bergman 1995) (Table 5.13). Goldstein (1971) observed the growth of approximately 15,000 seven-year-olds and reported that maternal smoking during pregnancy resulted in a 0.6 cm reduction in height after accounting for social class, birth weight, and gender. In a large birth cohort, Rantakallio (1983) observed a 0.4 to 0.6 cm reduction in height at 14 years of age in children of mothers who smoked compared with children whose mothers were nonsmokers. Neither study adjusted for postpartum smoking. Barr and colleagues (1984) examined associations between maternal smoking during pregnancy and infant size at eight months (weight, length, and head circumference) and reported no differences between infants of smokers and infants of nonsmokers. Fox and colleagues (1990) examined the growth of children at three years of age in relation to prenatal smoking; after adjusting for multiple confounders including postpartum smoking, they found no differences in height and weight. In a study of 2,622 children, Eskenazi and Bergman (1995) found that pregnancy serum cotinine levels when divided into low, medium, and high tertiles were associated with a -3 cm, -3 cm, and -8 cm reduction in the heights, respectively, of children of mothers who had smoked during pregnancy compared with children of nonsmoking mothers. These authors reported that this effect was largely due to a prenatal exposure rather than to a postpartum secondhand smoke exposure.

Studies examining associations between maternal smoking during pregnancy and the child's cognitive development also have reported mixed results.

Key results

- There was a strong association between maternal smoking and SIDS* for mothers who smoked 1–9 cigarettes/day during pregnancy compared with nonsmokers (adjusted OR = 1.6–2.5), and for mothers who smoked   10 cigarettes/day during pregnancy (adjusted OR = 2.3–3.8)
- SIDS rates increased with the amount smoked for all U.S. and Swedish racial and ethnic groups
- Smoking is one of the most important preventable risk factors for SIDS, and smoking prevention programs have the potential to substantially lower SIDS rates

- The RR of low birth weight in the second pregnancy compared with not smoking during either pregnancy was 1.82 for those who smoked during the second pregnancy only and 1.87 for those who smoked during both pregnancies
- The highest risk of fetal mortality (RR = 1.79) occurred among mothers who did not smoke during the first pregnancy, but who smoked   1 pack/day during the second pregnancy
- Women with the highest RR (1.65) for neonatal deaths were those who reduced their smoking during the second pregnancy but did not stop

Several studies reported associations with smoking during pregnancy and subsequent cognitive development, behavioral outcomes, and educational achievements of infants and children of varying ages (Rantakallio 1983; Naeye and Peters 1984; Sexton et al. 1990) (Table 5.13). Many studies adjusted for several potentially important confounders, and six reported a dose-response relationship (Fogelman and Manor 1988; Weitzman et al. 1992; McCartney et al. 1994; Fried et al. 1997, 1998; Obel et al. 1998) (Table 5.13). The outcomes examined in these studies were babbling abilities in eight-month-old infants, performances on standardized tests of cognitive abilities in school-age children, auditory processing in school-age children, behavioral problems as reported by parents and teachers, and educational achievements of young adults. A few studies had information on both prenatal and postpartum smoking by mothers and parents; two of these studies reported that a prenatal but not a postpartum secondhand smoke exposure was associated with adverse outcomes (Weitzman et al. 1992; McCartney et al. 1994). Yet, in both studies, prenatal and postpartum smoking was significantly associated with adverse developmental outcomes. Many studies examined multiple outcomes, and not all were significantly associated with smoking during pregnancy. Overall, observed differences between smokers and nonsmokers were relatively small.

Three studies reported no association between maternal smoking during pregnancy and adverse cognitive or behavioral outcomes (Fergusson and Lloyd 1991; Baghurst et al. 1992; Eskenazi and Trupin 1995).

Fergusson and Lloyd (1991) studied children aged 12 years and adjusted for several potential confounders, including postpartum smoke exposure. Once confounders were accounted for, no differences between children of mothers who smoked and children of mothers who did not smoke during their pregnancies were observed. In a study of more than 2,000 five-year-old children, Eskenazi and Trupin (1995) found that active smoking during pregnancy did not result in cognitive deficits in children according to results from the Raven Coloured Progressive Matrices Test and the Peabody Picture Vocabulary Test at five years of age. Thus, studies on cognitive development and behavioral problems report small or no differences among children of pregnant smokers compared with children of pregnant nonsmokers. Confounding by unmeasured factors cannot be ruled out as an explanation for the small differences, which may not be clinically meaningful.

Evidence Synthesis

The evidence on the relationship between maternal smoking during pregnancy and congenital malformations is mixed. Most studies report no association between maternal smoking and congenital malformations as a whole. This finding is not unexpected, as it is unlikely that smoking during pregnancy would be linked to all of the multiple etiologic pathways involved in the various malformations.

Table 5.13   Studies on the association between maternal smoking and cognitive development, behavioral problems, and growth in children

Study	Study period	Population	Definition of smoking
Goldstein 1971	1958–1965	14,848 children aged 7 years	Smoking status after the fourth month of pregnancy: • None • Medium: 1–10 cigarettes/day • Heavy: >10 cigarettes/day
Rantakallio 1983	1966–1981	3,688 children: 1,844 had mothers who smoked during pregnancy and 1,844 controls	• Light smokers: smoked <10 cigarettes/day • Heavy smokers: smoked 10 cigarettes/day at the end of the second month of pregnancy
Barr et al. 1984	NR*	453 infants 8 months of age	Average nicotine use was calculated by multiplying the number of cigarettes/day by nicotine content of the brand used by each woman
Naeye and Peters 1984	1959–1976	9,024 children	• Nonsmokers • Light smokers: 1–19 cigarettes/day • Heavy smokers: 20 cigarettes/day
Fogelman and Manor 1988	1958–1981	8,200 young adults aged 23 years	Number of cigarettes/day smoked after the fourth month of pregnancy (0, 1–9, 10–19, 20)
Sexton et al. 1990	NR	364 children 3 years of age	• Women who smoked >10 cigarettes/day at the beginning of pregnancy were recruited and followed. At the eighth month, they were classified either as quitters or smokers • Quitters quit smoking during the pregnancy • Smokers smoked throughout the pregnancy

*NR = Data were not reported.

Key results

- Nonsmoking mothers had children 0.6 cm taller than those of heavy smoking women
- If birth weight is excluded from the analysis, the difference in height between the two groups rises to 1.0 cm
- Smoking during pregnancy influences height partly by lowering the birth weight, and partly by an effect over and above its effect on birth weight

- Children of smokers were more prone to respiratory diseases, were shorter, and did not perform as well in school compared with controls
- Smoking mothers differed from controls in social class and health status and were more often unemployed and without families. Even when these factors were taken into account, maternal smoking had an effect on the children's physical and mental development

- Maternal smoking during pregnancy was not significantly related to infant size at 8 months
- At birth, nicotine exposure was more strongly associated with infant size than was alcohol exposure, but by 8 months most of the nicotine effects had dissipated and alcohol, not nicotine, remained significantly related to infant size at 8 months

- Hyperactivity, short attention span, and lower scores on spelling and reading tests were more frequent for children whose mothers had smoked throughout pregnancy
- Cognitive abnormalities were mild, with achievement test scores only 2 to 4% lower in children whose mothers smoked during pregnancy
- Fetal hypoxemia may contribute to behavioral abnormalities in children of smokers

- There was weak evidence for a relationship between smoking during pregnancy and self-reported heights of the offspring after several confounding variables were controlled for, but the article does not specify if the offspring are shorter or taller
- The average difference in height between children whose mothers smoked 20 cigarettes/day during the second half of pregnancy and those whose mothers did not was 0.93 cm in males and 1.83 cm in females
- The relation of smoking during pregnancy with educational achievements of the offspring, measured by the highest qualification achieved, was strong after controlling for confounding factors

- Children whose mothers quit smoking compared with those whose mothers continued to smoke performed at a statistically significant higher level on cognitive tests
- Statistical adjustments for environmental factors, characteristics of the child, and fetal maturity did not account for these observed differences
- Findings suggest that quitting smoking after becoming pregnant may prevent some cognitive damage to the fetus

Table 5.13 Continued

Study	Study period	Population	Definition of smoking
Bauman et al. 1991	1960–1967	19,044 children born to women enrolled in a health plan	• Whether the mother or her husband smoked cigarettes at the time of the examination • Average number of cigarettes/day by both parents
Fergusson and Lloyd 1991	NR	A birth cohort of children followed for 12 years (1,265 at birth, reduced to 1,020 at 12 years due to attrition)	Maternal cigarette smoking during pregnancy was measured by an estimated typical daily cigarette use for each trimester (0, 1–10, 11–20, >20)
Baghurst et al. 1992	May 1979–May 1982	548 children from a cohort study	Nonsmokers had never smoked, or had smoked no more than five cigarettes during the pregnancy
Weitzman et al. 1992	1979–1986	NR	• Maternal smoking status: <1 pack/day or ≥1 pack/day • Children's exposure: prenatal only (mother smoked only during pregnancy) • Passive only (mother smoked only after pregnancy) • Prenatal plus passive
Fergusson et al. 1993	1977–1992	1,265 children	• During pregnancy: mean number of cigarettes/day during each trimester • After pregnancy: estimated average daily cigarette use of the mother from the child's birth to 5 years of age
Olds et al. 1994	April 1978–September 1980	400 families: mothers and their children	Maternal prenatal smoking classified by cigarettes smoked/day (0, 1–9, ≥10)

†CI = Confidence interval.

Key results

- Parental smoking was associated with children's performance on at least one cognitive measure, and the effect persisted after the inclusion of controls
- Children of parents who were smokers but had quit by the time of the examination performed better than children whose smoking parents continued to smoke
- There was a dose-response relationship between parental smoking and cognitive performance

- Children whose mothers smoked during pregnancy scored significantly lower on standardized tests of intelligence, reading, and mathematical ability than children whose mothers did not smoke
- After adjusting for confounding covariates, there was no detectable relationship between maternal smoking and her child's cognitive ability
- Results suggest that smoking does not have a causal effect on children's cognitive ability, which may be influenced by the disadvantaged home environment from which these children come

- Differences in mean developmental test scores between children whose mothers smoked and those whose mothers did not smoke differed slightly
- The results were not statistically significant when adjusted for socioeconomic status, quality of home environment, and the mother's intelligence, suggesting that social and environmental factors are major confounders of the association between exposure to maternal smoking and neuropsychological development in childhood

- Children's behavior problems were associated with exposures to maternal cigarette smoking, with evidence suggesting a dose-response relationship
- Children whose mothers smoked both during and after pregnancy had 1.17 additional problems associated with smoking <1 pack/day and 2.04 additional problems associated with smoking 1 pack/day
- Children whose mothers smoked <1 pack/day were 1.41 times as likely to have extreme behavior problem scores and 1.54 times as likely if their mothers smoked 1 pack/day both during and after pregnancy

- Children whose mothers smoked >20 cigarettes/day had mean problem behavior scores between 0.16 and 0.56 standard deviations higher than those of children whose mothers were nonsmokers
- Smoking after pregnancy was not significantly associated with increased rates of childhood problem behaviors
- Smoking during pregnancy may be associated with small but detectable increases in the risks of problem behaviors in childhood

- Children whose mothers smoked 10 cigarettes/day during pregnancy had intellectual test scores that were 4.35 points lower (95% CI[†], 0.02–8.68) than scores of children whose mothers did not smoke during pregnancy
- The greatest difference in children's intellectual functioning was found in cigarette smoking measured at the end of pregnancy
- Maternal cigarette smoking during pregnancy poses a unique risk for neurodevelopmental impairment among children

Table 5.13   Continued

Study	Study period	Population	Definition of smoking
Eskenazi and Bergmann 1995	1964–1967	2,622 women enrolled in a children's health and development study	• Nonsmokers: women who had never smoked or had quit before pregnancy • Smokers: number of cigarettes/day (0, 1–9, 10–19, 20–29, 30)
Eskenazi and Trupin 1995	1964–1967	2,124 children aged 5 years from a children's health and development study	NR
Fried et al. 1997	1978	131 children aged 9–12 years with ascertained prenatal exposures to marijuana and cigarettes	• Smoking during pregnancy was measured by nicotine scores (average number of cigarettes/day multiplied by the nicotine content of the specified brand) • Categorized as nonsmoking, light, or heavy (0 mg nicotine/day, >0 but <16 mg nicotine/day, and 16 mg nicotine/day; 16 mg nicotine/day = approximately 1 pack of cigarettes of average strength)
Obel et al. 1998	1991–1992	2,302 singletons without any disability born at a hospital in a 1-year period	• Nonsmoking • 1–9 cigarettes/day • 10–19 cigarettes/day • 20 cigarettes/day
Kelmanson et al. 2002	1999–2000	250 singletons aged 2–4 months born during study period	• Maternal smoking during pregnancy (yes/no) • Maternal exposure during pregnancy to others who smoked (yes/no)

‡OR = Odds ratio.

Key results

- Children of mothers who were heavy smokers during pregnancy were shorter at 5 years of age than children of nonsmokers
- The effect appears to be attributable to in utero exposure rather than postnatal secondhand smoke exposure during early childhood
- The study was not able to demonstrate whether women who quit smoking during pregnancy can prevent long-term sequelae on growth

- Children whose mothers smoked during pregnancy had somewhat higher adjusted Raven and PPVT (child cognitive development) scores than children of nonsmokers, although they did not differ in activity level
- Children who were exposed to tobacco smoke during childhood had lower adjusted Raven and PPVT scores and were rated more active by their mothers; the differences may be attributed to uncontrolled confounding of sociobehavioral factors
- The possibility that secondhand smoke smoke exposure during childhood may be more hazardous to neurodevelopment than prenatal exposure cannot be ruled out

- There was a dose-dependent relationship between prenatal cigarette exposure and lower language and reading scores of the children
- Maternal exposure to secondhand smoke during pregnancy had no effect on either reading or language outcomes, whereas the child's exposure to secondhand smoke adversely affected language but not reading

- There was a dose-response association between the number of cigarettes/day during pregnancy and babbling abilities of infants
- Smoking 10 cigarettes/day during pregnancy almost doubled the risk (OR[‡] = 2.0 [95% CI, 1.1–3.6]) of the infant's being a nonbabbler at 8 months of age; the risk was higher for children who were breastfed for less than 4 months (OR = 2.7 [95% CI, 1.3–5.8])

- Infants born to smoking mothers had a higher frequency of low birth weight (p = 0.031)
- Smoking during pregnancy was significantly associated with the infant's intensity of reactions (p = 0.0039)
- There was no significant association between smoking during pregnancy and infant activity, rhythmicity, approachability, adaptability, mood, persistence, distractibility, and threshold

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For selected malformations, oral clefts in particular, several studies have reported positive associations with smoking. The biologic evidence on the etiology in general for oral clefts is scant, therefore making it difficult to establish a causal role of smoking. Recent studies on interactions between genes and the environment are contributing further to understanding the etiology of oral clefts and the role of smoking, but much work is still needed.

The data on maternal smoking and elevated rates of SIDS are abundant and consistent in the literature. However, evidence is not available to determine whether prenatal smoking alone is causally related to SIDS. Studies have demonstrated that prenatal smoking combined with postpartum passive exposure elevates the risk beyond that for a passive exposure to smoking alone. Some data on biologic plausibility are emerging. One hypothesized mechanism is that exposure to cigarette smoke during pregnancy has effects on the fetal respiratory system and the brain that may, in turn, contribute to SIDS.

Studies examining relationships between maternal smoking during pregnancy and subsequent physical growth of the child report mixed findings. Moreover, the magnitude of reported differences between children of smokers and nonsmokers, especially for physical growth, is extremely small. Information on the mechanisms by which the physical and cognitive development of children are affected by exposures to prenatal smoking is not available and potential confounding is a concern.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts.

3. The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children.

Implications

Mothers who smoke increase their children's risk of SIDS substantially; smoking during pregnancy and after the child's birth should be a target for forceful and effective interventions. Future studies of smoking and congenital malformations should selectively build on the accumulating evidence of the few malformations for which there are elevated risks. Although further studies may elucidate the relationship between prenatal smoking and the risk of SIDS, and subsequent physical and cognitive development, study design issues may be too challenging to overcome. Specifically, the challenges are the identification of a sizable group of infants who are only exposed prenatally and the ability to adjust for the multiple confounders that may intervene between pregnancy and infant or child outcomes.

Conclusions

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality.

2. The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women.

Pregnancy and Pregnancy Outcomes

3. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

4. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

5. The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption.

6. The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia.

7. The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation.

8. The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight.

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9. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general.

10. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts.

11. The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neuro-cognitive development of children.

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Chapter 6
Other Effects

Introduction

This chapter addresses evidence on smoking and health effects over a range of specific diseases and non-specific but adverse consequences. The associations reviewed appear to reflect both specific and non-specific pathways of injury by tobacco smoke. The evidence indicates that smoking should be considered not only a cause of specific diseases and conditions, but a contributing factor to nonspecific morbidity and a diminished quality of life.

Diminished Health Status

This section focuses on the question of whether cigarette smokers have poorer health in comparison with nonsmokers, beyond the already well-characterized burden of morbidity and mortality from the specific diseases caused by smoking. The hypothesis that smoking might impair health in general draws plausibility from the toxicologic richness of tobacco smoke, the well-documented systemic distribution of tobacco smoke components and metabolites, and the effects on host defenses, including the immune system. Additionally, impairment of organ function short of the level at which clinical disease is diagnosed may leave the smoker vulnerable to otherwise well-tolerated threats to health. For example, the reduction of lung function found in many smokers who do not have overt chronic obstructive pulmonary disease (COPD) may increase the risk for developing a more severe illness with a respiratory infection, or having a respiratory complication following surgery.

This section reviews studies that have addressed a number of health status indicators (Figure 6.1) including direct reports of health status or responses to an instrument that provides a health status index, and indirect indicators such as medical services utilization data. When interpreting the findings of these studies, consideration needs to be given to the potential causal pathways linking smoking to a poor health status, the assessment and measurement of health status, and the potential for biases, such as from confounding, to affect associations of smoking with these outcome measures.

For the diseases caused by smoking, direct causal pathways are implicit. For example, substantial evidence supports the hypothesis that smoking causes lung cancer through the direct deposition of tobacco smoke carcinogens in the respiratory tract. For some of the outcome measures considered in this section, pathways are far less certain and may be both direct and indirect. Increased absenteeism might reflect, for example, the tendency of smokers to have more severe respiratory illnesses than nonsmokers, possibly attributable to the effects of smoking on respiratory defenses or because smokers tend to have a lower level of lung function.

The outcomes considered in this section have multiple determinants. Health status itself is an integrative measure reflecting the net consequences of the many varied factors that determine health and well-being. To the extent that smokers differ from non-smokers in these factors, there is a potential for confounding to distort associations of smoking with the outcome measures. Studies show, for example, that smokers and nonsmokers differ in aspects of lifestyle and in their approaches to health care (e.g., the use of preventive services such as multiphasic testing [Oakes et al. 1974] and screening [Beaulieu et al. 1996; Edwards and Boulet 1997]). Additionally, the suite of relevant confounding factors may differ from outcome to outcome, and for some outcomes there is uncertainty as to the relevant confounding factors. Some of the individual characteristics that affect the decision to start smoking and to continue to smoke also may be determinants of risk for the outcomes considered here.

Figure 6.1   A conceptual model for the relationship between cigarette smoking and diminished health status
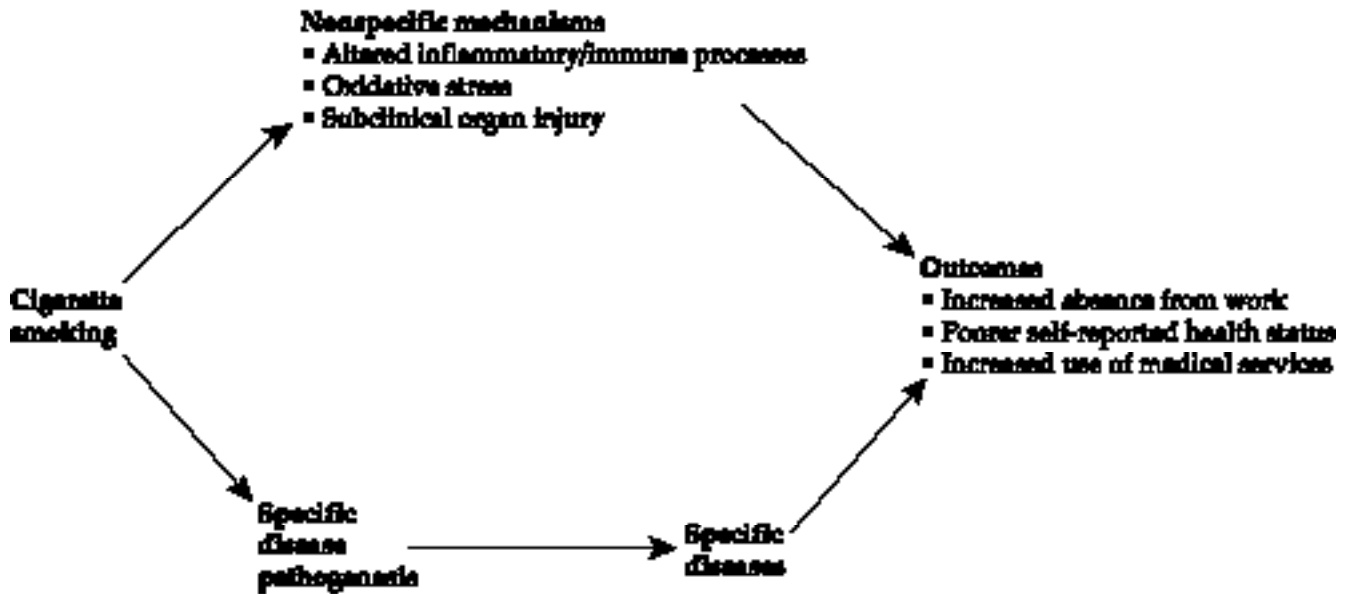
Conclusions of Previous Surgeon General's Reports

Extensive research over time has identified cigarette smoking as a cause of specific diseases, and many reports from the Surgeon General have focused on smoking and these diseases. These reports have also addressed more general and nonspecific adverse consequences of smoking, such as increased rates of absenteeism from work or the utilization of medical services among smokers in comparison with nonsmokers. Conclusions from the reports that relate to these outcomes are listed in Table 6.1, including findings on general respiratory morbidity. Reports of increased morbidity from common and frequent viral and bacterial respiratory infections among smokers have been reviewed (U.S. Department of Health and Human Services [USDHHS] 1990) and are among the topics covered in Chapter 4 of this report. However, the overall health status of smokers compared with nonsmokers has not been comprehensively addressed in prior Surgeon General's reports.

Biologic Basis

Cigarette smoke, inhaled through the mouth into the lungs, reaches lung airways and alveoli, where the tobacco smoke components pass into the systemic circulation (Murray 1986). The airways and alveoli themselves are exposed to the gaseous and particulate components of tobacco smoke as many of these components readily pass through the alveolar-capillary membrane into the alveolar capillaries and then circulate throughout the body. Nicotine, for example, which is among these components, reaches the brain within 10 seconds after smoke is inhaled (USDHHS 1988). It is distributed throughout the body and has been found in breast milk (Schwartz-Bickenbach et al. 1987; Schulte-Hobein et al. 1992; Golding 1997) and in cervical mucus (Prokopczyk et al. 1997). Carbon monoxide, a diffusible gas, moves from the alveoli into the capillaries where it binds tightly to the hemoglobin of the red blood cells. Benzo[*a*]pyrene, a well-characterized carcinogen in tobacco smoke, can be found bound to the blood cells in the epithelial cells of the airways of smokers and in their major organs. The effects of smoking on host defenses and aspects of immune function have been covered in prior reports (USDHHS 1990, 1994) and again in this report. These effects may have the consequence of increasing risks for infections, whether of the respiratory tract or other organs. However, there has been less research to date on infections beyond those of the respiratory tract. This systemic distribution of tobacco smoke components underlies the associations between smoking and disease that are well documented for many organs including cardiovascular disease, stroke,

Table 6.1   Conclusions from previous Surgeon General's reports concerning smoking as a cause of diminished health status and respiratory morbidity

Statement	Surgeon General's report
"Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers." (p. 302)	1964
"Even relatively young cigarette smokers show increased respiratory symptoms and decreased ventilatory function." (p. 31)	1967
"Cigarette smokers have higher rates of disability than nonsmokers, whether measured by days lost from work among the employed population, by days spent ill in bed, or by the most general measure — days of 'restricted activity' due to illness or injury." (p. 24)	1967
"Cigarette smokers show an increased prevalence of respiratory symptoms, including cough, sputum production, and breathlessness, when compared with nonsmokers." (pp. 9–10)	1971
"Respiratory infections are more prevalent and severe among cigarette smokers, particularly heavy smokers, than among nonsmokers." (p. 10)	1971
"Investigations of high school students have demonstrated that abnormal pulmonary function and pulmonary symptoms are more common in smokers than nonsmokers." (p. 48)	1972
"Cigarette smokers have also been shown to have a significantly longer duration of respiratory symptoms following mild viral illness than nonsmokers." (p. 78)	1975
"In addition to an increased risk of COPD, cigarette smokers are more frequently subject to and require longer convalescence from other respiratory infections than nonsmokers. Also, if they require surgery, they are more likely to develop postoperative respiratory complications." (p. 61)	1975
"The age-adjusted incidence of acute conditions (e.g., influenza) for males who had ever smoked was 14 percent higher, and for females 21 percent higher, than for those who had never smoked cigarettes." (p. 1-12)	1979
"A wide variety of alterations in the immune system have been observed due to cigarette smoking." (p. 1-18)	1979
"Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms." (p. 1-18)	1979
"Cigarette smokers have an increased frequency of respiratory symptoms, and at least two of them, cough and sputum production, are dose-related." (p. 1-18)	1979

Table 6.1   Continued

Statement	Surgeon General's report
"The relationship between smoking and an increased prevalence of respiratory symptoms in the adult has been well established in studies of hospital and clinic patients, working groups, total communities, and representative samples of the community." (p. 6-20)	1979
"In summary, many recent studies demonstrate a higher frequency of respiratory symptoms in women who smoke as compared to women who do not smoke. This is true in surveys including children, adolescents, young adults, working age, and elderly women. The effect of cigarette smoking is related in terms of both the number of cigarettes and years smoked." (p. 156)	1980
"Relationships between smoking and cough or phlegm are strong and consistent; they have been amply documented and are judged to be causal." (p. 47)	1984
"Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is the overwhelmingly most important cause of cough, sputum, chronic bronchitis, and mucus hypersecretion." (p. 48)	1984
"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (p. 349)	1990
"Former smokers have better health status than current smokers as measured in a variety of ways, including days of illness, number of health complaints, and self-reported health status." (p. 92)	1990

Sources: U.S. Department of Health, Education, and Welfare 1964, 1967, 1971, 1972, 1975, 1979; U.S. Department of Health and Human Services 1980, 1984, 1990.

and cancers of the kidney and urinary bladder. The widespread distribution may also lead to more general effects on health.

This same systemic distribution may have non-specific effects as well, contributing to a reduction in health status. Exposure to tobacco smoke components causes smoke-specific diseases such as bladder cancer (carcinogens in urine come in contact with the bladder) and atherosclerosis, probably reflecting multiple underlying mechanisms with inflammation having a central role (Cross et al. 1999). Underlying mechanisms might include heightened oxidative stress and reduced antioxidant defenses, increased inflammatory activity, reduced host defenses against infection, and lowered reparative capacities of tissues. The evidence on these mechanisms is at varying levels of development. This section focuses on oxidative stress as an example, selected because the available literature is extensive.

Oxidative Stress

Oxidative stress refers to an increased exposure to oxidants and/or a decreased antioxidant capacity, caused by oxygen radicals that mutate DNA, promote atherosclerosis, and lead to chronic lung injury. Oxidative stress is now hypothesized to be a general mechanism underlying aging and many of the chronic diseases associated with aging, contributing to the development of cancer, cardiovascular disease, and COPD (Ames et al. 1995). Mounting evidence points to chronic oxidative stress as one mechanism whereby smoking affects health. Smoking is associated with

evidence of chronic systemic inflammation, perhaps a consequence of the chronic oxidative stress experienced by the smoker (Cross et al. 1999; Hecht 1999). The oxidant load posed by cigarette smoke is substantial; the tar component is estimated to contain 10^{18} oxygen radicals per gram of tar and the gas component to have as many as 10^{15} other organic radicals per puff (Repine et al. 1997).

A number of comparisons between smokers and nonsmokers have been made with respect to measures of biomolecular oxidative damage, including oxidative injury to DNA, proteins, and lipids. A widely used assay for quantifying oxidative damage to DNA is 8-hydroxydeoxyguanosine (8-OH-dG). The assay measures hydroxyl radical-induced DNA damage at C8 of guanine (Lagorio et al. 1994), which has been linked experimentally to cigarette smoke condensate (Leanderson and Tagesson 1990). Cultured human lung cells exposed to cigarette smoke had 70 percent higher 8-OH-dG levels than unexposed cells (Leanderson and Tagesson 1992). DNA from the lung tissue of smokers had 42 percent higher 8-OH-dG levels than the DNA from nonsmokers, and 8-OH-dG concentrations increased according to the number of cigarettes smoked per day (Asami et al. 1997).

Studies comparing 8-OH-dG levels in DNA from smokers and nonsmokers are summarized in Table 6.2. In general, regardless of the biologic material, smokers tend to have greater damage. A strong dose-response association with the number of cigarettes smoked was observed in one study (Lodovici et al. 2000), but an inverse dose-response trend was observed in another (van Zeeland et al. 1999). When levels of 8-OH-dG in circulating lymphocytes were compared before and after cigarettes were smoked, Kiyosawa and colleagues (1990) observed that 8-OH-dG levels increased 54 percent after smoking. A similar but less frequently used approach to determine biomolecular oxidative damage is to assay 8-hydroxyguanine, which has been found in leukocyte DNA (Asami et al. 1997) and in urine (Suzuki et al. 1995) of smokers at concentrations at least 90 percent higher than in nonsmokers.

Oxidative damage to proteins can occur in both amino acid residues and the peptide backbone in protein, and can be assessed by assaying protein carbonyls (Reznick et al. 1992; Eiserich et al. 1995). Studies document that exposing human plasma (Reznick et al. 1992; Eiserich et al. 1995; Panda et al. 1999) or saliva (Nagler et al. 2000) to cigarette smoke increased protein carbonyl concentrations by more than 300 percent. Compared with unexposed guinea pigs, guinea pigs

exposed to cigarette smoke had plasma protein carbonyl concentrations more than 30 times greater (Panda et al. 2000). In humans, protein carbonyl concentrations in 15 smokers were 61 percent higher than in 5 comparison nonsmokers (Lee et al. 1998).

Isoprostanes constitute a specific measure of lipid peroxidation and serve as good general markers of oxidative injury (Morrow and Roberts 1996). Free radicals catalyze the peroxidation of arachidonic acid to F2-isoprostanes (Morrow and Roberts 1996). Circulating (Morrow et al. 1995) and urinary (Morrow et al. 1995; Reilly et al. 1996) isoprostane levels have been shown to be markedly higher in smokers than in nonsmokers (Table 6.2). Circulating (Morrow et al. 1995; Pilz et al. 2000) and urinary (Reilly et al. 1996; Pilz et al. 2000) isoprostane concentrations decreased at least 20 percent within two weeks of smoking cessation. Babies of smoking mothers had concentrations of isoprostane levels in their umbilical arteries and veins more than 110 percent higher than babies of nonsmoking mothers (Obwegeser et al. 1999).

Another widely used measure of free radical catalyzed lipid peroxidation is thiobarbituric acid reactive substances (TBARS) (Bonithon-Kopp et al. 1997). Comparisons of TBARS between smokers and nonsmokers have shown that (1) current smokers have higher TBARS levels—sometimes strikingly higher, (2) levels of TBARS rise after smoking, and (3) the influence of smoking on increased lipid peroxidation can be offset somewhat by administering the antioxidant micronutrients vitamins C and E (Table 6.2).

Antioxidant Depletion

Even as smokers are exposed to the oxidative stress of regularly inhaling cigarette smoke, substantial evidence shows that blood levels of individual antioxidant micronutrients are lower in current smokers than in nonsmokers. This association has been clearly demonstrated for vitamin C (McClean et al. 1976; Bolton-Smith et al. 1991; Ross et al. 1995; Lykkesfeldt et al. 1997) and for total and selected carotenoids including -carotene, -carotene, and cryptoxanthin (Aoki et al. 1987; Stryker et al. 1988; Bolton-Smith et al. 1991; Pamuk et al. 1994; Ross et al. 1995; Brady et al. 1996; Alberg et al. 2000). For vitamin C (Brook and Grimshaw 1968; Buiatti et al. 1996; Marangon et al. 1998) and several of the specific carotenoids (Comstock et al. 1988; Nierenberg et al. 1989; Buiatti et al. 1996; Marangon et al. 1998), circulating concentrations tend to decline with increasing number of cigarettes smoked.

Table 6.2   Studies on the association between smoking and oxidative injury

Study	Population	Group
8-OH-dG* in DNA from peripheral leukocytes		
Kiyosawa et al. 1990	10 healthy male volunteers, aged 20–22 years, blood drawn before and 10 minutes after smoking 2 cigarettes in 10 minutes	Total
Takeuchi et al. 1994	79 healthy male factory workers, aged 25–59 years	Current and never Former and never
Degan et al. 1995	180 smokers and 73 nonsmokers	Total
Lee et al. 1998	20 healthy volunteers, 15 smokers, aged 19–31 years	Total
van Zeeland et al. 1999	102 healthy adults, aged 25–45 years	Current and never Former and never
Lodovici et al. 2000	56 healthy male and female volunteers, aged 18–64 years	Current and never Former and never
8-OH-dG in DNA from urine		
Loft et al. 1992	83 randomly selected persons, aged 40–64 years	Total
Tagesson et al. 1993	129 persons (30 asbestos-exposed workers, 28 rubber workers, 30 azo dye factory workers, 41 controls)	Total Controls Asbestos-exposed Rubber Azo dye
Lagorio et al. 1994	65 randomly sampled gas station attendants, Italy	Current and never Former and never
Tagesson et al. 1996	343 workers from the Swedish art glass industry	Total Men Women
Protein carbonyls in plasma		
Lee et al. 1998	20 healthy volunteers, 15 smokers, aged 19–31 years	Total

*8-OH-dG = 8-hydroxydeoxyguanosine.

Results			
Precessation	**Postcessation**	**Percentage difference**	**Comments**
3.3 (before smoking)	5.1 (after smoking)	54.5	8-OH-dG/10^6 dG
1.10 (never)	1.075 (current)	-2.3	8-OH-dG/10^5 dG; numbers were
1.10 (never)	1.00 (former)	-9.1	abstracted from figure
5.94	7.14	20.2	8-OH-dG mol/10^5 mol dG
2.21	3.61	63.3	8-OH-dG/10^5 dG
34.0 (never)	29.3 (current)	-13.8	8-OH-dG/10^6 dG
34.0 (never)	35.2 (former)	3.5	
15.3 (never)	33.1 (current)	116.3	8-OH-dG/10^6 dG
15.3 (never)	17.8 (former)	16.3	
2.13	3.20	50.2	8-OH-dG pmol/24 hours
1.367	1.478	8.1	Weighted average; 8-OH-dG
1.01	1.13	11.9	µmol/mol creatinine
1.38	1.41	2.2	
1.60	1.34	-16.3	
2.10	1.88	-10.5	
1.32 (never)	1.41 (current)	6.8	8-OH-dG µmol/mol creatinine
1.32 (never)	1.29 (former)	-2.3	
11.5	13.4	16.5	Weighted average; 8-OH-dG
12.6	14.1	11.9	nmol/L
9.3	12.1	30.1	
1.59	2.56	61.0	Protein carbonyl/nmol/mg of protein

Table 6.2   Continued

Study	Population	Group
Isoprostanes in plasma		
Morrow et al. 1995	Pilot: 16 smokers, 8 nonsmokers Main study: 10 smokers, 10 age- and gender-matched nonsmokers	Pilot: free Pilot: esterified Main: free Main: esterified Main: cessation/free Main: cessation/esterified
Pilz et al. 2000	47 smokers ready to quit smoking, aged 30–66 years	Total: cessation
Isoprostanes in urine		
Morrow et al. 1995	10 smokers, 10 age- and gender-matched nonsmokers	Total
Reilly et al. 1996	24 chronic smokers, 24 age- and gender-matched controls, aged 20–47 years	Total Moderate Heavy Cessation
Practicò et al. 1998	6 smokers, 6 nonsmokers, aged 31–45 years	Total IPF_{2a} pg/ng creatinine Total 8-iso PGF_{2a} pg creatinine
Pilz et al. 2000	47 smokers ready to quit smoking, aged 30–66 years	Total: cessation
Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)		
Harats et al. 1989	16 smokers, 12 age-matched nonsmokers, aged 23–56 years	Total (stored) Total (fresh)

[†]LDL = Low-density lipoprotein.

Results			
Precessation	**Postcessation**	**Percentage difference**	**Comments**
90	166	84.4	
290	496	71.0	
103	242	135.0	
345	574	66.4	
250	156	60.3	2 weeks after cessation
624	469	33.0	
490	300	63.3	pmol/L (serum in plasma) 3 weeks after cessation
415	870	109.6	pmol/nmol creatinine
63.7	122.5	92.3	pmol/mmol creatinine
54.1	92.7	71.3	
54.1	176.5	226.2	dose-response relationship
145.5	114.6	27.0	
1,525	740	106.1	Cox-dependent and independent
270	95	184.2	excretion in human urine
580	330	75.8	3 weeks after cessation; pg 8-epi-PGF_{2a}/mg creatine
0.287	0.198	44.9	Smokers had not smoked for
0.180	0.154	16.9	24–40 hours Plasma: nmol/mL LDL[†]: nmol/mg protein

Table 6.2   Continued

Study	Population	Group
Thiobarbituric acid reactive substances (TBARS) in malondialdehyde (MDA)		
Harats et al. 1990	17 smokers before and 2 weeks after vitamin C supplementation; 10 smokers before and 90 minutes after smoking	Study I No treatment Vitamin C treatment Study II: TBARS in LDL No treatment Vitamin C treatment Vitamin E treatment Study II: Plasma TBARS No treatment Vitamin C treatment Vitamin E treatment
Scheffler et al. 1990	17 male smokers, 21 male nonsmokers, mean age 30–32 years	Time course of TBARS in LDL during incubation 0 hours 1 hour 2 hours 3 hours 4 hours 5 hours 6 hours
Scheffler et al. 1992	17 smokers, 21 nonsmokers	Incubation for 3 hours 1 week storage
Duthie et al. 1993	242 adults, aged 45–69 years	Total
Miller et al. 1997	107 nonsmokers, 14 smokers, mean age 48–49 years	Total
Mosca et al. 1997	90 adults, aged 39–80 years	Total: former vs. never
Motoyama et al. 1997	40 healthy males, 20 smokers, 20 nonsmokers, aged 26–35 years	Total Smokers: pre/postsmoking
Berr 1998	74 men and 815 women, aged 59–71 years	Men Women
Durak et al. 1999	61 adults, aged 25–81 years	Total

	Results		
Precessation	**Postcessation**	**Percentage difference**	**Comments**
Before smoking	After smoking		Plasma: nmol/mL
0.106	0.187	76.4	LDL: nmol/mg protein
0.138	0.145	5.1	
0.584	1.275	118.3	
0.683	1.333	95.2	
0.627	0.663	5.7	
0.106	0.197	85.4	
0.107	0.118	10.3	
0.119	0.123	3.4	
			LDL: nmol/mL
1	1	0	
1	1	0	
9	4	125	
14	7	100	
14	7	100	
14	7	100	
14	7	100	
14.2	7.3	94.5	
12.0	9.8	22.4	
1.87	1.76	6.3	nmol/mL
24	21	14.3	μmol/mL
0.05 (former)	0.07 (never)	-28.6	LDL: μmol/nmol
1.8	1.3	38.5	nmol/mL
2.7 (after smoking)	1.7 (before smoking)	35.3	After: 10 minutes
			Before: at least 8 hours of abstaining from smoking
2.97	2.90	2.41	μmol/L in plasma
3.06	2.96	3.4	
0.55	0.31	77.4	nmol/g tissue

Whether the differences in antioxidant levels across smoking categories reflect direct depletion or differing dietary intake has been controversial. If smoking directly depletes antioxidant micronutrients, the effect would presumably be acute. In fact, levels of vitamin C and selected carotenoids increased when measured in persons after 84 hours without smoking a cigarette (Brown 1996), and an experimental exposure of plasma equivalent to six puffs of cigarette smoke completely depleted the ascorbic acid present in the serum (Handelman et al. 1991; Eiserich et al. 1995). When measurements were taken at baseline and 20 minutes after smoking a cigarette, decreases in circulating micronutrient concentrations were observed (Yeung 1976).

Smoking and the Leukocyte Count

Studies show that smokers when compared with nonsmokers have generally heightened inflammation, increased white blood cell counts that remain elevated after cessation, and increased levels of other markers of inflammation such as C-reactive protein (Allen et al. 1985; Das 1985; de Maat et al. 1996; Tracy et al. 1997; Danesh et al. 1999).

The association between smoking and the leukocyte count has been extensively investigated, with numerous studies showing that current smokers have higher leukocyte counts than nonsmokers (Table 6.3). In most studies, the increase was 20 percent or more in smokers compared with nonsmokers and was present across strata of age, gender, and race. The leukocyte count increases with the number of cigarettes smoked per day and with the depth of inhalation. Similar dose-response trends were evident in other studies that did not lend themselves to inclusion in the summary tables (Petitti and Kipp 1986; Schwartz and Weiss 1991). Dose-response trends tend to be weaker when examined in relation to either pack-years[1] or duration of smoking, suggesting that smoking has an immediate effect on the leukocyte count.

The findings from former smokers are consistent with both an immediate and a persistent effect of smoking. In comparisons with lifetime nonsmokers (Table 6.4), former smokers consistently have higher white blood cell counts, but the difference is smaller than that between current smokers and lifetime nonsmokers. In most of the studies, the leukocyte counts for former smokers were only about 5 percent greater than those for lifetime nonsmokers. The excess is persistent

(Petitti and Kipp 1986; Schwartz and Weiss 1991; Sunyer et al. 1996), although it decreases with increasing duration of cessation, becoming closer to the average counts found in lifetime nonsmokers (Yarnell et al. 1987; Hansen et al. 1990b). A short-term (overnight) abstention from cigarettes did not strongly influence the counts (Noble and Penny 1975).

Prospective cohort studies have tracked changes in leukocyte counts in relation to changes in smoking. In a study of Kaiser Permanente enrollees in the San Francisco Bay area, the leukocyte counts increased 12 percent among those who started smoking during the follow-up, but it decreased 7 percent among smokers who had quit during the follow-up (Friedman et al. 1973). In a subsequent study that compared leukocyte counts of 9,392 persistent smokers with those of 3,825 smokers who had quit, the quitters experienced significantly higher declines (Friedman and Siegelaub 1980). In a cohort of homosexual men seronegative for human immunodeficiency virus (HIV), Sunyer and colleagues (1996) observed that decreases in smoking were followed by decreased white blood cell counts, and increases in smoking were followed by increased white blood cell counts. Furthermore, changes in white blood cell counts were proportional to changes in smoking patterns (Table 6.5).

These observations of inflammatory markers, particularly the leukocyte counts, are consistent with the induction of systemic chronic inflammation in smokers, perhaps reflecting the substantial oxidant load from habitual cigarette smoking. Studies of former smokers suggest that this state of inflammation does not simply reflect an acute effect. These observations support one of the mechanisms, oxidative stress, proposed as contributing to the general effects of smoking on health.

Epidemiologic Evidence

Absenteeism

Absenteeism from work is frequent and costly (Steers and Rhodes 1978); its multiple causes include individual and organizational factors (Steers and Rhodes 1978). Researchers investigating the effect of smoking on absenteeism face the challenges of controlling for potential confounding by individual-level factors such as alcoholism, and specifying how smoking could act in combination with other factors at both

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[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

individual and group levels. While the literature is extensive (Table 6.6), the studies vary in the success with which these challenges have been met, partially reflecting the extent and quality of available data.

Current Smokers

In studies with varying designs conducted in diverse locations, cigarette smokers consistently have had higher rates of absenteeism than nonsmokers (Table 6.6). The evidence also indicates that the duration of sickness absences tends to be longer for smokers and smokers miss more cumulative worktime than nonsmokers. The association between smoking and absenteeism has been observed in both men and women of all ages. Sickness absences have been measured in a variety of ways, including lost worktime per unit of time, episodes of absenteeism, and the duration of absences. The finding that smoking is associated with absenteeism, regardless of the index used, documents consistency of the observed association. Although most studies were cross-sectional or retrospective in design, two were prospective cohort studies (North et al. 1993; Niedhammer et al. 1998) and another studied smoking histories in relation to workplace attendance records during the preceding nine years (Holcomb and Meigs 1972). The findings of these prospective studies confirm that smoking preceded the absenteeism. In a few studies, the association with smoking was observed primarily in men but not in women (Green et al. 1992; North et al. 1993), but in general the findings have been consistent across all of the subgroups studied. Of the 30 studies that were the sources for the data abstracted into Table 6.6, 17 studies found that absenteeism among smokers was at least 20 percent greater than among nonsmokers in all subgroups.

Two additional reports not included in the table also provide evidence of an association between smoking and absence frequency (Ferguson 1973; Donaldson et al. 1999). In a study of 516 men employed in four occupational groups in Australia, Ferguson noted that ". . .the employee with repeated absence also tended (p <0.10), more often than the resister" (employee without repeated absences) ". . .to smoke more than 15 cigarettes daily" (Ferguson 1973, p. 336). In a study of 146 lumber company employees, a tobacco use scale was not correlated (r = 0.01) with absenteeism (Donaldson et al. 1999).

In several studies summarized in Table 6.6 that assessed the relationship between current smoking and absenteeism (Athanasou 1979; Andersson and Malmgren 1986; Hawker and Holtby 1988; Bertera 1991), current smokers were compared with all nonsmokers, including former smokers. As discussed in the following section, absenteeism rates among former smokers are persistently elevated compared with those of lifetime nonsmokers. Thus, using an "unexposed" comparison category that includes former smokers along with lifetime nonsmokers will dilute associations that would be estimated when using a "pure" unexposed category consisting solely of persons who have never smoked.

In the two studies that assessed the dose-response relationship with the number of cigarettes smoked, the likelihood of being absent increased strongly with the number of cigarettes smoked per day (Lowe 1960; Holcomb and Meigs 1972). In a retrospective cohort study of 226 male factory employees in Connecticut that included eight years of follow-up, the rate of long-term absences increased 43 percent, 57 percent, and 100 percent compared with nonsmokers for those who smoked less than one pack, one pack, and more than one pack of cigarettes per day, respectively (Holcomb and Meigs 1972). In a study of more than 3,300 male General Electric employees in England, the number of days absent for medical reasons increased 11 percent, 13 percent, 26 percent, and 57 percent compared with nonsmokers for those who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes per day, respectively (Lowe 1960).

This body of evidence shows increased absenteeism among smokers, while providing only limited information on the reasons for the absences. A significant proportion of sickness absences in smokers would be expected to be due to smoking-associated illnesses. Athanasou and colleagues (1981) hypothesized that smoking acts as a susceptibility factor, increasing the risks for other harmful occupational exposures. In one study, smoking was associated with a significantly increased likelihood of absences resulting from problems as diverse as back symptoms, digestive tract symptoms, and neck and upper limb symptoms (Dimberg et al. 1989). A recent review summarizing 38 studies showed an increased risk for back pain in smokers compared with nonsmokers in the majority of studies (Goldberg et al. 2000). In another study, absences were elevated not only for "medical reasons" but also for "other" reasons (Lowe 1960). Substantial evidence also documents that smokers are more likely than nonsmokers to have on-the-job injuries (Lowe 1960; Naus et al. 1966; Reynolds et al. 1994; Forrester et al. 1996). Because smoking increases absences for a broad set of health problems, and not just specific smoking-associated illnesses, the underlying causal pathways are likely to be multiple and general, reflecting the systemic nature of the effects of smoking.

Table 6.3   Studies on the association between current smoking and white blood cell counts

Study	Population	Group
Howell 1970	2,483 men, aged 40–54 years	Total
Corre et al. 1971	4,264 men, aged 46–52 years	Total
Friedman et al. 1973	86,488 Kaiser Permanente enrollees	Men Women
Okuno 1973	106 men, aged 20–39 years	Total
Parulkar et al. 1973	130 Indian men, aged 16–60 years	Total
Billimoria et al. 1975	121 men and women	Men Women
Fisch and Freedman 1975	14,961 women, aged 18–60 years	Total
Helman and Rubenstein 1975	800 healthy patients, aged 20–69 years	Men Women
Noble and Penny 1975	40 male medical students, aged 20–30 years	Total
Parulkar et al. 1975	379 Indian men, aged 20–60 years	Total
Silverman et al. 1975	263 persons, aged 20–78 years	Total
Tibblin et al. 1979	1,462 women, aged 38–60 years	Total
Dodsworth et al. 1981	737 men and women, aged 18–64 years	Men Women
Zalokar et al. 1981	7,206 men, aged 43–53 years, France	Total
Heinemann et al. 1982	30 male students	Total
Mellstrom et al. 1982	449 men, aged 70 years, Goteberg, Sweden	Total
Nancy et al. 1982	100 male smokers, 100 male nonsmokers	Total
Chan-Yeung et al. 1984	2 cohorts of men (652 cedar mill workers, 440 office workers), British Columbia	Powell River Kitimat
Sparrow et al. 1984	1,510 men, aged 23–80 years	Total

| Results (white blood cell counts) | | | |
Smokers	Nonsmokers	Percentage difference	Comments
7,257	5,818	24.7	Per mm³ of blood
6,549	5,705	14.8	Per mm³ of blood
8.2 8.3	7.1 7.3	15.5 13.7	10^{-3} per mm³ of blood; weighted averages
6,719	5,440	23.5	Per mm³ of blood; weighted average for smokers
8,868	6,369	39.2	Per mm³ of blood
8.0 7.0	5.5 5.8	45.5 20.7	10^{-3} per mm³ of blood
7.59	6.26	21.2	10^{-3} per mm³ of blood; weighted averages
8.7 8.8	7.1 7.1	22.5 23.9	10^{-3} per mm³ of blood; weighted average
7,625	5,934	28.5	Per mm³ of blood
9,782	7,299	34.0	Per mm³ of blood
6,803	6,023	13.0	Per mm³ of blood
6.1	4.9	24.5	10^{-3} per mm³ of blood; weighted average for smokers
7.2 7.2	6.1 6.5	14.8 10.8	10^{-3} per mm³ of blood
5,740	7,280	26.8	10^{-3} per mm³ of blood
7.85	6.95	12.9	10^{-3} per mm³ of blood
6.3	5.3	18.9	10^{-3} per mm³ of blood
9,156	7,310	25.3	Per mm³ of blood
8.4 7.6	6.7 6.2	25.4 22.6	10^{-3} per mm³ of blood; weighted averages
8,400	6,830	23.0	Per mm³ of blood; weighted average for smokers

Table 6.3   Continued

Study	Population	Group
Vanuxem et al. 1984	43 persons, France	Total
Carel and Eviatar 1985	35,000 Israelis, aged 20–80 years	Men Women
Nielsen 1985	82 healthy persons, aged 21–74 years	Total
Husgafvel-Pursiainen 1987	70 persons, mean age 38 years	Total
Yarnell et al. 1987	4,445 men, aged 45–59 years, from 2 communities in the United Kingdom	Caerphilly Speedwell
Chan-Yeung et al. 1988	750 male aluminum smelter workers	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Total
Olsen et al. 1991	1,900 Dow Chemical Company employees	Men Women
Casasnovas et al. 1992	572 military academy cadets, mean age 19 years	Total
Mühlhauser et al. 1993	288 patients with diabetes	Men Women
Mercelina-Roumans et al. 1994	712 pregnant women	Total
Hogarty et al. 1995	6,837 men and women, mean age 58 years	Men Women
Bovill et al. 1996	5,201 persons, aged >64 years	Men Women
Calori et al. 1996	27 monozygotic twin pairs discordant for smoking	Total
Jensen et al. 1998	434 persons	Total

Results (white blood cell counts)			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
8.0	5.8	37.9	10^{-3} per mm³ of blood
8.2	7.2	13.9	10^{-3} per mm³ of blood
7.9	7.1	11.3	
7.6	5.9	28.8	10^{-3} per mm³ of blood
9.3	6.8	36.8	10^{-3} per mm³ of blood; weighted average for smokers
8.0	5.9	35.6	10^{-3} per mm³ of blood; weighted average for smokers
8.2	6.0	36.7	
7,560	6,113	2.37	Per mm³ of blood; weighted average for smokers
7,553	6,094	28.9	Per mm³ of blood
8,290	6,340	30.8	Per mm³ of blood
7,790	6,460	20.6	
8,194	7,332	11.8	Per mm³ of blood
8.1	6.4	26.6	10^{-3} per mm³ of blood
7.6	6.8	11.8	
10.7	9.1	17.6	10^{-3} per mm³ of blood
7.0	6.2	11.4	10^{-3} per mm³ of blood; smokers included all ever smokers
6.8	6.4	6.3	
7.6	6.3	20.6	10^{9} per liter of blood
7.3	6.1	19.7	
6.2	5.2	8.4	10^{3} per µL of blood
7.6	5.8	31.0	10^{-3} per mm³ of blood

Table 6.4   Studies on the association between former smoking and white blood cell counts

Study	Population	Group
Friedman et al. 1973	86,488 Kaiser Permanente enrollees	Men: 38,279 Women: 48,207
Tibblin et al. 1979	1,462 women, aged 38–60 years	Total
Zalokar et al. 1981	7,206 men, aged 43–53 years, France	Total
Mellstrom et al. 1982	449 men, aged 70 years, Goteberg, Sweden	Total
Chan-Yeung et al. 1984	2 male cohorts, British Columbia	652 cedar mill workers 440 office workers
Sparrow et al. 1984	1,510 men, aged 23–80 years	Total
Knoke et al. 1987	2,225 white men with high cholesterol	Total
Yarnell et al. 1987	4,445 men, aged 45–59 years, in 2 communities	Quit <1 year Quit 1–4 years Quit 5–9 years Quit 10 years
Chan-Yeung et al. 1988	750 male aluminum smelter employees	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Quit 1–2 years Quit 2–3 years Quit 3–5 years Quit 5–10 years Quit 10 years
Olsen et al. 1991	1,900 Dow Chemical Company employees	Men Women
Sunyer et al. 1996	2,435 patients, aged >18 years	Total

Results (white blood cell counts)			
Former smokers	**Never smokers**	**Percentage difference**	**Comments**
7.3	7.1	2.8	10^{-3} per mm³ of blood;
7.7	7.3	5.5	weighted averages
5.1	4.9	4.1	10^{-3} per mm³ of blood
5,840	7,280	1.7	Per mm³ of blood
5.8	5.3	9.3	10^{-3} per mm³ of blood
6.8	6.7	1.5	10^{-3} per mm³ of blood;
6.3	6.2	1.6	weighted averages
6,900	6,830	1.0	Per mm³ of blood
5,558	5,355	3.8	Per mm³ of blood
6.96	5.95	17.0	10^{-3} per mm³ of blood;
6.64	5.95	11.6	weighted averages
6.38	5.95	7.2	
6.15	5.95	3.4	
6,302	6,113	3.1	Per mm³ of blood
6,371	6,094	4.5	Per mm³ of blood
6,343	6,094	4.1	
6,297	6,094	3.3	
6,285	6,094	3.1	
6,212	6,094	1.9	
6,650	6,340	4.9	Per mm³ of blood
7,110	6,460	10.1	
6,501	6,265	3.8	Per mm³ of blood

Table 6.5   Studies on the percentage difference in white blood cell counts stratified by smoking patterns

Study	Population	Measure of dose	Group
Howell 1970	2,483 men, aged 40–54 years	Number of cigarettes/day	Total
Corre et al. 1971	4,264 men, aged 46–52 years	Inhalation[†] Number of cigarettes/day Number of cigarettes/day	Total Noninhalers[‡] Inhalers
Okuno 1973	106 men, aged 20–39 years	Number of cigarettes/day	Total
Fisch and Freedman 1975	14,961 women, aged 18–60 years	Number of cigarettes/day	Total
Parulkar et al. 1975	379 Indian men, aged 20–60 years	Inhalation Duration of smoking Number of cigarettes/day	Total
Silverman et al. 1975	268 persons, aged 20–78 years	Pack-years[§]	Total
Tibblin et al. 1979	1,462 women, aged 38–60 years	Number of cigarettes/day	Total
Dodsworth et al. 1981	737 men and women, aged 18–64 years	Number of cigarettes/day	Men Women
Zalokar et al. 1981	7,206 French men, aged 43–53 years	Inhalation Number of cigarettes/day	Total
Sparrow et al. 1984	1,510 men, aged 23–80 years	Number of cigarettes/day	Total
Tell et al. 1985	439 Norwegians, aged 14–16 years	Number of cigarettes/day	Males Females
Petitti and Kipp 1986	63,041 enrollees in Kaiser Permanente	Number of cigarettes/day	White men White women Black men Black women
Husgafvel-Pursiainen 1987	70 persons, mean age 38 years	Number of cigarettes/day	Total
Knoke et al. 1987	2,225 white men with high cholesterol	Number of cigarettes/day	Total

*NR = Data were not reported.
[†]Inhalation = Inhaling cigarette smoke.
[‡]Noninhalers = Not inhaling cigarette smoke.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

| Nonsmokers (referent) | Percentage difference | | | | | | Comments |
| | Smokers, by category of dose (1 = low) | | | | | | |
	1	2	3	4	5	6	
0	22.0	30.1	NR*	NR	NR	NR	None
0	6.3	23.5	NR	NR	NR	NR	None
0	1.7	7.4	9.8	10.0	NR	NR	
0	10.8	21.5	27.7	29.7	NR	NR	
0	18.9	37.9	NR	NR	NR	NR	
0	10.9	28.1	NR	NR	NR	NR	Weighted averages
0	31.5	36.8	NR	NR	NR	NR	None
0	31.5	34.9	35.5	38.4	NR	NR	
0	28.1	28.1	40.1	38.9	NR	NR	
0	6.5	12.9	16.9	14.2	11.2	27.2	None
0	8.2	24.5	24.5	34.7	38.8	NR	None
0	12.9	1.6	17.7	14.5	29.0	NR	None
0	4.9	3.3	13.1	16.4	31.1	NR	
0	6.5	26.8	NR	NR	NR	NR	None
NR	12.5	24.6	29.3	33.6	NR	NR	
0	19.4	29.2	NR	NR	NR	NR	None
0	5.8	13.5	NR	NR	NR	NR	None
0	-3.8	16.4	NR	NR	NR	NR	
0	10.4	17.9	25.4	23.9	31.3	NR	None
0	8.5	15.5	21.1	22.5	19.7	NR	
0	10.0	13.3	21.7	18.3	18.3	NR	
0	4.5	10.4	13.4	16.4	10.4	NR	
0	47.1	33.8	NR	NR	NR	NR	None
0	21.9	36.8	46.6	49.0	54.9	NR	None

Table 6.5   Continued

Study	Population	Measure of dose	Group
Yarnell et al. 1987	4,445 men, aged 45–59 years, in 2 communities	Number of cigarettes/day	Caerphilly Speedwell
Chang-Yeung et al. 1988	750 male aluminum smelter workers	Number of cigarettes/day	Total
Hansen et al. 1990b	12,866 men, aged 35–37 years	Number of cigarettes/day Inhalation[†]	Total Total
Olsen et al. 1991	1,900 Dow Chemical Company employees	Number of cigarettes/day Pack-years[§]	Men Women Men Women
Sunyer et al. 1996	2,435 patients, aged >18 years	Number of cigarettes/day	Total
Jensen et al. 1998	434 (298 smokers, 136 nonsmokers)	Number of cigarettes/day	Total

[‡]Inhalation = Inhaling cigarette smoke.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Former Smokers

The evidence is consistent that former smokers are less likely to be absent from work compared with persistent smokers. Former smokers tend to have somewhat higher absenteeism rates than persons who have never smoked (Table 6.7), but the increases are much smaller than those for current smokers. The analyses performed by Wooden and Bush (1995) with former smokers (n = 4,812) in the 1989–1990 Australian National Health Survey illustrate the seemingly paradoxic relationship between quitting smoking and absenteeism. In a multiple regression model that included both the duration of active smoking and time since quitting, the number of years that a former smoker had smoked remained a strong predictor of absenteeism, and the likelihood of absences declined gradually over time since cessation (Wooden and Bush 1995). Similarly, Manning and colleagues (1989) found differences between recent and sustained quitters, and observed considerably higher absenteeism rates for recent quitters compared with long-term quitters. These results indicate that both prior smoking history and time since quitting are factors strongly associated with absenteeism, but in opposite directions. This pattern may arise because some smokers may quit when diagnosed with an illness caused by smoking, and the recent quitters may thus already have a smoking-induced illness that predisposes them to lost worktime.

In interpreting evidence linking smoking to a diminished health status, including absenteeism, untangling the direct effects of smoking from the indirect effects is challenging, as smokers and nonsmokers may differ in potential confounding factors. Nonetheless, given the scope of the evidence available and the diversity of the populations studied, the literature does provide insights into the role of smoking as a cause of absenteeism.

With regard to confounding, alcohol use is a major factor of concern. Alcohol use has been linked to absenteeism in some studies, and smokers drink more than nonsmokers (Smith 1970; Turner 1988; Ault

Nonsmokers (referent)	Percentage difference						Comments
	Smokers, by category of dose (1 = low)						
	1	2	3	4	5	6	
0	30.4	37.2	40.1	NR	NR	NR	None
0	33.4	36.4	41.8	NR	NR	NR	
0	17.7	24.7	28.7	NR	NR	NR	None
0	11.2	22.1	25.5	28.2	30.7	NR	None
0	12.5	18.6	19.7	23.9	27.0	NR	
0	11.8	32.0	45.6	NR	NR	NR	None
0	2.2	23.8	34.4	NR	NR	NR	
0	13.9	26.3	32.3	42.4	NR	NR	
0	3.1	29.4	24.1	34.5	NR	NR	
0	2.4	13.5	26.4	32.1	NR	NR	None
0	31.0	46.6	NR	NR	NR	NR	None

et al. 1991; Marmot et al. 1993; Vasse et al. 1998). Smokers are also more likely to be heavy alcohol drinkers and to use illicit substances (Merrill et al. 1999; Best et al. 2000; Brain et al. 2000; Dawson 2000), and heavy alcohol and illicit substance use, rather than cigarette smoking, could increase the likelihood of workplace absences. Studies that adjusted for alcohol consumption have generally (Hendrix and Taylor 1987; Bush and Wooden 1995; Wooden and Bush 1995), but not universally (Ault et al. 1991), found smoking to be associated with frequent absences, implying that the association of smoking with alcoholism is not due to confounding. Studies were not found that accounted for illicit substance use in assessing the association between smoking and workplace absences. Less likely is the possibility that the association between smoking and absences reflects confounding by characteristics that are linked both to smoking (see the section on "Health Status" later in this section) and to an increased risk for frequent absences. For example, women are consistently absent from work more often than men (Leigh 1983; Pines et al. 1985; Steinhardt et al. 1991). But women assume a disproportionate share of family responsibilities such as staying home with sick children, and the relative importance of smoking may therefore be less. Observations of persons with "psychosocial problems" (Leijon and Mikaelsson 1984) and anxiety/neuroses (Taylor 1968; Ferguson 1973) document increased risks for absenteeism, and if such persons are more likely to smoke, confounding is possible. Given the range of populations studied, confounding by psychosocial factors seems unlikely.

Of the relevant pathway factors leading to health-related absences, age is the primary demographic characteristic that is a potential modifying or confounding factor. Socioeconomic status, another potential confounding or modifying factor, is inherently restricted in studies within occupational groups. Age is associated with both absenteeism (Pines et al. 1985) and health status. The association between smoking and absenteeism has been observed consistently across a broad spectrum of age strata in the summarized

Table 6.6   Studies on the association between current smoking and absenteeism

Study	Population	Group
Lowe 1960	3,341 male General Electric Company employees, England	Total Medical reasons Other reasons
Holcomb and Meigs 1972	226 male factory employees	Total
Wilson 1973	1970 National Health Interview Survey, persons aged 17 years	Total Men Women 17–44 years 45–64 years 65 years
Athanasou 1979	424 persons, aged 15–67 years	Men Women
U.S. Department of Health and Human Services 1980	Representative sample of U.S. population aged 17 years	1965 Men Women 1977 Men Women
Janzon et al. 1981	1,037 Swedish men, aged 47–48 years	Total
Smith et al. 1981	826 staff members from 12 Australian organizations	Men Women

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Number of days absent during the year			None
11.19	9.81	4.1	
6.59	5.49	20.0	
4.61	4.32	6.7	
Total days lost per person-year			Short-term: <7 days (unverified medical
6.37	4.42	44.1	absences)
Absence rate: short-term			Long-term: 10 days (verified medical
0.96	0.38	152.6	absences) during 1956–1964
Days lost: short-term			
1.89	0.95	98.9	
Absence rate: long-term			
0.10	0.07	42.9	
Days lost: long-term			
4.48	3.47	29.1	
Mean workdays lost per year			None
6.3	4.4	43.2	
5.8	3.7	56.8	
7.4	5.1	45.1	
5.8	3.8	52.6	
7.2	5.7	26.3	
7.7	4.3	79.1	
Duration of sickness absence (days)			Nonsmokers included never smokers plus
1.15	0.68	69.1	former smokers
1.05	1.03	1.9	
Workdays lost per year due to illness and injury per currently employed persons			None
5.9	4.6	28.3	
6.6	4.8	37.5	
5.9	4.2	40.5	
6.6	5.7	15.8	
Percent who used sick leave >3 times during the past year			None
13	4	225.0	
Mean number of days off work			Ratio of days off work for smokers compared
1.59	1.0	59.0	with nonsmokers
1.36	1.0	36.0	

Table 6.6   Continued

Study	Population	Group
Leigh 1983	1,200 participants in the 1973 Quality of Employment survey, based on a nation-wide probability sample	Men White collar Blue collar Women White collar Blue collar
Parkes 1983	221 nursing students, aged 18–25 years	Total
Andersson and Malmgren 1986	1,313 Saab employees, aged 50–59 years, Sweden	Wage earners Salaried
Van Tuinen and Land 1986	406 Missouri Department of Health employees	Total Men Women
Hendrix and Taylor 1987	463 U.S. Department of Defense employees	Total
Blake et al. 1988	1,230 army recruits in basic training	Total
Hawker 1988	252 female student nurses	Total
Dimberg et al. 1989	2,814 Volvo employees, Sweden	Total
Gallop 1989	169 pulp and paper industrial company employees	Self-reported records (n = 82) Payroll records
Manning et al. 1989	324 employees of 2 companies, aged 20–75 years	Baseline Short-term Long-term 1-year follow-up Short-term Long-term

*OR = Odds ratio.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean number of absences during the past 2 weeks			OR*
1.07	1.0	7.0	
0.72	1.0	-28.0	
1.50	1.0	50.0	
1.89	1.0	89.0	
1.23	1.0	23.0	
2.19	1.0	119.0	
Mean number of absences during 6 months			None
3.46	1.95	77.4	
Mean number of days absent			Nonsmokers included never smokers plus former smokers
26	24	8.3	
20	16	25.0	
Mean hours of sick leave per month			None
5.0	4.3	16.3	
4.5	3.7	21.6	
5.4	4.7	14.9	
Average number of sick days in the past 6 months			None
3.2	2.9	10.3	
Mean time spent in the clinic for visits related to upper respiratory infections (hours)			Not absenteeism per se; military conditions controlled confounding
30.6	17.3	76.9	
Percent absent >7 days (yes/no)			Nonsmokers included never smokers plus former smokers
37.5	15.0	150.0	
Average days lost in 1 year			None
21	14	50.0	
Mean illness absences last year			Payroll records were used to verify self-reported records
5.1	4.1	24.4	
10.3	7.9	30.4	
Mean hours absent per month			Short-term: 2 days
2.15	1.69	27.2	Long-term: >2 days
1.44	0.78	84.6	
1.73	1.17	47.9	
1.85	1.67	10.8	

Table 6.6   Continued

Study	Population	Group
Batenburg and Reinken 1990	907 employees from 4 worksites, employed at least 12 months	Men by age Total <20 years 20–29 years 30–39 years 40–49 years 50 years Women by age Total <30 years 30–39 years 40 years
Jones et al. 1990	1,893 Johnson & Johnson Company employees, aged 17–45 years	1979 1980 1981
Ault et al. 1991	2,406 (subset of 5,000) randomly sampled U.S. families; data were collected in 1967	Total
Bertera 1991	45,976 DuPont employees	Total Total
Low and Mitchell 1991	30 steel foundry workers, mean age 33.5 years	Total Total Total
Green et al. 1992	5,826 employees of 21 Israeli factories, aged 20–64 years	Men 20–44 years 45–64 years Women 20–44 years 45–64 years Men 20–44 years 45–64 years Women 20–44 years 45–64 years

Results			Comments
Smokers	**Nonsmokers**	**Percentage difference**	
Sickness absence hours			Authors noted that male nonsmokers aged
3.9	3.5	11.4	50 years had medical conditions predisposing
3.7	3.4	8.8	them to absenteeism
4.0	3.6	11.1	
4.0	3.3	21.2	
3.6	2.9	24.1	
3.9	4.5	-13.3	
3.6	3.1	16.1	
3.0	3.1	-3.2	
3.8	2.7	40.7	
4.1	3.6	13.9	
Mean sick hours per year			None
49.5	31.4	45.2	
52.8	37.7	40.1	
54.2	38.5	40.8	
Days absent from work			The association disappeared when the effects of
8.37	6.49	29.0	other job characteristics were properly assessed
Mean annual illness days			Nonsmokers included never smokers plus
3.69	2.79	32.3	former smokers
Mean annual illness costs			
$3,971.27	$3,011.23	31.9	
Mean number of absence episodes during the year			It is unclear how the total percentage difference
6.0	5.0	20.0	could occur, given the results for the number
Mean duration of episodes in days			and duration of absence episodes
2.0	1.0	100.0	
Total days absent during the year			
6.0	9.0	-33.3	
Mean days lost over 2 years			The percentages noted in italics were adjusted
9.99	7.40	*35.0*	for age and occupation (and also present cause-
8.57	6.44	33.1	specific data)
14.45	11.15	29.6	
15.19	16.13	*-5.8*	
13.91	13.69	1.6	
17.49	24.93	-29.8	
Mean days per absence episodes			
5.17	4.65	11.2	
9.09	7.51	21.0	
3.86	4.04	-4.5	
7.07	7.66	-7.7	

Table 6.6   Continued

Study	Population	Group

Ryan et al. 1992, 1996	2,537 U.S. Postal Service employees	Total
		  1-year follow-up
		  2-year follow-up

North et al. 1993	10,314 London civil servants, aged 35–55 years, prospective cohort	Men Women Men Women
Halpern and Warner 1994	1990 U.S. National Health Interview Survey (nationally representative sample)	Total
Post et al. 1994	405 workers at an animal feed mill, mean ages 38 years (clerks) and 42 years (blue collar), Netherlands	Clerks Blue collar
Bush and Wooden 1995	1989 Australian National Health Survey; n = 21,984 employed persons from randomly selected households	Men Women
Tsai et al. 1997	2,287 Shell Oil Company employees, mean age 36 years	Men Women Men Women
Niedhammer et al. 1998	12,555 men (aged 40–50 years) and women (aged 35–50 years), prospective cohort	Men Women Men Women

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean absence rate			None
5.4	4.1	31.7	
7.9	5.8	36.2	
Periods of absence: short			Adjusted rate ratios; short-term: unverified
1.46	1.0	46.0	medical absences; long-term: verified medical
1.09	1.0	9.0	absences
Periods of absence: long			
1.81	1.0	81.0	
1.37	1.0	37.0	
Work-loss days past 2 weeks			
1.48	1.0	48.0	OR
Limitations of ability to work			
1.27	1.0	27.0	OR
Absence prevalence rate			
2.36	1.0	136.0	OR
1.64	1.0	64.0	OR
Any absence 2 weeks before the interview			Adjusted OR; also adjusted for health status
1.43	1.0	43.0	and health indicators
1.32	1.0	32.0	
Average duration of absence (days)			None
6.1	3.5	74.3	
6.8	3.6	88.9	
Morbidity frequency rate			
28.5	13.3	114.3	
20.4	13.2	54.5	
Periods of absence			Adjusted rate ratios
1.24	1.0	24.0	
1.26	1.0	26.0	
Absence days			
1.45	1.0	45.0	
1.26	1.0	26.0	

results, implying that the association does not reflect confounding by age.

Only a few studies provide prospective data concerning absenteeism following smoking cessation; the findings suggest that smoking cessation is associated with better attendance at work. A particularly informative study conducted with employees of a North Carolina pharmaceutical company compared the attendance patterns of former smokers before and after quitting with attendance patterns of a matched group of persistent smokers (Jackson et al. 1989). In the time preceding smoking cessation by the cessation group, the persistent smokers tended to have fewer absences than the smokers who went on to stop smoking. However, during the three years following cessation, the mean number of annual sick days declined among those who quit. Absences continued to increase for persistent smokers, leading to a widening gap in absences between the two groups. The study was small, with only 70 persons participating. In a randomized trial of nine worksite smoking cessation programs, employees who were smokers at baseline had a significant reduction (p = 0.002) in self-reported sick days after stopping smoking (Jeffrey et al. 1993). In another study evaluating a workplace health promotion program that reduced smoking prevalence, the authors reported significant reductions in absenteeism for program participants but not for nonparticipants (Wood et al. 1989).

The evidence that reduced absenteeism follows cessation complements findings based on comparisons of current smokers with nonsmokers. The reduced rate after cessation supports a causal interpretation, rather than attributing the association to an indirect pathway or to confounding factors.

In summary, there is consistent evidence demonstrating that employees who are current smokers have a greater likelihood of absences from work compared with employees who have never smoked. Additional evidence is needed on dose-response trends and, more importantly, on changes in absence rates before and after smoking cessation. Other reviewers have concluded that reduced absenteeism could lead to potential savings that can be accrued from smoking cessation programs in the workplace (Kristein 1983; Warner et al. 1996).

Medical Services Utilization

Medical services utilization provides another measure of the global effects of smoking on health. The most important utilization indicators in studies on smoking can be grouped into three general categories:

(1) costs, (2) outpatient visit rates, and (3) hospitalization rates. Interpreting these findings requires consideration of the many factors influencing medical services utilization. Smokers, for example, are less likely than nonsmokers to use preventive services such as screening (Beaulieu et al. 1996; Edwards and Boulet 1997). However, the high incidence of smoking-induced diseases among smokers will tend to drive their medical care needs. The socioeconomic and educational differences between smokers and nonsmokers also complicate data interpretation because of potential confounding. Comparisons of smokers within well-defined groups, such as particular workforces or health care plans, should provide unbiased comparisons.

Costs

In evaluating the relationship between smoking and medical care costs, only those studies directly addressing expenditures were considered (Table 6.8). The literature on comparative lifetime costs of medical care for smokers and nonsmokers based on assumed models and projections was not considered relevant to this chapter. Of the seven studies reviewed, six showed the medical costs of smokers to be greater by at least 15 percent in at least one subgroup. In one study of enrollees in a health maintenance organization, smokers had costs 25 percent higher than nonsmokers among those younger than 65 years of age, but few differences were observed in those age 65 years or older (Terry et al. 1998). Only the study by Vogt and Schweitzer (1985) on enrollees in Kaiser Permanente found no differences between smokers and nonsmokers.

Two studies not included in Table 6.8 are also relevant. In a population of retirees followed for one year, smoking was associated with added health care costs of more than $1,900 per year per pack of cigarettes smoked per day, after adjusting for age, gender, education, seat belt use, and alcohol consumption (Leigh and Fries 1992). In a study conducted as part of a worksite health promotion program in Birmingham, Alabama, smokers were found to have incurred more costs than nonsmokers, but the data were not presented (Weaver et al. 1998).

Outpatient Services

In several studies (Table 6.8), smokers were at least 15 percent more likely than nonsmokers to use outpatient services (Peters and Ferris 1967; Palmore 1970; Chetwynd and Rayner 1986; Freeborn et al. 1990);

one study found an increased likelihood of 6 percent (Rice et al. 1986). In studies that stratified age and gender, strong associations with smoking were observed in particular groups. Male smokers were more frequent users of outpatient services than were male nonsmokers, but this difference was not found among females in one study (Oakes et al. 1974). In another study, this gender difference occurred in young but not old persons (Ashford 1973). Three studies showed only small differences in the use of outpatient services between smokers and nonsmokers (Vogt and Schweitzer 1985; Halpern and Warner 1994; Miller et al. 1999).

The frequency of outpatient visits does not appear to increase with the number of cigarettes smoked (Peters and Ferris 1967; Balarajan et al. 1985; Marsden et al. 1988). However, regardless of the number of cigarettes smoked, some studies documented a large difference in the number of visits by smokers compared with nonsmokers.

Hospitalization

In all but one of the studies considered (Terry et al. 1998), smokers had higher hospitalization rates than nonsmokers; the differences were at least 10 percent. In two other studies that stratified age and gender, one study found an association in males but not in females (Oakes et al. 1974), and the other study found an association only among younger females (Ashford 1973).

Additional studies corroborate the results summarized in Table 6.8. In a study of a cohort of retirees followed for one year, the number of packs of cigarettes smoked per day was significantly associated with the number of days hospitalized (Leigh and Fries 1992). In a study of 1,000 veterans accessing the Veterans Administration system in Connecticut, tobacco users were significantly more likely (p <0.01) than nonusers to be hospitalized, and tobacco users were significantly more likely (p<0.01) than nonusers to be hospitalized and to spend more days in the hospital (Benedetto et al. 1998). In a study of Kaiser Permanente enrollees in Oregon, Pope (1982) observed a weak, nonsignificant correlation between a smoking index and hospitalization rates in the youngest age group for men and women (aged <35 years), but this association was not present in the other age groups studied.

Dose-response data are available from two prospective cohort studies (Table 6.9). In the Coronary Drug Project, the five-year hospitalization rates for smokers compared with nonsmokers plateaued at the lowest smoking category, and were more compatible with a threshold relationship than with a nonthreshold

dose-response relationship. However, it was unclear whether these analyses accounted for the higher mortality rates experienced by smokers relative to nonsmokers during the follow-up period (Coronary Drug Project Research Group 1976). In a two-year follow-up of smokers in the American Cancer Society Cancer Prevention Study I (CPS-I) a strong dose-response relationship was present: compared with those who smoked 1 to 9 cigarettes per day, those who smoked 10 to 19, 20 to 39, and 40 or more cigarettes per day had an increased likelihood of hospitalization during the follow-up period of 8.5 percent, 14.6 percent, and 28.0 percent, respectively (Hammond 1965). In a cross-sectional survey of U.S. military personnel that compared smokers with nonsmokers, those who smoked one-half of a pack or less, one pack, and one and one-half packs or more per day had increases in self-reported days hospitalized of 28.1 percent, 6.3 percent, and 54.7 percent, respectively (Marsden et al. 1988).

Former Smokers

Studies comparing the use of medical services by former smokers with lifetime nonsmokers are summarized in Table 6.10. Costs were 26 percent higher for former smokers in one study (Pronk et al. 1999), and higher for some services but not higher overall in another study (Vogt and Schweitzer 1985). In every study, former smokers were more likely than lifetime nonsmokers to use outpatient services. In a study conducted in the United Kingdom that was stratified by age and gender, smokers were more likely than nonsmokers to have general practice health care providers visit their homes for an illness (Ashford 1973). The use of outpatient services by smokers remained elevated compared with that of nonsmokers long after smoking cessation (Halpern and Warner 1994). For hospitalizations the findings were mixed, with three studies showing higher rates in former smokers (Van Peenen et al. 1986; Kaplan et al. 1992; Halpern and Warner 1994). In one of these studies, however, the difference was eliminated after adjusting for age, and in two other studies there were only small differences between former smokers and lifetime nonsmokers. In another study that stratified age and gender, former smokers were more likely than lifetime nonsmokers to be hospitalized in some strata, but less likely in others, without a consistent pattern (Ashford 1973).

These studies generally have not taken into account prior smoking history and time since quitting, nor have they considered whether development of a

Table 6.7   Studies on the association between former smoking and absenteeism

Study	Population	Group
Holcomb and Meigs 1972	226 male factory employees	Total
Wilson 1973	1970 National Health Interview Survey, persons aged 17 years	Total Men Women 17–44 years 45–64 years 65 years
U.S. Department of Health and Human Services 1980	Nationally representative population sample, aged 17 years, United States	1965 Men Women 1977 Men Women
Janzon et al. 1981	1,037 Swedish men, aged 47–48 years	Total
Gallop 1989	169 pulp and paper industrial company employees	Total self-reported records (n = 82) Payroll records
Jackson et al. 1989	70 persons (started with 100—50 matched former and persistent smokers), North Carolina pharmaceutical company	Persistent smokers 3 years precessation 2 years precessation 1 year precessation Former smokers 1 year postcessation 2 years postcessation 3 years postcessation

Former smokers	Nonsmokers	Percentage difference	Comments
	Results		
Total days lost per person per year			Short-term: <7 days unverified medical absences
6.37	4.42	44.1	Long-term: 10 days verified medical absences
Absence rate: short-term			
0.75	0.38	97.4	
Absence rate: long-term			
0.10	0.07	42.9	
Mean workdays lost per year			None
5.2	4.4	18.2	
5.1	3.7	37.8	
5.3	5.1	3.9	
4.3	3.8	13.2	
5.7	5.7	0	
8.6	4.3	100.0	
Workdays lost per year due to illness and injury per currently employed persons			None
6.8	4.6	47.8	
6.7	4.8	39.6	
6.1	4.2	45.2	
5.4	5.7	-5.3	
Percent using sick leave >3 times during the past year			None
7	4	75.0	
Mean illness absences last year			Payroll records were used to verify self-reported records
4.7	4.1	14.6	
9.1	7.9	15.2	
Annual mean ranked sick days			Ranked using absent days minus days due to personal leave, death in family, jury duty
Persistent	Former		
32.9	38.1	-13.6	
30.7	40.3	-23.8	
36.5	34.5	5.8	
38.3	32.7	17.1	
41.0	30.0	36.7	
42.1	28.9	45.7	
44.7	26.3	70.0	

Table 6.7   Continued

Study	Population	Group

Manning et al. 1989	324 employees of 2 companies, aged 20–75 years	Baseline
		  Short-term absences
		    Recent quitters
		    Sustained quitters
		  Long-term absences
		    Recent quitters
		    Sustained quitters
		1-year follow-up
		  Short-term absences
		    Recent quitters
		    Sustained quitters
		  Long-term absences
		    Recent quitters
		    Sustained quitters

Low and Mitchell 1991	30 steel foundry workers, mean age 33.5 years	Total

Halpern and Warner 1994	1990 U.S. National Health Interview Survey (nationally representative sample)	Time since cessation
		  0–2 months
		  3 months–1 year
		  2–4 years
		  5–10 years
		  11–19 years
		   20 years

Post et al. 1994	405 workers at an animal feed mill, mean ages 38 years (clerks) and 42 years (blue collar), Netherlands	Clerks Blue collar
Bush and Wooden 1995	1989 Australian National Health Survey, n = 21,984 employed persons from randomly selected households	Men: 12,839 Women: 9,145

*OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
Mean hours absent per month			Short-term: 2 days
			Long-term: >2 days
2.21	1.69	30.8	Sustained: >1 year
1.47	1.69	-13.0	Recent: 1 year
1.38	0.78	76.9	
0.68	0.78	-12.8	
2.21	1.17	88.9	
1.15	1.17	-1.7	
1.90	1.67	13.8	
1.95	1.67	16.8	
Mean number of absence episodes during the year			None
4.5	5.0	-10.0	
Mean duration of episodes			
1.0	1.0	0	
Total days absent			
6.0	9.0	-33.3	
Work-loss days during the past 2 weeks			OR*
2.69	1.0	169.0	
1.47	1.0	47.0	
1.45	1.0	45.0	
1.31	1.0	31.0	
1.41	1.0	41.0	
1.26	1.0	26.0	
Absence prevalence			
0.74	1.0	-26.0	OR
1.22	1.0	22.0	OR
Any absence 2 weeks before the interview			OR was adjusted for demographics (age,
1.33	1.0	33.0	gender, ethnicity, marital status, education,
1.19	1.0	19.0	location of residence); job characteristics
			(employment status, hours worked, income,
			occupation, industry); and health risk factors
			(alcohol use, physical exercise, body weight);
			additional factors measured overall health
			and happiness (more specific information
			was not provided)

Table 6.7   Continued

Study	Population	Group
Wooden and Bush 1995	4,812 randomly sampled former smokers, Australian National Health Survey	
		Total Time since cessation 1–4 years 5–9 years 10–19 years 20 years
Niedhammer et al. 1998	9,065 men (aged 40–50 years) and 3,490 women (aged 35–50 years), prospective cohort	Men Women Men Women

disease led to quitting. The extent of smoking before quitting is a determinant of risk, and risks fall for many diseases as the duration of quitting lengthens. The somewhat inconsistent findings may reflect (1) the heterogeneity of former smokers in these studies and (2) analysis strategies that did not fully account for risk determinants in the former smokers. In an analysis of the 1990 National Health Interview Survey data that accounted for time since quitting, former smokers had significantly more hospital admissions until 10 years following cessation, at which point former smokers and lifetime nonsmokers had similar numbers of hospital admissions (Halpern and Warner 1994).

The clinical trials of Wagner and colleagues (1995) provide additional evidence. Two cessation trials followed participants and collected medical care utilization data. After six years of follow-up, quitters experienced reductions in outpatient visits, hospital admissions, and hospital days in both trials compared with persistent smokers. In contrast, medical care utilization continued to increase among persistent smokers: 7 to 15 percent for outpatient visits, 30 to 45 percent for hospital admissions, and 75 to 100 percent for days spent in the hospital. These divergent patterns in the use of medical care services resulted in substantially greater rates of hospitalization, hospital days, and outpatient visits for persistent smokers.

Age

Several studies suggest that smoking may have a greater impact on the youngest age groups compared with older age groups. More frequent use of outpatient (Peters and Ferris 1967; Newcomb and Bentler 1987) and inpatient (Newcomb and Bentler 1987) services among smokers than among nonsmokers has been observed even in adolescents and young adults, suggesting that the differences observed in smoking and nonsmoking older adults are not solely a result of smoking-induced diseases. In fact, in a few studies higher levels of service utilization were observed among smokers than among nonsmokers in the younger age groups, but such differences were either not present or were reversed in the oldest age groups. This pattern is evident in the cross-sectional analyses of the 1970 U.S. National Health Interview Survey data, a random sample of U.S. households in which both smoking men and smoking women had a markedly higher number of days hospitalized per year than their nonsmoking counterparts until they reached their mid-40s, at which point the differences between smokers and nonsmokers became more subtle (Weinkam et al. 1987).

In general, compared with nonsmokers, smokers tend to incur more medical costs, to see physicians more often in the outpatient setting, and to be

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
ORs for incidence of absence during past 2 weeks (modeled)			Adjusted for several potential confounders
1.04	1.0	4.0	
0.53			
0.50			
0.32			
0.22			
Periods of absence			Adjusted rate ratios
1.10	1.0	10.0	
1.03	1.0	3.0	
Days absent			
1.06	1.0	6.0	
1.05	1.0	5.0	

admitted to the hospital more often. Among patients admitted to the hospital, smokers have longer lengths of stay and incur greater expenses per admission than nonsmokers. Less information is available concerning the use of medical services such as prescription drugs and emergency department visits, but increases for smokers compared with nonsmokers have also been observed with respect to these outcomes (Chetwynd and Rayner 1986; Miller et al. 1999). Although smokers use more palliative care services, as demonstrated by this review, smokers have been less likely than nonsmokers to use preventive services such as multiphasic testing (Oakes et al. 1974) and screening (Beaulieu et al. 1996; Edwards and Boulet 1997).

Postoperative Complications

In comparison with nonsmokers, smokers have been hypothesized to be at a higher risk for postoperative complications because of a greater frequency of chronic diseases, impaired pulmonary reserve, altered immune responses, and impaired wound healing. Higher rates of postoperative complications in smokers could contribute to the greater costs that they incur for health care services.

Substantial clinical and experimental research has been conducted on the relevant effects of smoking on host defenses, immune responses, and wound healing. As reviewed elsewhere in this report and in a previous Surgeon General's report (USDHHS 1990), smoking produces a range of effects on respiratory defense mechanisms that may increase the risk for postoperative pneumonia. Compromised lung function and the presence of COPD increase the risks for respiratory complications, including respiratory failure. The increased likelihood of coronary heart disease (CHD) in smokers increases the risk for cardiac events during and after surgery. In animal and clinical models, exposure to tobacco smoke and nicotine specifically impaired aspects of wound healing (Brown et al. 1986; Silcox et al. 1995; Haverstock and Mandracchia 1998; Jorgensen et al. 1998; Hollinger et al. 1999).

The literature on postoperative complications is extensive and diverse in the scope of complications associated with smoking. Table 6.11 provides evidence for lower survival rates after surgery for smokers compared with nonsmokers and suggests that this increased mortality may reflect a range of specific and nonspecific consequences of smoking, including a greater risk for postoperative complications related to the surgery. A number of reports address specific surgical complications such as flap failures, wound infections, and poor orthopedic outcomes. A similarly diverse set of reports consistently shows that smoking also increases the risk of respiratory complications.

Table 6.8   Studies on the association between current smoking and medical service costs

Study	Population	Group
Costs		
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
Freeborn et al. 1990	515 HMO enrollees, aged >17 years	Group I (1970–1974) Group II (1970–1979)

Penner and Penner 1990	20,831 employees enrolled in a fee-for-service plan	Total
		  Average cost per admission
		  Average inpatient cost per day

Hodgson 1992	U.S. National Health Interview Survey, persons aged >17 years	Men Women
Callahan et al. 1998	12,581 patients who had at least 2 ambulatory visits plus 1 hospitalization, 1993–1996, aged >60 years	Total
Terry et al. 1998	5,780 HMO enrollees, aged >18 years	Aged <65 years Aged 65 years
Pronk et al. 1999	6,589 adult HMO enrollees, Minnesota	Total
Outpatient services		
Peters and Ferris 1967	Harvard/Radcliffe students	Total
Palmore 1970	268 community volunteers, aged 60–94 years at baseline	Total

*HMO = Health maintenance organization.
†NR = Data were not reported.

Results			
Smokers	Nonsmokers	Percentage difference	Comments
$18,515	$19,772	-6.4	None
12,412	11,958	3.8	
6,819	6,923	-1.5	
93,234	93,326	-0.1	
$ 238	$ 206	15.5	Average ambulatory care costs
231	225	2.7	
			None
$ 3,716.28	$ 3,188.19	16.6	
459.56	241.74	90.1	
$35,914	$27,276	31.7	None
52,902	42,783	23.7	
$17,362	$ 8,560	102.8	Average costs over 4 years
$ 119	$ 95	25.3	Charges per month
255	258	-1.2	
NR[†]	NR	18.0	Absolute values were not reported; adjusted for age, gender, race, body mass index, physical activity, and comorbidity conditions
9.25	7.52	23.0	Clinic visits, Harvard 1964–1965
33.0	26.0	26.9	Percentage with 3 doctor visits per year; nonsmokers/slight present use of tobacco vs. moderate present use/heavy present use of tobacco; nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, 1–2 cigars and/or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and/or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as 11 cigarettes per day, 5 cigars and/or pipes per day, constant use of snuff, or constant use of chewing tobacco

Table 6.8   Continued

Study	Population	Group
Outpatient services		

Ashford 1973	32,319 residents of Exeter, United Kingdom, aged 15 years	Home visits
		  Men: 15–29 years
		                  30–44 years
		                  45–59 years
		                    60 years
		  Women: 15–29 years
		                  30–44 years
		                  45–59 years
		                    60 years
		Hospital outpatient
		  Men: 15–29 years
		                  30–44 years
		                  45–59 years
		                    60 years
		  Women: 15–29 years
		                  30–44 years
		                  45–59 years
		                    60 years

Oakes et al. 1974	2,557 HMO enrollees, aged 20 years	Men: Total
		                  20–39 years
		                  40–59 years
		                    60 years
		Women: Total
		                  20–39 years
		                  40–59 years
		                    60 years

Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Chetwynd and Rayner 1986	978 women, aged 18–60 years	Illness episodes General practitioner visits Specialist visits Outpatient visits Chiropractor visits

Rice et al. 1986	1979 National Health Interview Survey participants	Total
		  Aged 17–44 years
		  Aged 45–64 years
		  Aged 65 years

Freeborn et al. 1990	515 HMO enrollees, aged >65 years	Group I (1970–1974) Group II (1970–1979)

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
			Number of visits during the survey year
0.21	0.17	23.5	
0.28	0.18	55.6	
0.43	0.33	30.3	
1.4	2.3	-39.1	
1.3	1.1	18.2	
0.67	0.64	4.7	
0.44	0.49	-10.2	
2.1	2.2	-4.5	
0.62	0.45	37.8	
0.47	0.38	23.7	
0.52	0.46	13.0	
0.46	0.57	-19.3	
0.56	0.46	21.7	
0.51	0.45	13.3	
0.48	0.52	-7.7	
0.47	0.59	20.3	
3.4	2.8	21.4	Mean number of office visits during the past year
3.1	2.4	29.2	
3.2	2.4	33.3	
5.4	3.9	38.5	
4.2	4.8	-12.5	
5.0	5.4	-7.4	
3.5	4.0	-12.5	
3.3	5.0	-34.0	
3,690	3,667	0.6	Total office visits
3.31	2.56	29.3	Smokers = ever smokers
5.71	4.90	16.5	
0.83	0.45	84.4	
0.81	0.64	26.6	
0.16	0.12	33.3	
5.2	4.9	6.1	Physician visits per person per year
4.7	4.4	6.8	
5.3	4.9	8.2	
7.0	6.6	6.1	
6.12	5.33	19.8	Office visits per year
6.18	5.30	16.6	

Table 6.8   Continued

Study	Population	Group		
Outpatient services				
Halpern and Warner 1994	1990 U.S. National Health Interview Survey	Total		
Miller et al. 1999	1987 National Medical Expenditure Survey, n = 38,446	Total		
Hospitalizations/inpatient services				
Palmore 1970	268 community volunteers, aged 60–94 years at baseline	Total		
Ashford 1973	32,219 residents of Exeter, United Kingdom, aged 15 years	Men:	15–29 years	
			30–44 years	
			45–59 years	
			60 years	
		Women:	15–29 years	
			30–44 years	
			45–59 years	
			60 years	
Oakes et al. 1974	2,557 HMO enrollees, aged >20 years	Men:	20–39 years	
			40–59 years	
			60 years	
		Women:	20–39 years	
			40–59 years	
			60 years	
Coronary Drug Project Research Group 1976	2,789 men with a history of myocardial infarction, aged 30–64 years at baseline	Total		

‡OR = Odds ratio.

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.01	1.00	1.0	Physician visits in the past year; OR[‡]
0.7417	0.7379	0.5	Probability of ambulatory expense
38.0	33.0	15.2	Percentage with ≥1 operation; nonsmokers/slight present use of tobacco vs. moderate present use/heavy present use of tobacco; nonsmokers had never used tobacco; slight present use of tobacco was defined as 1–4 cigarettes per day, 1–2 cigars and/or pipes per day, occasional use of snuff, or occasional tobacco chewing; moderate present use was defined as 5–10 cigarettes per day, 3–4 cigars and/or pipes per day, frequent use of snuff, or frequent tobacco chewing; heavy present use was defined as ≥11 cigarettes per day, ≥5 cigars and/or pipes per day, constant use of snuff, or constant use of chewing tobacco
1.0	0.4	150.0	Average number of days hospitalized during the survey year
0.9	0.8	12.5	
0.8	0.6	25.0	
1.0	0.7	42.9	
1.8	1.2	50.0	
1.2	1.1	9.1	
0.9	0.8	12.5	
1.2	1.5	-20.0	
9	6	50.0	Percentage hospitalized during the past year
7	8	-12.5	
26	11	136.4	
14	17	-17.6	
6	10	-40.0	
13	15	-13.3	
55.2	49.7	11.1	5-year hospitalization rates

Table 6.8   Continued

Study	Population	Group
Hospitalizations/inpatient services		
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Chetwynd and Rayner 1986	978 women, aged 18–60 years	Hospitalized Emergency admissions
Rice et al. 1986	1979 National Health Interview Survey participants	Total
Van Peenen et al. 1986	AMOCO Corporation white male employees	Total
Freeborn et al. 1990	515 HMO enrollees, aged >65 years	Group I (1970–1974) Group II (1970–1979)
Penner and Penner 1990	20,831 employees enrolled in a fee-for-service plan	Total Admissions per 1,000 employees Days per 1,000 employees Average length of stay (days)
Kaplan et al. 1992	630 residents of a southern California community, aged >65 years	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Total
Terry et al. 1998	5,780 HMO enrollees (n = 3,825, aged 18–64 years; n = 1,955, aged 65 years)	Aged <65 years Aged 65 years Aged <65 years Aged 65 years
Miller et al. 1999	1987 National Medical Expenditure Survey, n = 38,446	Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
801.5	668.6	19.9	Nonobstetric hospital days
0.22	0.15	46.7	Smokers = ever smokers
0.09	0.06	50.0	
1.3	0.8	62.5	Smokers = ever smokers
2.7	2.4	12.5	Average number of insurance claims during the second quarter of 1984, the number submitted divided by the number eligible (for whom smoking habits were known) multiplied by 100, then adjusted for age; the difference is smaller after adjusting for age
0.17	0.15	13.3	Hospital admissions per year
0.17	0.15	13.3	
			None
126.66	75.82	63.1	
800.39	381.21	110.0	
6.47	5.03	38.6	
42.3	31.9	32.6	Age-adjusted hospitalization rates Prospective study
1.30	1.00	30.0	ORs for hospital admissions
6	8	-25.0	Percentage with any inpatient service
6	15	-60.0	
$113	$ 95	18.9	Charges per month
324	258	25.6	
0.1236	0.1113	11.1	Probability of having a hospital expense

Table 6.9   Studies on the association between the amount smoked and medical service utilization rates

Study	Population	Group
5-year hospitalization rates		
Hammond 1965	69,069 male smokers, U.S. men aged 50–69 years	Total
Coronary Drug Project Research Group 1976	2,789 men with a history of myocardial infarction, aged 30–64 years at baseline	Total
Marsden et al. 1988	17,328 active U.S. military personnel, aged >17 years	Total
Medical encounters during the past 30 days		
Peters and Ferris 1967	Harvard/Radcliffe students	Total
Balarajan et al. 1985	United Kingdom General Household Survey, 1980, participants	Outpatient visits Consultations with a physician
Marsden et al. 1988	17,328 active U.S. military personnel, aged >17 years	Total

Health Status

Comparisons of self-rated health statuses in smokers and nonsmokers provide further evidence of the global effects of smoking on health. Although self-ratings are inherently subjective, they provide direct evidence of the relationship of smoking to a diminished health status. Consonant with the complex concept of "health," health status is itself a multidimensional construct, challenging to measure and approached with varied measurement methods, including direct questions on perceived health status and standardized scales. For example, the Short Form 36 (SF-36) is a standardized, 36-item scale that measures eight dimensions of health (Lyons et al. 1994), three of which have a direct relevance to this review: general health perceptions (five items), physical health (four items), and mental health (five items). Table 6.12 (smokers versus nonsmokers), Table 6.13 (dose-responses), and Table 6.14 (former smokers versus nonsmokers) summarize the evidence. Studies were grouped according to the aspect of health status measured: symptoms/illnesses/health complaints, perceived health status (poor/good), physical function, physical status, general health status, life satisfaction/dissatisfaction, well-being, quality of life, tiredness, and mental health. In some studies "poor" health was measured whereas in others "good" health was measured, so the anticipated directions of the effects of smoking vary with the specified outcome.

Studies with varying designs, as well as studies measuring physical health status (Table 6.12), have shown uniformly that smokers tend to rate their general health status lower than do nonsmokers. Studies that do not include sufficient data to summarize in the tables obtained similar results. A study of 558 Bank of America retirees in California comparing smokers with nonsmokers showed that smoking was strongly associated with a higher number of sick days confined to home (Leigh and Fries 1992). In an analysis of 1990 National Health Interview Survey data, the perception

Nonsmokers (referent)	Percentage difference			Comments
	Smokers, by category of dose (1 = low)			
	1	2	3	
Not applicable	Referent	8.5	14.6	None
0	13.9	8.7	11.5	None
0	28.1	6.3	54.7	Days hospitalized in the past year
0	33.9	21.1	30.3	Years smoked
0	46.0	46.0	43.0	None
0	12.0	8.0	9.0	
0	-1.7	6.2	31.1	Number of cigarettes per day in the past year

of health status held by current smokers was significantly lower than that held by nonsmokers (Erickson 1998). In a multiple regression analysis of data collected from approximately 18,000 men and women in Finland, which included variables for sociodemographic characteristics, family life, morbid conditions, pain, psychosocial problems, and relative weight, smoking was associated with a significantly lower perceived health status in men but not in women (Fylkesnes and Førde 1991). In a random sample of 1,200 adults in South Wales, United Kingdom, the mean score on the SF-36 general health perception scale among participants who had ever smoked was 7.8 points lower than for those who had never smoked (Lyons et al. 1994). A study using the same scale with 921 U.S. male military veterans showed that current smoking was significantly inversely correlated with good general health perceptions (Schnurr and Spiro 1999). In a telephone survey of Newfoundland residents, the likelihood of rating one's health as good declined in proportion to the number of cigarettes smoked per day; those who had never smoked were more than four times more likely than smokers of more than 30 cigarettes per day to rate their health as good (Segovia et al. 1989). In a survey of 1,623 patients from nine medical practices in Scotland who had a history of smoking, persistent smokers rated their general health 8.0 percent lower than former smokers rated theirs on the SF-36 scale (Tillmann and Silcock 1997). Among 2,502 enrollees in an Oregon health maintenance organization, smoking was negatively correlated with general health status for both men and women, an observation that extended to measures of mental and physical health status (Pope 1982).

Smokers in at least one subgroup were at least 10 percent more likely than nonsmokers to rate their health as poor, including studies that compared self-reported chronic conditions (Balarajan et al. 1985;

Table 6.10 Studies on the association between former smoking and medical services utilization costs and rates

Study	Population	Group
Costs		
Vogt and Schweitzer 1985	2,582 adult HMO* enrollees	Laboratory X-ray Surgery Total
Pronk et al. 1999	6,589 adult HMO enrollees, Minnesota	Total
Outpatient services		
Peters and Ferris 1967	Harvard/Radcliffe college students	Total

Ashford 1973	32,219 residents of Exeter, United Kingdom, aged >15 years	Home visits
		  Men: 15–29 years
		               30–44 years
		               45–59 years
		               60 years
		  Women: 15–29 years
		               30–44 years
		               45–59 years
		               60 years
		Hospital outpatient
		  Men: 15–29 years
		               30–44 years
		               45–59 years
		               60 years
		  Women: 15–29 years
		               30–44 years
		               45–59 years
		               60 years

Oakes et al. 1974	2,557 HMO enrollees, aged >20 years	Men: Total
		           20–39 years
		           40–59 years
		           60 years
		Women: Total
		           20–39 years
		           40–59 years
		           60 years

*HMO = Health maintenance organization.
†NR = Data were not reported.

Results			
Former smokers	Nonsmokers	Percentage difference	Comments
$21,150	$19,772	7.0	None
13,419	11,958	12.2	
8,639	6,923	24.8	
94,254	93,326	1.0	
NR[†]	NR	25.8	Absolute values were not reported; adjusted for age, gender, race, body mass index, physical activity, and comorbidity conditions
10.09	7.52	34.2	Clinic visits, Harvard, 1964–1965
			Number of visits during the survey year
0.28	0.17	64.7	
0.28	0.18	55.6	
0.46	0.33	39.4	
2.1	2.3	-8.7	
2.7	1.1	145.5	
0.78	0.64	21.9	
0.58	0.49	18.4	
3.3	2.2	50.0	
0.69	0.45	53.3	
0.37	0.38	-2.6	
0.39	0.46	-15.2	
0.69	0.57	21.1	
0.56	0.46	21.7	
0.44	0.45	-2.2	
0.73	0.52	40.4	
0.57	0.59	-3.4	
3.3	2.8	17.9	Mean number of office visits during the past year
2.7	2.4	12.5	
2.9	2.4	20.8	
4.3	3.9	10.3	
5.9	4.8	22.9	
5.1	5.4	-5.6	
7.4	4.0	-85.0	
5.0	5.0	0.0	

Table 6.10 Continued

Study	Population	Group
Outpatient services		
Balarajan et al. 1985	1980 General Household Survey, United Kingdom	Outpatient visits Stopped >1 year Stopped <1 year Consultations with a physician Stopped >1 year Stopped <1 year
Vogt and Schweitzer 1985	2,482 adult HMO enrollees	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit 0–2 months Quit 3 months–1 year Quit 2–4 years Quit 5–10 years Quit 11–19 years Quit 20 years
Hospitalizations/inpatient services		
Ashford 1973	32,219 residents of Exeter, United Kingdom, aged >15 years	Men: 15–29 years 30–44 years 45–59 years 60 years Women: 15–29 years 30–44 years 45–59 years 60 years
Vogt and Schweitzer 1985	2,582 adult HMO enrollees	Total
Van Peenen et al. 1986	AMOCO Corporation white male employees	Total
Kaplan et al. 1992	630 residents of a southern California community, aged >65 years	Total

†OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.40	1.0	40.0	OR[†] for prevalence of chronic illness after adjustment for age, gender, and socioeconomic group
1.25	1.0	25.0	
1.19	1.0	19.0	
1.47	1.0	47.0	
4,115	3,667	12.2	Total office visits
1.20	1.0	20.0	OR for the number of physician visits during the past year
1.47	1.0	47.0	
1.32	1.0	32.0	
1.24	1.0	24.0	
1.25	1.0	25.0	
1.18	1.0	18.0	
1.0	0.4	150.0	Average number of days hospitalized during the year
0.2	0.8	-75.0	
0.4	0.6	-33.3	
1.4	0.7	100.0	
1.7	1.2	41.7	
1.0	1.1	-9.1	
1.9	0.8	137.5	
1.55	1.5	0.0	
704.3	668.6	5.3	Nonobstetric hospital days
3.0	2.4	25.0	There was no difference after adjusting for age
41.0	31.9	28.5	Age-adjusted rates of hospitalization; prospective study

Table 6.10 Continued

Study	Population	Group
Hospitalizations/inpatient services		
Halpern and Warner 1994	1990 U.S. National Health Interview Survey participants	Quit 0–2 months Quit 3 months–1 year Quit 2–4 years Quit 5–10 years Quit 11–19 years Quit 20 years
Terry et al. 1998	5,780 HMO enrollees, aged >18 years	Age <65 years Age 65 years

Halpern and Warner 1994), acute conditions (Balarajan et al. 1985), and physical symptoms (Macnee 1991; York and Hirsh 1995). An increasing number of cigarettes smoked per day was consistently associated with increased risks for symptoms or illnesses (Balarajan et al. 1985; Marsden et al. 1988; Joung et al. 1995), and with a greater likelihood of rating one's health as poor (Joung et al. 1995; Poikolainen et al. 1996; Manderbacka et al. 1999) (Table 6.13), with differences between the highest and lowest exposure categories of about 30 percent or greater in every study that assessed dose-response trends (Table 6.13). For several measures of poor health, the differences between former smokers and lifetime nonsmokers (Table 6.14) tended to be even more striking than for comparisons between current smokers and lifetime nonsmokers, probably because of the increased likelihood of quitting among those experiencing symptoms or diagnosed with illnesses.

A few studies examined reports of fatigue or tiredness. In a survey of New Zealand women who worked at home, smokers were 71 percent more likely than nonsmokers to report frequently feeling tired for no reason (Chetwynd and Rayner 1986). In a study of retired persons in the United States, after adjusting for age, current smokers were 60 percent more likely than lifetime nonsmokers to report becoming very tired easily (Rimer et al. 1990); former smokers were 25 percent more likely than lifetime nonsmokers to report getting very tired easily (Rimer et al. 1990).

Smokers tend to rate their general level of well-being lower than do nonsmokers whether well-being is measured directly (Dennerstein et al. 1994), assessed overall as quality of life (Sippel et al. 1999), or rated by degrees of general satisfaction with life (Blair et al. 1980) (Table 6.12). Similar findings have been observed when former smokers were compared with lifetime nonsmokers (Table 6.14) (Blair et al. 1980; Sippel et al. 1999). Conversely, compared with lifetime nonsmokers, current smokers tend to rate themselves as more dissatisfied with life (Table 6.12) (Kaprio and Koskenvuo 1988), but few differences in the prevalence rates of life dissatisfaction were observed between former smokers and nonsmokers (Table 6.14) (Kaprio and Koskenvuo 1988).

With respect to mental health and well-being, smokers tend to rate themselves slightly lower on measures of mental health or mental well-being (Wakefield et al. 1995; Wooden and Bush 1995; Sippel et al. 1999). In addition, smokers are more likely than nonsmokers to have psychological symptoms such as depressed mood and phobic anxiety (Matarazzo and Saslow 1960; Macnee 1991; Schoenborn and Horm 1993). In the South Wales study, not included in the summary tables, current smokers had a mean SF-36 mental health score that was slightly but not significantly lower than that of people who had never smoked (Lyons et al. 1994). Former smokers also tend to rate themselves less favorably than do nonsmokers

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.79	1.0	79.0	ORs for hospital admissions
2.59	1.0	159.0	
1.25	1.0	25.0	
1.32	1.0	32.0	
1.04	1.0	4.0	
1.0	1.0	-3.0	
7	8	-12.5	Percentage with any inpatient use
16	15	6.7	

(Table 6.14). The differences between former smokers and lifetime nonsmokers were small with respect to mental health and well-being (Wetzler and Ursano 1988; Wooden and Bush 1995; Sippel et al. 1999), but were more marked on measures of symptoms or morbidity (Table 6.14) (Lilienfeld 1959; Lindenthal et al. 1972; Macnee 1991). A strong dose-response trend was observed between smoking frequency and depressed moods in nationally representative U.S. data from the National Health Interview Survey (Schoenborn and Horm 1993). However, dose-response trends generally did not occur for mental health measures (Table 6.13) (Lindenthal et al. 1972; Wetzler and Ursano 1988; Stansfeld et al. 1993).

Studies of physical functioning, or functional status, among elderly populations also provide relevant evidence. Although they are not a focus of this review, such studies have provided prospective evidence that cigarette smoking is associated with accelerated declines in physical function (Pinsky et al. 1987; Guralnik and Kaplan 1989; Berkman et al. 1993; Strawbridge 1993). An analysis of data from the Honolulu Heart Study showed that smoking was inversely associated with freedom from clinical illnesses, physical impairment, and cognitive impairment (Reed et al. 1998).

The evidence provides a clear indication that smokers perceive their health as poorer than nonsmokers perceive theirs. Smokers report more symptoms (including mental health symptoms) and illness episodes, feel more tired, and have lower ratings for physical health status. Compared with nonsmokers, smokers even report lower overall levels of well-being for reasons that may at least partially reflect their diminished health status. The consistent indications of a poorer health status among smokers compared with nonsmokers across numerous health status dimensions provide direct evidence that smoking is associated with a diminished health status.

Evidence Synthesis

This section reviewed evidence on smoking and a diverse but interrelated set of measures of health status. Although the measures are nonspecific and likely to be affected by factors other than smoking, there is abundant and consistent evidence that smokers generally have a poorer health status than nonsmokers. This section reviewed findings on self-reported health statuses, absenteeism, and medical services utilization rates, as well as complications of surgical care. For each of these outcomes, the weight of the evidence indicates an adverse effect from smoking. There are many studies with differing designs and a variety of populations. The strength of the association with smoking is variable across the outcome measures and across study

Table 6.11   Studies on the association between smoking and complications of surgery

Study	Population	Outcome studied
Postoperative and wound-healing complications		
Abidi et al. 1998	Retrospective study, 63 consecutive patients with fractures of the calcaneus who underwent open reduction and internal fixation during a 3-year period	Postoperative and wound complications
Golosow et al. 1999	Retrospective study, 91 patients with sternal wound-healing complications between January 1990 and December 1996, seen at the Indiana University Medical Center and affiliated hospitals	Operative procedure and outcome
Goodman et al. 1999	Retrospective study, 48 spinal cord-injured patients with pressure ulcers, seen at a tertiary referral Veterans hospital between 1992 and 1997	Wound healing and postoperative complications
Spelman et al. 2000	693 patients undergoing CABG* between December 1, 1996, and November 30, 1997	Surgical wound infections (SWIs) and postoperative bacteremia
Postoperative complications		
Ashraf et al. 1995	48 consecutive patients who underwent cardiovascular surgery	Mortality
Watterson et al. 1995	556 women who had transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction	Postoperative complications
D'Agostino et al. 1996	Prospective study, 1,835 consecutive patients undergoing first-time isolated CABG between March 1990 and July 1995 in Massachusetts	Postoperative risk of stroke
Kroll et al. 1996	854 consecutive free flaps	Successful outcome
Samuels et al. 1996	All patients aged <40 years who had a CABG at the Allegheny University Hospital in Pennsylvania, between July 1990 and June 1995	Postoperative cardiac-related events
Utley et al. 1996	Prospective study, 2,916 patients with a history of 1 CABG	Preoperative and postoperative characteristics

*CABG = Coronary artery bypass graft.

Results

A history of active smoking was correlated with an increase in time to heal the wound in the outpatient group; risk factors for wound complications: high body mass index, extended time between injury and surgery, smoking, and single layered closure

Smoking history, chronic obstructive pulmonary disease, steroid use, previous sternotomy, age, diabetes, operation time, emergency operation, elevated white blood cell count, fever, and positive wound or blood cultures all correlated with one another

Chronic smokers had longer courses of antibiotic therapy, but smoking did not correlate with other variables, including wound-healing complications

Diabetes, obesity, and previous cardiovascular procedures were independent predictors of SWIs, and obesity was a risk factor for bacteremia

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Smoking was related to later mortality (p = 0.04) in a univariate model

Risk of hernia formation was higher among those smoking at the time of surgery (p = 0.0001); risk factors for any complication were associated with smoking (p <0.002)

Smoking was a significant predictor of carotid stenosis (p <0.0001)

Smoking, age, and previous irradiation had no significant effects on flap failure rates

A history of smoking was a risk factor (83%); most patients resumed smoking, did not return to work, and did not take lipid-lowering drugs after surgery

Smoking was not predictive of mortality or morbidity; 7.5% of nonsmokers and 4.7% of smokers needed an intra-aortic pump; a recent myocardial infarction was more common in smokers

Table 6.11   Continued

Study	Population	Outcome studied
Postoperative complications		
Arend et al. 1997	All renal transplants from the Leiden Renal Transplant Database performed between 1966 and 1994 in the Netherlands	Patient survival
Boucher et al. 1997	329 consecutive patients aged 70 years, who had undergone cardiac surgery between January 1990 and December 1993 in a university-affiliated tertiary care hospital in Montreal, Canada	Long-term survival and functional status
Brooks-Brunn 1997	Prospective model-building study, convenience sample of 400 patients who underwent abdominal surgical procedures between January 1993 and August 1995	Postoperative pulmonary complications
Espehaug et al. 1997	Register-based matched case-control study with 674 cases who had total hip replacements, and 1,343 controls with primary hip operations only, reported to the Norwegian Arthroplasty Register from 1987–1993	Poor total hip replacement prognosis
Gentile et al. 1997	93 patients with at least 6 months of postoperative surveillance, identified through a vascular registry	Intrinsic vein graft stenosis (postoperative) in lower extremities
Lindquist et al. 1997	Prospective study, 45 edentulous patients (21 smokers and 24 nonsmokers), followed for 10 years after treatment with a fixed implant-supported prosthesis in the mandible	Bone loss around mandibular implants
Nettleman et al. 1997	Retrospective study, 266 patients	Mortality from postoperative myocardial infarction
Rockman et al. 1997	606 patients (183 patients with preoperative strokes compared with 423 who only experienced transient ischemic attacks [TIAs]), who underwent consecutive carotid endarterectomies from 1988–1993 in New York	Perioperative stroke rates after endarterectomy
Sasajima et al. 1997	Retrospective study, 71 patients (97% smokers) who had autogenous vein bypasses in Japan	Patency rates (blood flow in veins remaining open)

†RR = Relative risk.
‡CI = Confidence interval.
§OR = Odds ratio.

Results

A slightly increased mortality risk in the first year after a transplant for smokers, patients aged >40 years, men, and persons with hypertension or diabetes

Current smoking on admission was associated with postoperative mortality; RR[†] = 3.6 (95% CI[‡], 1.4–10.0)

Smoking within the past 8 weeks was an independent risk factor (adjusted OR[§] = 2.27)

Smoking had no overall effect, but former smokers had a 2.8 increased risk compared with nonsmokers

Smoking was associated with the development of a vein graft flow disturbance (p = 0.03)

Mean bone loss around mandible was approximately 1 mm greater in smokers than in nonsmokers and related to the amount of cigarette smoking; smokers with poor oral hygiene were at a greater risk, especially for peri-implant bone loss

Current smoking was an independent risk factor (RR = 2.3 [95% CI, 1.2–4.7])

Patients with preoperative strokes who smoked had a greater risk for a perioperative stroke compared with those with asymptomatic TIAs or who experienced only TIAs (52 vs. 40.6%, p = 0.01)

The nonsmoking group had higher rates than the smoking group (66.8 vs. 34.7%, p <0.05)

Table 6.11   Continued

Study	Population	Outcome studied
Postoperative complications		
Bluman et al. 1998	Prospective cohort study, 410 patients scheduled for noncardiac elective surgery at the Veterans Administration Medical Center in Syracuse, New York	Postoperative pulmonary complications
Medina et al. 1998	Retrospective study, 62 patients (40 with Crohn's disease [CD] and 22 with ulcerative colitis [UC]) with previous surgery for inflammatory bowel disease, compared with 202 patients (69 with CD and 133 with UC) in a control group with inflammatory bowel disease but without previous surgery	Development of inflammatory bowel disease in patients with CD and UC
Fujisawa et al. 1999	369 patients with stage I non-small-cell lung carcinoma	10-year survival rate
Kinsella et al. 1999	Retrospective study, 91 patients (38 current smokers, 12 former smokers, and 41 nonsmokers) with facial skin defects reconstructed with local flaps	Postoperative complications
Lavernia et al. 1999	202 patients (25 smokers and 177 nonsmokers) undergoing arthroplasty of the hip and knee	Short-term complications, resource consumption, length of hospital stay
Pereira et al. 1999	408 patients in a tertiary university hospital, analyzed prospectively for preoperative and postoperative pulmonary complications in Brazil	Pulmonary function and complication rate
Sinclair et al. 1999	17,638 consecutive outpatients who had surgery	Postoperative nausea and vomiting
Sorensen et al. 1999	333 unselected consecutive patients between January 1993 and October 1996 in 1 surgical department, who underwent colon or rectal resection with anastomosis in Denmark	Anastomotic leakage
Warner et al. 1999	135 patients undergoing abdominal surgery with a history of smoking or reduced pulmonary function	Pulmonary function and complications

Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Results

Complications occurred in 22% of current smokers, 12.8% of former smokers, and 4.9% of nonsmokers; adjusted OR = 5.5 (95% CI, 1.9–16.2) for current smokers vs. nonsmokers, 4.2 (95% CI, 1.2–14.8) for former smokers; OR for current smokers who reduced their smoking 1 month before surgery = 6.7 (95% CI, 2.6–17.1)

The number and type of complications after surgery were not related to smoking habits; inflammatory bowel disease recurred earlier in smokers among the CD patients (p >0.05)

Increased mortality risk with increasing age and >30 pack-years of smoking

23 patients (25%) had complications (smokers = 37%, former smokers = 17%, and nonsmokers = 17%; p <0.03); all full-thickness skin losses and cellulitis occurred in active smokers; former smokers had a complication rate similar to that of nonsmokers

Smokers, compared with nonsmokers, were younger and had fewer comorbidities, significantly longer surgical times, higher charges, and required more anesthesia (maybe for a more severe illness); former smokers had better short-term outcomes than did current smokers

Postoperative complication rate = 14%; predictors in univariate analyses: age >50 years, smoking, presence of chronic pulmonary disease, surgery duration >210 minutes, and comorbidity (p <0.04)

Smoking was an independent risk factor; age, gender, duration and type of anesthesia, previous postoperative nausea and vomiting, and surgery type also were independent risk factors

Smokers had increased risks compared with nonsmokers (RR = 3.18 [95% CI, 1.44–7.00])

Pack-years of smoking, age, site of incision, and current smoking status were predictors of airway obstruction bronchospasm (OR = 6.9 [95% CI, 1.2–38.4]); pack-years of smoking were not associated with the need for endotracheal intubation (OR = 1.1 [95% CI, 0.4–3.2]) or with prolonged intensive care or readmission

Table 6.11 Continued

Study	Population	Outcome studied
Postoperative complications		
Chan et al. 2000	67 consecutive patients (84% smokers) who underwent surgical resection of esophageal carcinoma from January 1989 to December 1996	5-year survival rate
Chimbira and Sweeney 2000	327 consecutive patients (85 smokers and 242 nonsmokers) undergoing arthroscopic knee surgery, who had standard anesthetic pre- and postoperative drugs	Postoperative nausea and vomiting
Kotani et al. 2000	30 smoking and 30 nonsmoking patients who had propofol-fentanyl general anesthesia in Japan	Types of alveolar immune cell and macrophage aggregation
Wetterslev et al. 2000	Healthy cardiopulmonary patients who had combined general and thoracic epidural anesthesia for abdominal surgery	Postoperative hypoxemia and complications
Wound-healing complications		
Camilleri et al. 1996	111 consecutive recipients of Becker breast expanders	Wound infection
Erdmann et al. 1997	66 patients with flaps raised from the posteromedial border of the leg	Wound healing
Takeishi et al. 1997	114 patients who had transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction in Japan	Wound healing complications

populations, probably reflecting the nonspecificity of these measures and the differing mixes of potential confounding and modifying factors across studies. In general, there is evidence for an increasing severity of outcome measures with an increasing number of cigarettes smoked, and current smokers tend to have worse outcomes than former smokers. Studies have addressed potential confounding factors to a limited extent, depending on the availability of data on relevant factors. Given the diversity of populations, study designs, and consistency of findings, confounding alone does not seem to be a satisfactory explanation for the overall pattern of findings. A single, unifying biologic basis for the association of smoking with the outcome measures cannot be postulated, but there are many well-supported direct and indirect mechanisms that may link smoking to the adverse effects documented in this section.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

Results

Poor outcomes (18% survival rate) mainly because most tumors were in advanced stages when resected

6% of smokers compared with 15% of nonsmokers were affected (p <0.05)

Smoking was associated with macrophage aggregation, but with markedly reduced phagocytic and microbicidal activity

Smoking 20 pack-years was associated with a 47% higher incidence compared with smoking <20 pack-years (p <0.006)

Heavy smoking was a risk factor (p <0.05)

Peripheral vascular disease and heavy smoking were contributory factors to suboptimal healing

Smoking was associated with a greater risk (p = 0.03)

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2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Implications

Although preventing the specific diseases caused by smoking has been a public health priority for a long time, cigarette smoking also causes a substantial and costly burden of nonspecific morbidity. Smokers have a poorer health status, lose more time from work, and use medical care services at a higher rate than their nonsmoking peers. These adverse effects occur among younger smokers even before the burden of smoking-induced diseases becomes apparent at middle age and older.

Table 6.12 Studies comparing the health status of smokers and nonsmokers

Study	Population	Group
Mean number of illness episodes during the past year		
Chetwynd and Rayner 1986	Survey of 978 women who worked at home, Christchurch, New Zealand, aged 18–60 years	Total Aged 18–29 years Aged 30–44 years Aged 45–60 years
Self-reported chronic conditions		
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Total
Physical symptoms (% reporting)		
Macnee 1991	240 men and women, mean age 33 years	Total
Physical symptoms (mean number)		

York and Hirsch 1995	425 alcohol drinkers, alcoholics and social drinkers, aged 20–59 years	Alcoholics
		  Men
		  Women
		Social drinkers
		  Men
		  Women

Self-reported poor health		
Palmore 1970	268 male volunteers, aged 60–94 years	Total
Wilson and Elinson 1981	3,092 adults, aged 20–64 years, National Survey of Personal Health Practices and Consequences	Men Women
Seidell et al. 1986	455 men and 790 women, aged 26–66 years	Men Women
Pearson et al. 1987	864 HMO[†] enrollees, mean age 52 years	Total
Orleans et al. 1989	1,163 African American life insurance policyholders, mean age 39 years	Total
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Total
Poikolainen et al. 1996	6,040 men and women, Finland, aged 25–64 years	Total

*OR = Odds ratio.
†HMO = Health maintenance organization.

Results			Comments
Smokers	**Nonsmokers**	**Percentage difference**	
3.31	2.56	29.3	None
3.58	2.58	38.8	
3.14	2.57	22.2	
2.62	2.42	8.3	
1.27	1.0	27.0	OR*
25.2	21.5	17.2	None
5.11	4.75	7.6	Alcoholics were recruited from local alcoholism treatment centers; social drinkers were nominated for participation by alcoholics; teetotalers were excluded
7.11	6.14	15.8	
1.02	0.98	4.1	
1.83	1.43	28.0	
28.6	22.9	24.9	Percentage that rated their health was worse than the self-perceived average
24.8	21.3	16.4	Percentage with a physical health status score of 1–3 (poor)
37.0	33.9	9.1	
6.8	7.3	-6.8	Number of health complaints
10.2	9.0	13.8	
14.0	7.4	89.2	Percentage reporting fair/poor health
22.5	11.3	99.1	Percentage reporting fair/poor health
1.62	1.0	62.0	OR
48.8	40.7	19.9	Percentage reporting suboptimal health

Table 6.12 Continued

Study	Population	Group	
	Self-reported poor health		
Bobak et al. 1998	Sample of 1,599 Russians, aged >18 years	Total	
Pampalon et al. 1999	1992–1993 Quebec Health and Social Survey (n = 20,739), mean age 41 years	Total	
	Self-perceived good/excellent health (% reporting)		
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men:	Iowa East Boston New Haven Piedmont
		Women:	Iowa East Boston New Haven Piedmont
York and Hirsch 1995	425 alcohol drinkers, alcoholics and social drinkers, aged 20–59 years	Alcoholics Men Women Social drinkers Men Women	
	Self-perceived good physical function (% reporting)		
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men:	Iowa East Boston New Haven Piedmont
		Women:	Iowa East Boston New Haven Piedmont
	Physical health status		
Belloc and Breslow 1972	Random sample of Alameda County, California, residents, aged >20 years	Men Women	
Reed 1983	542 HMO enrollees	Total	

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.29	1.0	29.0	OR was adjusted for age, gender, education, alcohol, and marital status
1.34	1.0	34.0	OR for reporting fair/poor health status
64.4	74.6	-13.8	None
58.0	69.1	-16.1	
54.8	68.8	-20.9	
42.8	60.1	-28.8	
58.3	72.6	-19.7	
59.1	54.3	8.8	
55.2	60.8	-9.2	
53.6	54.5	-1.7	
			Health score
0.43	0.65	-33.8	
0.76	1.29	-41.1	
0.18	0.12	50.0	
0.26	0.30	-13.3	
59.1	70.5	-16.2	None
53.3	64.2	-17.0	
64.8	71.0	-8.7	
56.3	71.5	-21.2	
42.5	61.5	-30.9	
49.4	45.8	7.9	
48.9	57.1	-14.4	
49.4	50.9	-2.9	
0.51	0.47	8.5	Higher scores reflect poorer physical health status measured by ridits (mean rank sums)
0.52	0.48	8.3	
0.50	0.49	2.0	Higher scores reflect poorer physical health status, measured by ridits (mean rank sums); age and gender adjusted

Table 6.12   Continued

Study	Population	Group
Physical health status		
Pearson et al. 1987	864 HMO enrollees, mean age 52 years	Total
Wooden and Bush 1995	23,813 Australians	Total
General health status (health status questionnaire Short Form 36 [SF-36])		
Wakefield et al. 1995	3,010 Australians, aged >15 years	Aged 15–29 years Aged 30 years
Sippel et al. 1999	619 HMO members with asthma	Total
Life dissatisfaction		
Kaprio and Koskenvuo 1988	7,094 Finns, twin cohort, men aged 20–54 years, women aged 20–39 years	Men: 20–34 years 35–54 years Women: 20–39 years
General life satisfaction		
Blair et al. 1980	504 employees, mean age 34 years	Men Women
Overall well-being		
Dennerstein et al. 1994	Random sample of 1,503 women, Melbourne, Australia, aged 45–55 years	Total
Overall quality of life		
Sippel et al. 1999	619 HMO members with asthma	Total
Tiredness for no reason (% reporting)		
Chetwynd and Rayner 1986	Survey of 978 women who worked at home, Christchurch, New Zealand, aged 18–60 years	Total
Getting very tired easily (% reporting)		
Rimer et al. 1990	3,147 American Association of Retired Persons members, aged 50–102 years	Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
42.4	39.9	6.6	Percent reporting low physical health
2.090	2.316	-9.8	Higher scores reflect better physical health status (4-point scale, 4 = best)
71.0	77.4	-8.3	Smokers = ever smokers
69.1	74.6	-7.4	
53	66	-19.7	Higher scores reflect better health status (100 = best, 0 = worst)
8.8	8.4	4.8	Based on a psychological scale; details were not specified
9.1	8.3	9.6	
8.7	8.2	6.1	
28.4	32.9	-13.7	Age-adjusted proportion with a high level of general life satisfaction
15.4	35.4	-56.5	
1.43	1.57	-8.9	Higher scores reflect a greater sense of well-being
2.1	1.8	16.7	Higher scores reflect a poorer quality of life (10-point scale, 1 = best, 10 = worst)
36	21	71.4	None
32	20	60.0	Age-adjusted

Table 6.12   Continued

Study	Population	Group
Mental health (health status questionnaire Short Form 36 [SF-36])		
Wakefield et al. 1995	3,010 Australians, aged >15 years	Aged 15–29 years Aged 30 years
Sippel et al. 1999	619 HMO members with asthma	Total
Mental well-being		
Wooden and Bush 1995	23,813 Australians	Total
Psychosomatic symptoms		
Matarazzo and Saslow 1960	294 persons from 3 populations: psychiatric patients, student nurses, and university undergraduates	Psychiatric patients Student nurses Undergraduates Men Women
Psychological symptoms		
Macnee 1991	240 men and women, mean age 33 years	Total
Depressed mood (%)		
Schoenborn and Horm 1993	1991 National Health Interview Survey, random sample, U.S. adults (n = 43,732)	Men Women
Health behavior efficacy expectations, health status		
Grembowski et al. 1993	2,523 Medicare beneficiaries	Total Total

Results			
Smokers	**Nonsmokers**	**Percentage difference**	**Comments**
73.6	75.2	-2.1	Smokers = ever smokers
78.6	80.6	-2.5	
69	76	-9.2	Higher scores reflect better mental health (100 = best, 0 = worst)
2.223	2.300	-3.3	Higher scores reflect better mental health (4-point scale, 4 = best)
13.9	12.1	14.9	Mean score on Saslow Psychosomatic Screening Inventory (higher = more symptoms)
8.2	6.3	30.2	
3.9	3.3	18.2	
6.1	3.7	64.9	
8.8	7.9	11.4	Symptom checklist: range from 0–40; higher scores equal more symptoms based on a 10-item measure
10.3	5.8	77.6	None
15.8	10.0	58.0	
2.96	9.78	-69.7	Scales of 0 to 10 (0 = low and 10 = high); efficacy expectations of health behaviors (exercise, dietary fat, weight control, smoking, and alcohol consumption) and resulting health status expectations
7.66	9.69	-21.0	

Table 6.13   Studies evaluating the dose-response relationship between the number of cigarettes smoked per day and health status

Study	Population	Group
Mean number of illnesses in the past 30 days		
Marsden et al. 1988	17,328 active U.S. military personnel	Total
Self-reported poor health status (number of health complaints)		
Seidell et al. 1986	455 Dutch men and 790 Dutch women, aged 26–66 years	Men Women
Subjective health complaints		
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Chronic conditions		
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Self-reported chronic conditions		
Balarajan et al. 1985	23,956 participants in the United Kingdom General Household Survey, aged >16 years	Total
Perceived poor health		
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Manderbacka et al. 1999	1991 Swedish Level of Living Survey (n = 5,306, aged 18–75 years)	Total
Physical health status		

Belloc and Breslow 1972	Random sample of Alameda County, California, residents, aged >20 years	Current smokers
		  Men
		  Women
		Former smokers
		  Men
		  Women

Physical health score		
Wiley and Camacho 1980	3,982 Alameda County residents, aged 20–70 years	Men Women

Nonsmokers (referent)	Percentage difference			Comments
	Smokers, by category of dose (1 = low)			
	1	2	3	
0	0.4	12.3	36.4	None
0	23.3	31.5		None
0	6.8	28.4		
0	71.0	137.0		None
0	29.0	43.0		None
0	7.0	31.0	76.0	None
0	75.0	101.0		None
0	33.0	37.0		Adjusted for age, gender, and risk
0	4.3	17.0		Ridits (higher score = poorer health); whether one inhales cigarette smoke, and the extent of such inhalation, appear highly correlated with physical health status
0	6.3	16.7		
0	6.4	14.9		
0	8.3	10.4		
0	-75.9	-265.5	-286.2	High scores = better physical health
0	50.0	-500.0	-375.0	

Table 6.13   Continued

Study	Population	Group
Self-reported health status		
Segovia et al. 1989	Sample of 3,300 residents of St. John's, Canada, aged >20 years	Total
Poikolainen et al. 1996, Poikolainen and Vartiainen 1997	6,040 men and women, Finland, aged 25–64 years	Total
Impaired psychological status		
Lindenthal et al. 1972	938 New Haven adults (aged >18 years), sample	Total
Psychological well-being		
Wetzler and Ursano 1988	6,675 U.S. Air Force personnel	Total

*NR = Data were not reported.

Nonsmokers (referent)	Percentage difference				Comments
	Smokers, by category of dose (1 = low)				
	1	**2**	**3**		
0	-16.3	19.1	-31.9		Percentage reporting good health; additional smoking categories, by increasing dose: -40.9, -67.4, -48.0, -76.2
0	0.2	45.7	NR*		Percentage reporting suboptimal health
0	35.8	-23.8	50.3		Based on a percentage with very impaired status; smoking frequency categories
0	1.7	3.3	NR		None

Table 6.14   Studies comparing the health status of former smokers and nonsmokers

Study	Population	Group
Perceived poor health		
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Self-reported poor health (number of health complaints)		
Seidell et al. 1986	455 Dutch men and 790 Dutch women, aged 26–66 years	Men Women
Subjective health complaints		
Lilienfeld 1959	903 residents, Buffalo, New York	Total
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Self-reported chronic conditions		
Balarajan et al. 1985	23,956 participants in the United Kingdom General Household Survey, aged >16 years	Quit >1 year Quit 1 year
Chronic conditions		
Joung et al. 1995	16,311 Dutch men and women, aged 25–74 years	Total
Physical symptoms		
Macnee 1991	240 men and women, mean age 33 years	Total
Concern about physical health (% reporting)		
Thomas 1960	657 medical students	Total
Getting very tired easily (% reporting)		
Rimer et al. 1990	3,147 American Association of Retired Persons members, aged 50–102 years	Total

*OR = Odds ratio.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
1.35	1.0	35.0	OR*
6.8 10.2	7.3 9.0	-6.8 13.8	None
18.9	18.3	3.3	Physical or health problem
1.32	1.0	32.0	OR
1.43 1.23	1.0 1.0	43.0 26.0	OR
1.49	1.0	49.0	ORs
36.6	21.5	32.8	Based on a scale from 0–120 (higher = more symptoms)
4.4	3.3	33.3	None
25	20	25.0	Age-adjusted

Table 6.14 Continued

Study	Population	Group
Self-reported poor health		
Halpern and Warner 1994	1990 U.S. National Health Interview Survey, random sample (n = 119,631), aged >17 years	Time since cessation 0–2 months 3 months–1 year 2–4 years 5–10 years 11–19 years 20 years
Manderbacka et al. 1999	1991 Swedish Level of Living Survey (n = 5,306), persons aged 18–75 years	Total
Self-reported health status		
Orleans et al. 1989	1,163 African American life insurance policyholders, mean age 39 years	Total
Poikolainen and Vartiainen 1997	6,040 men and women, Finland, aged 25–64 years	Total
General health status (health status questionnaire Short Form 36 [SF-36])		
Sippel et al. 1999	619 HMO[†] members with asthma	Total
Self-perceived good/excellent health (% reporting)		
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men: Iowa East Boston New Haven Piedmont Women: Iowa East Boston New Haven Piedmont

[†]HMO = Health maintenance organization.

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
			OR
3.03	1.0	203.0	
2.83	1.0	183.0	
2.03	1.0	103.0	
1.35	1.0	35.0	
1.42	1.0	42.0	
1.00	1.0	0.0	
1.45	1.0	45.0	OR; adjusted for age, gender, risk factors, health behaviors, and health
22.5	11.3	99.1	Percentage fair/poor
46.7	40.7	14.7	Percentage suboptimal
61	66	-7.6	Higher scores reflect a better health status (100 = best, 0 = worst)
63.8	74.6	-14.5	None
61.7	69.1	-10.7	
61.0	68.8	-11.3	
57.0	60.1	-5.2	
67.4	72.6	-7.2	
57.1	54.3	5.2	
63.6	60.8	4.6	
57.4	54.5	5.3	

Table 6.14   Continued

Study	Population	Group	
Good physical function (% reporting)			
Colsher et al. 1990	4 population-based cohorts, aged >65 years	Men:	Iowa East Boston New Haven Piedmont
		Women:	Iowa East Boston New Haven Piedmont
Physical health status			
Belloc and Breslow 1972	Random sample of Alameda County, California, residents aged >20 years	Men Women	
Reed 1983	542 HMO enrollees	Total	
Wooden and Bush 1995	23,813 Australians	Total	
Overall quality of life			
Sippel et al. 1999	619 HMO members with asthma	Total	
Mental health (health status questionnaire Short Form 36 [SF-36])			
Sippel et al. 1999	619 HMO members with asthma	Total	
Psychological symptoms			
Macnee 1991	240 men and women, mean age 33 years	Total	
Impaired psychological status			
Lindenthal et al. 1972	938 New Haven adults aged >18 years (sample)	Total	
Mental health: prevalence of psychiatric morbidity			
Stansfeld et al. 1993	9,962 men and women, Whitehall Study, aged 35–55 years	Men Women	

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
60.4	70.5	-14.3	None
58.6	64.2	-8.7	
65.7	71.0	-7.5	
64.2	71.5	-10.2	
49.0	61.5	-20.3	
44.9	45.8	-2.0	
47.9	57.1	-16.1	
49.8	50.9	-2.2	
0.51	0.47	8.5	Higher scores reflect a poorer health status, measured by ridits (mean rank sums)
0.51	0.48	6.3	
0.52	0.49	6.1	Higher scores reflect a poorer health status, measured by ridits (mean rank sums); age and gender adjusted
2.231	2.316	-3.7	Higher scores reflect a better health status (4-point scale, 4 = best)
2.4	1.8	33.3	Higher scores reflect a poorer quality of life (10-point scale, 10 = worst)
73	76	-3.9	Higher scores reflect a better mental health (100 = best, 0 = worst)
11.8	7.9	49.4	None
20.3	15.1	34.4	Percentage of very impaired
29.1	23.7	22.8	Smoking was also associated with a risk of physical symptoms in both genders
30.6	30.0	0.3	

Table 6.14   Continued

Study	Population	Group	
	Feeling discouraged/blue (depression)		
Lilienfeld 1959	903 residents, Buffalo, New York	Total	
	Psychological well-being		
Wetzler and Ursano 1988	6,675 U.S. Air Force personnel	Total	
	Mental well-being		
Wooden and Bush 1995	23,813 Australians	Total	
	Life dissatisfaction		
Kaprio and Koskenvuo 1988	7,094 Finns, twin cohort, men aged 20–54 years, women aged 20–39 years	Men:	20–34 years 35–54 years
		Women:	20–39 years
	General life satisfaction		
Blair et al. 1980	504 employees, mean age 34 years	Men Women	

Results			
Former smokers	**Nonsmokers**	**Percentage difference**	**Comments**
32.9	24.8	32.7	Percentage sometimes/very often
4.17	4.24	-1.7	None
2.285	2.300	-0.6	Higher scores reflect better well-being (4-point scale, 4 = best)
8.3	8.4	-1.2	Based on a psychological scale
8.5	8.3	2.4	
8.4	8.2	2.4	
27.5	32.9	-16.4	None
20.5	35.4	-42.1	

Loss of Bone Mass and the Risk of Fractures

In the United States, of the estimated 850,000 fractures per year in persons 65 years of age and older, nearly 300,000 are hip fractures (Apple and Hayes 1994; Centers for Disease Control and Prevention [CDC] 1996; Ray et al. 1997). Approximately 33 percent of women and 17 percent of men experience a hip fracture if they live to be 90 years old (Mazess 1982; Melton and Riggs 1987). Mortality in persons with a hip fracture is 12 to 20 percent higher than in persons without a hip fracture of similar age, race, and gender (Miller 1978; Jensen and Tondevold 1979; Weiss et al. 1983; Jensen 1984; Kenzora et al. 1984; Kreutzfeldt et al. 1984). The estimated annual costs for medical and nursing services related to hip fractures range from $7 billion to $10 billion (Ray et al. 1997). From July 1991 through June 1992, costs to Medicare for 10 types of fractures were estimated at $4.2 billion (Baron et al. 1996). Moreover, continued growth of the elderly population can be expected to dramatically increase the number of hip fractures, because hip fracture incidence rates increase exponentially with age (Melton and Riggs 1987; Melton et al. 1987). If these demographic and incidence trends continue, the number of hip fractures may well double or triple by the middle of the century (Kelsey and Hoffman 1987). With their frequency, adverse quality of life impacts, and economic costs, hip fractures are an urgent and major public health problem.

Bone mineral density (BMD) is one of the strongest indicators of the risk for a fracture. Several cohort studies have confirmed that even a single low BMD measurement is associated with the risk of a later fracture (Gärdsell et al. 1989; Hui et al. 1989; Cummings et al. 1993). For each standard deviation decrease in BMD, the estimated relative risk (RR) of fractures ranged from 1.5 to 2.6, depending on the site that was measured (Marshall et al. 1996). Therefore, discussions of the possible adverse effects from smoking on bone health should consider both BMD and fractures as outcome measures. An estimated 60 to 80 percent of the bone density variation is explained by genetic factors (Eisman 1999), leaving 20 to 40 percent of the variation attributable to nongenetic factors. Smoking is an important modifiable risk factor in both women and men.

Conclusions of Previous Surgeon General's Reports

Harmful effects of smoking on the skeleton have been recognized for several decades but the data were not sufficient to conclude that smoking adversely affects bone mass (USDHHS 1990); however, the most recent Surgeon General's report on women and smoking (USDHHS 2001) identified smoking as adversely affecting bone health and increasing the risks for fractures. The report concluded that smoking adversely affects bone density and increases the risks for hip fractures in postmenopausal women. Specifically, the conclusions were that (1) postmenopausal women who currently smoke have lower bone density than women who do not smoke; (2) women who currently smoke have an increased risk for hip fracture compared with women who do not smoke; and (3) the relationship among women between smoking and the risk for bone fracture at sites other than the hip is not clear (USDHHS 2001). However, because male osteoporosis also has been recognized as a considerable disease burden, the role of smoking in male bone health also deserves consideration.

Biologic Basis

Smoking has the potential for direct and indirect effects on skeletal health and the risk of fractures. Direct toxic effects of smoking on bone cells may be related to the physiologic effects of nicotine (Fang et al. 1991; Riebel et al. 1995) or possibly cadmium in tobacco smoke (Bhattacharyya et al. 1988). Indirect effects of smoking on bone cells may result from decreased intestinal calcium absorption (Krall and Dawson-Hughes 1999), reduced intake and lower levels of vitamin D (Brot et al. 1999), or alterations in the metabolism of adrenal cortical and gonadal hormones (Michnovicz et al. 1986; Khaw et al. 1988; Baron et al. 1995). These direct and indirect effects may account for the generally observed decrease in markers of bone formation such as osteocalcin in smokers compared with nonsmokers (Brot et al. 1999; Bjarnason and

Christiansen 2000). Smoking might also indirectly influence bone density through reduction in body weight, since body weight tends to be lower for smokers than for nonsmokers. This weight difference may itself lead to lower bone density and an increased risk for a fracture (Kiel et al. 1987; Cummings et al. 1995). Smokers also tend to have an earlier menopause than nonsmokers, thus extending the postmenopausal period of accelerated bone mineral loss (USDHHS 2001). Finally, smokers tend to be less physically active than nonsmokers and activity level is associated with bone density and hence risk for a fracture (Gregg et al. 1998).

In several analyses involving women, the lower weight of smokers compared with nonsmokers explains part of the increased risk for low BMD associated with smoking (Bauer et al. 1993). However, there are differences in BMD and in fracture rates between smokers and nonsmokers even after adjusting for weight differences, suggesting that the weight difference alone does not explain the effects of smoking (Kiel et al. 1992, 1996; Bjarnason and Christiansen 2000). The lower weight in smokers may increase the risk of fractures, such as hip fractures, through several mechanisms: reduced soft tissue mass overlaying the trochanter, resulting in less energy absorption from a fall on the hip; reduced weight loads on the skeleton; or reduced conversion of adrenal steroids into sex steroids in adipose tissue. The antiestrogenic effect of smoking also may contribute to osteoporosis in women (Jensen et al. 1985; Jensen and Christiansen 1988), and may reduce the benefits of hormonal replacement therapy (Komulainen et al. 2000). In a Finnish trial of osteoporosis prevention, smoking was associated with a nonresponse to hormonal therapy, as assessed by changes in BMD (Komulainen et al. 2000). Less consistent evidence for a blunted response to estrogen by smoking was reported from a Danish trial (Bjarnason and Christiansen 2000). Interestingly, although estrogen appears to be a critical hormone for male skeletal health (Slemenda et al. 1997; Khosla et al. 1998), smoking does not appear to modify the association between estradiol levels and bone density in men (Amin et al. 1999). Finally, smoking may increase the risk of fractures through reductions in physical performance capacity, thereby increasing the risk for falls (Nelson et al. 1994).

Bone Density in Young Men and Women

Epidemiologic Evidence

Increasingly refined measures of BMD have become available so that current studies use direct BMD measurements. Before such direct measurements were possible BMD was assessed using radiographs, with measurements typically focused on the widths of the cortical bones in sites such as the metacarpals. Direct quantitative assessments of the amount of mineral in various skeletal sites have now become possible with the advent of single and dual photon absorptiometry, followed by refinements such as single and dual x-ray absorptiometry, quantitative computed tomography, and quantitative ultrasonography. These techniques have all been used to generate the data summarized here.

In adults at any particular age bone mass is dependent on the peak mass achieved up to that age, and subsequent losses from the peak are attributable to aging and other factors. The pace of skeletal growth is rapid during infancy, slower during childhood, accelerated during puberty, and by 20 to 30 years of age the peak skeletal mass is attained (Kroger et al. 1992; Lu et al. 1996). Gains in BMD continue into the third decade after bone growth has ceased (Recker et al. 1992). After menopause, bone loss rates accelerate compared with premenopausal rates, and these rates are sustained or increase even more with aging (Ensrud et al. 1995). Age-related losses also occur in men (Jones et al. 1994). In the context of these age-related patterns, the role of smoking in the attainment of peak bone mass is reviewed along with studies of bone density and menopausal status. A literature search was conducted using the National Library of Medicine's PubMed system; the key words used were "bone mineral density," "bone density," "fracture," "smoking," and "cigarettes." In addition, all references from a key meta-analysis (Law and Hackshaw 1997) were also retrieved. Studies focusing on men mainly involve older age groups. The evidence on smoking and BMD comes primarily from cross-sectional and cohort studies. The cross-sectional studies assess the cumulative consequences of smoking on BMD growth and/or decline. Cohort studies can assess changes in BMD over time. Findings of the different types of studies are presented in Tables 6.15–6.17.

Table 6.15 Cross-sectional studies on the association between smoking status and bone density in women*

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
Premenopausal			
Fehily et al. 1992	22 (20–23)	104 current smokers 78 never/former smokers	Radius
Välimäki et al. 1994	24 (20–29)	9 current smokers 47 never smokers	Femur
McCulloch et al. 1990	28 (20–35)	25 current smokers 76 never/former smokers	Calcaneus
Ortego-Centeno et al. 1994	28 (SD = 7)	47 current smokers 54 never/former smokers	Femur
Daniel et al. 1992	29 (20–35)	25 current smokers 27 never/former smokers	Femur
Mazess and Barden 1991	30 (20–39)	23 current smokers 195 never/former smokers	Femur, lumbar spine, and radius
Sowers et al. 1992	36 (22–54)	31 current smokers 77 never/former smokers	Radius
Law et al. 1997	37 (35–39)	28 current smokers 72 never smokers	Radius
	42 (40–44)	63 current smokers 115 never smokers	Radius
	47 (45–49)	50 current smokers 107 never smokers	Radius
	52 (50–54)	14 current smokers 79 never smokers	Radius
Hopper and Seeman 1994	42 (27–49)	9 current smokers 9 never smokers	Femur
Johnell and Nilsson 1984	49 (49)	186 current smokers 185 never/former smokers	Radius

**Note:* See Figure 6.2 for results. The order of the studies in this table reflects the order of the regression lines in Figure 6.2.
†BMD = Bone mineral density.
‡SD = Standard deviation.
§CI = Confidence interval.
 BMC = Bone mineral content.

Findings

No differences in BMD[†] between smokers (0.71 g/cm² [SD[‡] = 0.07]) and nonsmokers (0.71 [0.06])

Mean BMD in g/cm² (SD) at hip = 0.914 (0.102) for smokers compared with 0.956 (0.100) for nonsmokers; adjusted for age, weight, and exercise

Mean BMD in g/cm² = 177.8 (54.1) for smokers compared with 190.6 (52.9) for nonsmokers

Femoral neck BMD in g/cm² (SD) for smokers = 0.796 (0.118), nonsmokers = 0.838 (0.123), p <0.05; lumbar spine for smokers = 1.025 (0.108), nonsmokers = 1.039 (0.106), p = not significant

Mean BMD in g/cm² (SD) = 1.16 (0.014) for smokers compared with 1.151 (0.014) for nonsmokers; adjusted for weight (p = 0.140)

Spine BMD was significantly lower for smokers compared with nonsmokers (t = 2.26, p <0.05)

Radial BMD loss in g/cm² (SD) = 0.71 (0.01) for smokers compared with 0.74 (0.008) for nonsmokers (p = 0.300)

Difference between current and nonsmokers = 0.43 (95% CI[§], -0.73–1.59)

Study of twin pairs found that BMD was lower for the twin who smoked more heavily

Distal BMC in mg/cm² = 320 (SD = 73) for smokers compared with 318 (77) for nonsmokers; proximal = 538 (68) for smokers compared with 533 (62) for nonsmokers; results were not significant

Table 6.15 Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
Postmenopausal			
Law et al. 1997	45 (39–49)	24 current smokers 56 never smokers	Radius
	52 (50–54)	31 current smokers 83 never smokers	Radius
	57 (55–59)	32 current smokers 135 never smokers	Radius
	62 (60–64)	27 current smokers 65 never smokers	Radius
Jensen and Christiansen 1988	50 (44–53)	56 current smokers 54 never/former smokers	Radius
Jensen et al. 1985	51 (44–56)	67 current smokers 69 never/former smokers	Radius
Slemenda et al. 1989	51 (45–57)	21 current smokers 63 never/former smokers	Radius and lumbar spine
McDermott and Witte 1988	53 (SD = 10)	24 current smokers 24 never smokers	Radius
Premenopausal			
Guthrie et al. 1996	54 (48–57)	7 current smokers 39 never/former smokers	Femur
Cheng et al. 1991	54 (50–60)	25 current smokers 82 never/former smokers	Calcaneus
Krall and Dawson-Hughes 1991	59 (40–70)	35 current smokers 267 never/former smokers	Femur
Hopper and Seeman 1994	62 (50–73)	7 current smokers 7 nonsmokers	Femur

[†]BMD = Bone mineral density.
[‡]SD = Standard deviation.
 BMC = Bone mineral content.
[¶]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings

Difference in BMD[†] between current smokers and nonsmokers = -0.17 g/cm² (95% CI, -1.88–1.54)

No odds ratio was given for smoking

BMC (g/cm) = 38.2 (95% CI, 20.9–48.7) in smokers compared with 38.0 (95% CI, 24.9–58.9) in nonsmokers

For current smokers of >20 pack-years[¶], midradius had a -0.0034 g/cm² (SD[‡] = 0.169) change in bone mass/year, distal radius = -0.0071 (0.0180), and lumbar spine = -0.0261 (0.0476); for current smokers of <20 pack-years, midradius = -0.0023 (0.0135), distal radius = -0.0113 (0.0366), and lumbar spine = 0.0136 (0.0800); and for nonsmokers, midradius = -0.0072 (0.0111), distal radius = -0.0071 (0.0172), and lumbar spine = -0.0120 (0.0409)

BMC (g/cm) midradius = 0.89 (0.03) for smokers compared with 0.87 (0.02) for nonsmokers (p = 0.66); distal radius = 0.87 (0.03) for smokers compared with 0.87 (0.03) for nonsmokers (p = 0.98)

Smoking was associated with a lower BMD

BMD (g/cm²) was lower among smokers (0.170 [SD = 0.025]) than nonsmokers (0.180 [0.029] p >0.05)

Mean BMD (g/cm²) of current smokers = 0.611 (SD = 0.012) for radius, 0.787 (0.015) for femoral neck, and 1.084 (0.021) for spine; for current nonsmokers radius = 0.614 (0.005), femoral neck = 0.793 (0.007), and spine = 1.080 (0.009)

Study of twins discordant for tobacco use, by menopause status, BMD was lower for the twin who smoked more heavily

Table 6.15   Continued

Study	Mean (range) age (years)	Smoking status	Site of bone density measurement
		Premenopausal	
Sowers et al. 1985	62 (55–80)	119 current smokers 278 never smokers	Radius
Hansen et al. 1991	63 (59–67)	61 current smokers 60 never/former smokers	Femur
Egger et al. 1996	66 (63–68)	23 current smokers 99 never smokers	Femur and lumbar spine
Holló et al. 1979	68 (61–75)	41 current smokers 125 never smokers	Radius
Nguyen et al. 1994	70 (>60)	102 current smokers 765 never smokers	Femur and lumbar spine
Jensen 1986	70 (70)	77 current smokers 103 never smokers	Radius
Johansson et al. 1992	70 (70)	38 current smokers 200 never smokers	Calcaneus
Rundgren and Mellström 1984	70 (70)	43 current smokers 243 never smokers	Calcaneus
	75 (75)	49 current smokers 364 never smokers	Calcaneus
	79 (79)	19 current smokers 218 never smokers	Calcaneus
Bauer et al. 1993	71 (65–84)	485 current smokers 4,367 never smokers	Radius
Kiel et al. 1996	74 (68–98)	77 current smokers 340 never smokers	Femur
Cheng et al. 1993	75 (75)	10 current smokers 161 never smokers	Calcaneus
Hollenbach et al. 1993	76 (60–89)	42 current smokers 320 never smokers	Femur

[†]BMD = Bone mineral density.
[‡]SD = Standard deviation.
 BMC = Bone mineral content.

Findings

Mean BMD† = 0.633 (SD‡ = 0.014) for smokers of 1–9,000 pack-days, and 0.637 (SD = 0.014) for >9,000 pack-days compared with 0.625 (SD = 0.005) for nonsmokers (findings were not significant); adjusted for age to 66 years and median muscle mass

Smokers had a lower BMD (g/cm^2) 0.69 (SD = 0.11) than nonsmokers 0.65 (0.09)

Mean (g/cm^2) change/decade of smoking = -0.015 (95% CI, -0.028 to -0.003) for lumbar spine and -0.004 (-0.012 to -0.003) for femoral neck; adjusted for age, weight, height, alcohol use, calcium intake, and physical activity

Smokers had a lower BMC (0.68 g/cm [SD = 0.10]) than nonsmokers (0.72 [0.10]), p <0.05

Lumbar spine BMD = 0.96 g/cm^2 (SD = 0.22) for current smokers, 1.03 (0.17) for former smokers, and 1.02 (0.19) for never smokers; femoral neck BMD = 0.73 (0.10) for current smokers, 0.78 (0.12) for former smokers, and 0.79 (0.13) for never smokers (p <0.05 for current smokers vs. nonsmokers for both comparisons)

40.3% of smokers and 44.7% of nonsmokers had some type of fracture (hip, proximal, distal radius, vertebral, or long bones)

r = 0.15, p <0.01 comparing current, former, and nonsmokers

Among 70-year-old current smokers, BMD (μm) = 784 (SD = 252) compared with former smokers (884 [280], p <0.05) and nonsmokers (928 [273], p <0.001); among current smokers aged 75 years, 759 (260) compared with former smokers (950 [282], p <0.05) and nonsmokers (878 [268], p <0.01); and among current smokers aged 79 years, 554 (258) compared with former smokers (748 [372], p <0.05) and nonsmokers (807 [329], p <0.001)

Percentage change in bone mass (g/cm^2) = -0.04 (95% CI, -0.9–0.8) for lifetime cigarettes smoked (per 20 pack-years)

Among estrogen users, current smokers had a lower BMD of the trochanter (0.589 g/cm^2) than nonsmokers (0.640, p = 0.05)

Current smokers had a lower mean BMD (0.114 g/cm^3 [SD = 0.023]) than nonsmokers (0.129 [0.036] p >0.05)

Current smokers had a lower mean femoral neck BMD (0.608 [SD = 1.008]) than nonsmokers (0.632 [0.005] p <0.01)

Table 6.16 Studies on the association between smoking status and bone density in men and women published since the 1997 meta-analysis by Law and colleagues

Study	Population/age (years)	Smoking status	Measurement/site
		Women	
Brot et al. 1997	433 perimenopausal Danish women aged 45–58 years; 87 were followed for 2 years	49% current smokers 39% never smokers 12% former smokers	A BMC* of the whole body was measured at enrollment and after 1 and 2 years
Takada et al. 1997	3,867 premenopausal and postmenopausal Japanese women aged 37–69 years	A dichotomous category for current smoking (yes/no), but no data were provided	BMD‡ at the distal radius 1/3 of the distance from the wrist to the elbow
Grainge et al. 1998	580 postmenopausal women aged 45–59 years	25.7% current smokers 74.3% nonsmokers at the time of the scan	BMD of the spine, hip, radius/ulna, and whole body
Smeets-Goevaers et al. 1998	5,896 perimenopausal white Dutch women aged 46–54 years	Never smokers; former or current smokers were said to be identified, but no data were provided	BMD of the spine
Cheng et al. 1999	200 white women aged 20–79 years	38% had a history of tobacco use (average 8.2 packs/year) 7% current smokers	BUA§ of the calcaneus
Gregg et al. 1999	393 women aged 45–53 years (7.4% white; 12.2% perimenopausal or post-menopausal)	9.2% current smokers	BUA and SOS ‖ of the calcaneus; BMD of the spine and hip
Jones and Scott 1999	263 premenopausal women; mean age 33 ± 4.5 years	45% current smokers	BMD of the spine, hip, and whole body
Varenna et al. 1999	6,160 postmenopausal Italian women; mean age 54.5 ± 6.4 years	74.9% never smokers 5.0% former smokers 20.1% current smokers	BMD of the spine

*BMC = Bone mineral content.
†Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
‡BMD = Bone mineral density.
§BUA = Broadband ultrasound attenuation.
 SOS = Speed of sound.

Findings

Smoking (pack-years[†]) was a significant and independent predictor of total BMC (p <0.001)

The combined variable of no drinking (consumption of alcohol 3 days/week) and current smoking has a statistically significant negative effect on radial BMD among older (56–69 years) women (p <0.05)

BMD was more strongly related to the number of months of smoking than to pack-years at all 5 sites (p <0.05 at all sites except the femoral neck)

Increased risks for a low BMD (osteopenia and osteoporosis) were associated with smoking (odds ratio = 1.25 [95% confidence interval, 1.08–1.44])

Smoking was not associated with the BUA (p >0.05)

Smoking was not significantly associated with the calcaneal BUA or SOS

Current smoking was associated with a significantly lower BMD at the hip and a lower BMD (not significant) at the spine and whole body

Smoking was not associated with BMD or a risk for osteoporosis

Table 6.16 Continued

Study	Population/age (years)	Smoking status	Measurement/site
		Women	
Kim et al. 2000	238 Korean women; mean age 24.2 ± 2.5 years scanned only as a reference population 552 postmenopausal Korean women; mean age 62.5 ± 8.2 years	Data were not reported	BUA[§] of the calcaneus
		Men	
Vogel et al. 1997	1,303 men of Japanese descent living in Hawaii; aged 61–82 years	35% never smokers 45% former smokers 20% current smokers	BMD[‡] of the calcaneus, and distal and proximal radius
Hagiwara and Tsumura 1999	1,736 Japanese men aged 20–64 years	35.5% nonsmokers 15.7% former smokers 48.8% current smokers	BMD of the calcaneus
Huuskonen et al. 2000	140 Finnish men aged 54–63 years	Mean pack-years = 19.0 (range 1–59.5)	BMD of the neck, trochanter, Ward's triangle, and L2–L4

[‡]BMD = Bone mineral density.
[§]BUA = Broadband ultrasound attenuation.

Findings

There was no association between a history of smoking and low quantitative ultrasound values after controlling for age and time since menopause

Current and former smokers had a 1.8–4.8% lower BMD in the calcaneus and distal radius

Men in the highest BMD quintile were younger, with a higher body mass index and a lower mean pack-year history than men in the lowest quintile

Correlation coefficient = 0.04, -0.01, 0.05, and -0.10 with pack-years for the neck, trochanter, Ward's triangle, and L2–L4 (p >0.05), respectively

Table 6.17   Cohort studies on the association between smoking status and the risk of bone loss in men and women

Study	Population/age (years)	Smoking status	Measurement/site
Slemenda et al. 1989	84 perimenopausal and postmenopausal women followed for 3½ years	Data were not reported	BMD* of the midradius, distal radius, and the lumbar spine
Krall and Dawson-Hughes 1991	320 postmenopausal women aged 40–70 years; 2-year calcium supplementation trial	55% never smokers 35% former smokers (>1 month before trial) 11% smoked during all or part of the trial	BMD of the radius, femoral neck, Os calcis, and the spine
Slemenda et al. 1992	111 male veterans of World War II or the Korean War born between 1916 and 1927, all twin pairs; 16-year follow-up	Monozygotic male twins (n = 57) had mean 10.9 ± 14.9 cigarettes/ day; dizygotic twins (n = 54) had mean 14.4 ± 15.9 cigarettes/day	BMD of the radius
Sowers et al. 1992	217 women aged 22–54 years; 5-year follow-up	Mean lifetime packs of cigarettes = 2,447	BMD of the distal radius
Jones et al. 1994	626 (385 women, 241 men); average follow-up was 2.5 years	Women had a median of 9 pack-years of smoking; men had a median of 31 pack-years of smoking	BMD of the hip and the spine
Vogel et al. 1997	1,303 Japanese American men aged 51–82 years; average follow-up was 5 years	20% current smokers 45% former smokers 35% never smokers	BMD of the distal and proximal radius and the calcaneus
Burger et al. 1998	1,856 Dutch men (mean age, 66.7 years), 2,452 Dutch women (mean age 67.2 years); average follow-up was 2 years	Current smokers Men (23%) Women (19%)	BMD of the hip

*BMD = Bone mineral density.
†Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Findings

Heavy smokers (20 pack-years[†]) had significantly (p <0.05) lower radial (midradius = 0.76 [standard deviation (SD) ±0.10] g/cm, distal radius = 0.83 [±0.12] g/cm²) and vertebral (lumbar spine = 0.82 [±0.16] g/cm²) BMD than nonsmokers (0.84 [±0.11], 0.91 [±0.13], and 0.94 [±0.15] g/cm², respectively); there were no significant differences between light smokers (<20 pack-years) and nonsmokers; there were no detectable effects of smoking on the rates of bone loss at any site

Adjusted mean (±SD) annualized rate of bone change from the radius was greater among smokers than nonsmokers (-0.914 [±2.624]%/year, n = 34, vs. 0.004 [±2.568]%/year, n = 278, respectively; p = 0.05); variables adjusted for include supplement type (placebo, citrate malate, or calcium carbonate), current alcohol status (user or nonuser), and caffeine intake; this same significant trend was observed at 3 other sites

-0.100 g/cm (standard error ±0.036) (p = 0.007) for cigarette smoking; the twin who smoked more lost more bone (p = 0.005); men with cigarette and alcohol use above median levels had the most rapid losses

In postmenopausal women, but not premenopausal women, smoking at baseline was associated with a lower BMD at follow-up

There were no differences in the rates of loss between current smokers and nonsmokers

Compared with never smokers, current smokers had significantly greater rates of bone loss: 29.4% from the calcaneus (p <0.001) and 33.8% from the distal radius (p <0.01); analyses were adjusted for age, height, weight, physical activity, and alcohol and thiazide use

Smoking was accompanied by a significantly higher rate of bone loss in both men and women (men, p = 0.02; women, p = 0.01); the association was stronger when not adjusting for body mass index

Table 6.17 Continued

Study	Population/age (years)	Smoking status	Measurement/site
Guthrie et al. 1998	224 women (74 premeno- pausal, 90 perimenopausal, and 60 postmenopausal); follow-up was 2 years	Premenopausal women 14% current smokers Early perimenopausal women 14% current smokers Late perimenopausal women 25% current smokers Postmenopausal women 15% current smokers	BMD* of the hip and the spine
Krall and Dawson- Hughes 1999	402 elderly men and women (32 smokers, 370 nonsmokers); 3-year placebo-controlled study	Smokers 42% men 53% women Nonsmokers 45% men 55% women	BMD at the femoral neck, total body, and the spine
Hannan et al. 2000	468 women, 273 men (mean age 74.5 years); average follow-up was 4 years	Current smokers Women (10%) Men (8%)	BMD of the hip, spine, and radius

*BMD = Bone mineral density.

Findings

Of the women who became postmenopausal during the study, 6 were current smokers and their mean annual change in spine BMD was slightly greater (-3.3%) than that of the 36 nonsmokers (-2.3%); p = 0.10

BMD losses (adjusted for baseline BMD, weight, age, gender, supplementation status, and dietary calcium intake) were higher in smokers than in nonsmokers at the femoral neck (-0.714 g/cm [standard error = (±0.285)%/year vs. 0.038 [±0.084]%/year, p <0.02]), and total body (-0.360 [±0.101]%/year vs. -0.152 [±0.030]%/year, p <0.05); there were no significant differences at the spine (0.260 [±0.252]%/year in smokers vs. 0.593 [±0.074]%/year in nonsmokers, p = 0.21)

Compared with women who had never smoked, female current smokers had no increase in bone loss; in men, current smokers had greater bone loss (4–5%) than never smokers

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Peak Bone Mass

Because BMD increases rapidly during adolescence, initiating smoking around the time of puberty might reduce peak BMD. However, the effects of smoking on the attained level of peak bone mass are uncertain because there are limited data on the skeletal effects of smoking during adolescence. Furthermore, it is possible that relatively short exposures in this age group would have little effect on bone density measurements. One prospective cohort study of children and adolescents (aged 9 to 18 years) in Finland repeatedly ascertained lifestyle factors and followed participants for 11 years, at which time they underwent bone density testing (Välimäki et al. 1994). In men, but not in women, smokers had lower BMD measurements of the hip and spine than did nonsmokers after adjusting for covariates. A cross-sectional study of 15-year-old Swedish adolescents did not find an association between smoking and total body bone mineral content (Lötborn et al. 1999). Findings were similar in a cross-sectional study of 500 children aged 4 to 20 years in the Netherlands, but only 32 were smokers (Boot et al. 1997).

Data are available from studies of premenopausal women, starting from the ages at which peak BMD is reached. A meta-analysis of cigarette smoking, BMD, and the risk for hip fractures (Law and Hackshaw 1997) identified 10 cross-sectional studies of premenopausal women (Johnell and Nilsson 1984; McCulloch et al. 1990; Mazess and Barden 1991; Daniel et al. 1992; Fehily et al. 1992; Sowers et al. 1992; Hopper and Seeman 1994; Ortego-Centeno et al. 1994; Välimäki et al. 1994; Law et al. 1997). Additional study populations included menopausal and postmenopausal women (Table 6.15). As shown in Table 6.15, the mean ages of women in the study samples ranged from 22 to 76 years. Because absolute bone density units varied among studies according to the bone site assessed and the measurement technique used, the difference between the average BMD of current smokers and nonsmokers in each of the studies was recorded as a proportion of one between-person standard deviation. In combining the studies, each bone density difference was weighted by the inverse of its variance and was age-adjusted only.

Bone densities were reported for current smokers compared with never smokers in most studies, but were reported for current compared with former and lifetime never smokers combined in a few studies. There was no evidence of a significant difference in BMD between smokers and nonsmokers in the premenopausal women (Figure 6.2). Two additional studies of premenopausal and postmenopausal women

performed since the 1997 meta-analysis also show no significant differences in BMD between smokers and nonsmokers (Table 6.16) (Takada et al. 1997; Gregg et al. 1999); however, a study of premenopausal women from Australia did find a significantly lower BMD in female current smokers that was not found in the subgroup of female smokers who participated in sports (Jones and Scott 1999). Cross-sectional data from the Danish Osteoporosis Prevention Study showed lower BMD in current smokers compared with lifetime nonsmokers in perimenopausal women (Hermann et al. 2000). It is appropriate to consider these results unadjusted for other covariates in that adjusting for one of the most important risk factors for bone density—weight—actually may mask an association. Smoking-induced weight loss may represent an intervening variable in the causal chain between smoking and bone density reduction.

One study from Spain assessed smoking and BMD in healthy young males (Ortego-Centeno et al. 1997). In this study, male volunteers aged 20 through 45 years were measured for BMD in the lumbar spine and proximal femur; blood biochemical markers were also assessed. BMD was significantly lower for smokers of 20 or more cigarettes per day compared with nonsmokers. In multiple regression analyses considering all smokers, smoking was not significantly associated with measures of BMD. Interpretations of these findings are limited by the cross-sectional data and the small sample size.

Smoking Cessation and Bone Mineral Density Loss

Two prospective cohort studies assessed smoking cessation and BMD in men and women (Hollenbach et al. 1993; Kiel et al. 1996). In a study in Rancho Bernardo, California, Hollenbach and colleagues (1993) found that smoking cessation later in life was beneficial for men and women in halting BMD loss at hip sites (intertrochanter, total hip, femoral neck, and trochanter) where BMD is reduced in smokers. In men, smoking cessation was followed by a reduction in the rate of loss of the spinal BMD, and women experienced a significant decrease in the rate of BMD loss at the midradius after quitting. In the Framingham study, current or former smoking (past 10 years) was not associated with a lower BMD loss at any skeletal site among women who had not taken estrogen but it was in women who had (Kiel et al. 1996). Former male smokers who had quit for less than 10 years had a lower BMD than men who had quit for 10 or more years, independent of weight, alcohol consumption, or caffeine use.

Figure 6.2   Differences (95% confidence intervals), as a proportion of 1 standard deviation (SD), in bone mineral density between female smokers and nonsmokers according to age and menopausal status
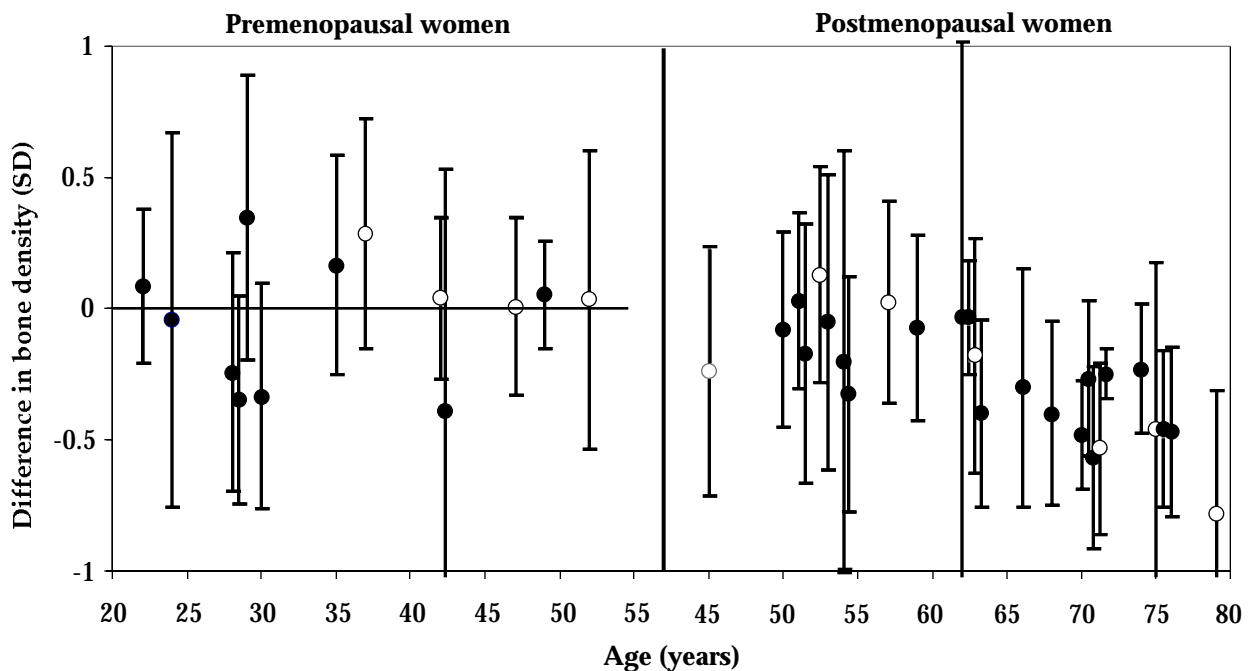
Note: Fitted regression lines are shown. The 11 open circles refer to two studies (Rundgren and Mellström 1984; Law et al. 1997); the 28 solid circles refer to the other studies in the order listed in Table 6.15 (Fehily et al. 1992 through Johnell and Nilsson 1984 for premenopausal women, and Law et al. 1997 through Hollenbach et al. 1993 for postmenopausal women). Source: Law and Hackshaw 1997, p. 843. Reprinted with permission.

Evidence Synthesis

Smoking, even at a young age, might increase risk for osteoporosis later in life if it reduces the peak bone mass attained, thereby compromising the peak from which decline begins. Only a few studies address smoking during adolescence, and the findings in women during the premenopausal years are conflicting, are not based on large studies, and do not provide strong evidence for an effect of smoking on BMD before menopause. For males, data are scant for this age range. Although an effect of smoking on BMD is plausible, the available evidence from observational studies is limited and inconsistent.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

Implications

The failure to demonstrate a causal relationship between smoking and bone density in young women does not detract from the basis for concern about smoking and osteoporosis in women. For women, smoking patterns established in younger years are likely to persist past menopause, and there is substantial evidence linking smoking to low bone density during menopause (see below). Future research should quantify the combined and cumulative effects of premenopausal and postmenopausal smoking on bone density. More research is needed in young men regarding the relationship between smoking and bone density.

Bone Density in Middle and Later Years of Life

Epidemiologic Evidence

In contrast to the findings for younger persons, findings of bone density studies performed in populations well beyond the years of peak bone mass demonstrate substantial differences between smokers and nonsmokers. As illustrated in Figure 6.2, based on the meta-analysis by Law and Hackshaw (1997), bone density was lower in smokers than in nonsmokers for postmenopausal women, and the difference increased linearly with age. For every 10-year increase in age, the bone density of smokers fell below that of nonsmokers by approximately 2 percent of the average bone density at the time of menopause, regardless of the skeletal site that was measured.

Since the publication of this meta-analysis, there have been additional studies of smoking and bone density in postmenopausal women and in men. Of four studies that did not demonstrate an association between smoking and bone density (Cheng et al. 1999; Varenna et al. 1999; Huuskonen et al. 2000; Kim et al. 2000), two had used quantitative ultrasound to measure bone status. Seven other studies did demonstrate statistically significant associations between smoking and BMD (Table 6.16) (Brot et al. 1997; Takada et al. 1997; Vogel et al. 1997; Grainge et al. 1998; Smeets-Goevaers et al. 1998; Hagiwara and Tsumura 1999; Hermann et al. 2000).

Data from cohort studies of older men and women also implicate smoking as a significant risk factor for bone loss (Table 6.17). Of the six studies that reported smoking data (three involving women and men, two involving women only, and one involving men only) (Sowers et al. 1992; Jones et al. 1994; Vogel et al. 1997; Burger et al. 1998; Guthrie et al. 1998; Hannan et al. 2000), three documented significantly more bone loss in female smokers than in female and male nonsmokers (Sowers et al. 1992; Burger et al. 1998; Guthrie et al. 1998), and three reported higher rates of loss among male smokers than among male nonsmokers (Vogel et al. 1997; Burger et al. 1998; Hannan et al. 2000). Interpretations of several of the studies are constrained by relatively small sample sizes and limited durations of follow-up.

Evidence Synthesis

Extensive and consistent data are available on BMD and smoking for perimenopausal and postmenopausal women and for older men. Data from cohort studies, which track changes in BMD over time, as well as from cross-sectional studies provide generally consistent evidence of increased rates of loss in postmenopausal women who smoke compared with nonsmokers. Smoking cessation appears to benefit BMD since limited data indicate higher rates of BMD loss for heavier smokers. Data are more limited for men. The 2001 Surgeon General's report (USDHHS 2001) found the evidence to be consistent for women and concluded that "Postmenopausal women who currently smoke have lower bone density than do women who do not smoke" (p. 321). There are a number of mechanisms that may underlie this finding.

Conclusions

1. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

2. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

Implications

Smoking has an adverse effect on bone density in middle and later years of life; for every 10-year increase in age, the bone density of female smokers falls below that of nonsmokers by about a 0.14 standard deviation, or 2 percent of the average bone density at the time of menopause in women. Because a 1.0 standard deviation decrease in bone density doubles the risk of fracture, and because fracture incidence increases with age (Melton and Riggs 1987; Melton et al. 1987), the proportion of all fractures attributable to smoking would be expected to increase for smokers who continue smoking into older ages. Attempts to decrease smoking as early in life as possible are likely to reduce fractures that would be caused by smoking in old age.

Because bone loss is relatively small over short periods of time, studies with longer durations of follow-up and minimal avoidable losses of participants at follow-up could add important information to the understanding of how smoking contributes to bone loss. Additional information is likely to come from studies of biochemical markers of bone turnover, which might further the understanding as to mechanisms whereby smoking accelerates bone loss.

Fractures

Epidemiologic Evidence

Hip fractures, the most frequently studied fractures in relation to smoking, account for a significant proportion of the morbidity and mortality attributed to osteoporosis. The meta-analysis by Law and colleagues (1997) reviewed 19 cohort and case-control studies of the risk of hip fractures in postmenopausal women according to whether they had COPDs. The studies differed with regard to the ages of the participants, duration of follow-up, and whether former smokers were included in the smoking or nonsmoking groups. Table 6.18 shows the characteristics of each of the 19 studies, demonstrating the range of ages at the time of the fracture. For the cohort studies, the duration of follow-up ranged from three years (Forsén et al. 1994) to 26 years (Kiel et al. 1992). Figure 6.3 shows the risk of hip fractures in smokers relative to nonsmokers according to age; the risks for smokers increased with increasing age. Major conclusions of the meta-analysis include (1) smoking has no material effect on bone density in premenopausal women; (2) postmenopausal bone loss is greater in smokers—an

Figure 6.3   Relative risk (95% confidence intervals) of hip fracture in smokers compared with nonsmokers in postmenopausal women according to age
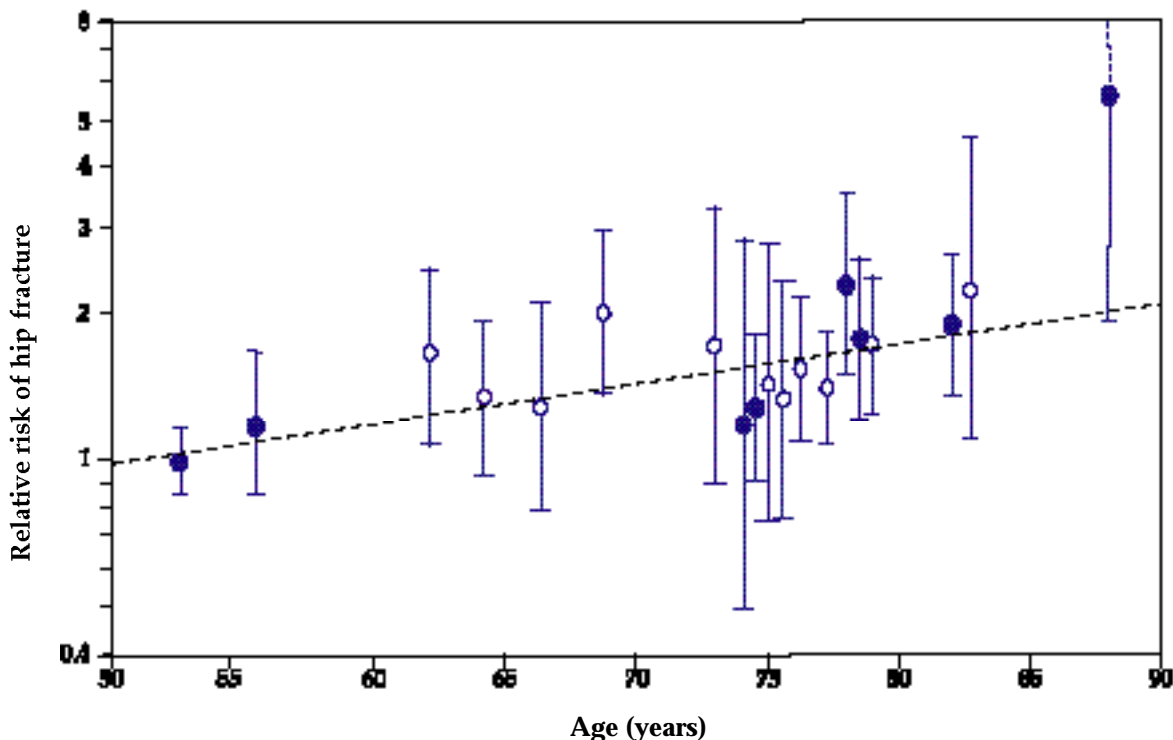
Note: Each cohort study (8 solid circles) and case-control study (11 open circles) is in the same order as in Table 6.18. Fitted regression (dotted) line is shown.
Source: Law and Hackshaw 1997, p. 844. Reprinted with permission.

additional 0.2 percent of bone mass each year; (3) in comparisons of women who are current smokers with women who are nonsmokers, the risk of hip fracture is estimated to be 17 percent greater at 60 years of age, 41 percent greater at 70 years, 71 percent greater at 80 years, and 108 percent greater at 90 years; and (4) the estimated cumulative risk of hip fracture to 85 years of age in women is 19 percent in smokers and 12 percent in nonsmokers; to 90 years it is 37 percent and 22 percent, respectively. The data for men were much more limited but suggested similar consequences.

Since the publication of the meta-analysis by Law and colleagues (1997), some (Forsén et al. 1998; Burger et al. 1999; Kanis et al. 1999; Melhus et al. 1999; Baron et al. 2001) but not all subsequent studies of hip fracture (Fujiwara et al. 1997; Clark et al. 1998; Mussolino et al. 1998) have continued to show an association between smoking and an increased risk of hip fracture (Table 6.19). These studies have used various designs and have been carried out in diverse populations.

Data on the association between smoking and fractures at other sites are more limited (Table 6.20). Studies from the 1980s and early 1990s that examined fractures other than those of the hip rarely found an association with smoking, although more recent studies have demonstrated positive associations between smoking and vertebral fractures (Scane et al. 1999; Lau et al. 2000), ankle fractures (Honkanen et al. 1998), and the general categories of nonhip fractures (Jacqmin-Gadda et al. 1998) and of all fractures (Huopio et al. 2000).

Smoking Cessation and Hip Fractures

The association between smoking cessation and the risk of hip fractures was examined in several studies, including three prospective cohort studies with follow-up periods of 5 to 12 years (Forsén et al. 1998; Cornuz et al. 1999; Høidrup et al. 2000) and two case-control studies (La Vecchia et al. 1991; Cumming and Klineberg 1994). In men, successful smoking cessation of at least five years decreased the risk of hip fracture compared with continuing smokers (Høidrup et al. 2000), although other investigations found that this risk remained elevated for men and women smokers compared with lifetime nonsmokers (Cumming and Klineberg 1994; Forsén et al. 1998). Two studies also found no decrease in the risk for hip fractures in

women after five years of smoking cessation (La Vecchia et al. 1991; Cornuz et al. 1999), and another found that no benefit from quitting for women, including premenopausal women, was observed until 10 years after cessation (adjusted RR = 0.7 [95 percent confidence interval (CI), 0.5–0.9] compared with current smokers) (Cornuz et al. 1999).

Evidence Synthesis

The evidence on smoking and fracture has been reviewed extensively in previous reports of the Surgeon General. The 1990 report considered evidence from eight case-control studies, noting that most showed an association with risk for fracture of the hip or vertebra. Five cohort studies, however, did not show a clear increase in risk and the report found the evidence to be inconclusive. Far more extensive data were available for the 2001 report, including substantially more studies of hip fracture in women. The case-control studies reviewed all indicated excess risk for hip fracture in smokers, with the RR ranging from 1.1 to 2.0. Six reports of cohort studies published subsequent to the 1990 report were also cited, all showing an increased risk for hip fracture in current smokers. The 2001 report (USDHHS 2001) concluded that "women who currently smoke have an increased risk for hip fracture compared with women who do not smoke" (p. 321).

This report extends the review of the 2001 report with additional studies and covers the evidence on men as well. The evidence consistently indicates an increased risk for women and men who smoke. Findings of some studies show a dose-response relationship between risk for hip fracture and the amount smoked. The RR tends to rise with age as would be expected, and the effect of smoking reflects sustained, additional bone loss beyond that associated with aging. The documented effects of smoking on BMD is consistent with the observational evidence on hip fracture.

For fracture sites other than the hip, the evidence has been less consistent. The 2001 Surgeon General's report found the evidence to be unclear. This report evaluated a number of studies for other sites, also finding the evidence to be mixed and limited in scope for any particular site.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Implications

The RR of hip fractures in smokers increases with age, and hip fracture incidence increases with age, implying that the proportion of hip fractures attributable to smoking increases with age. Smoking is one of the major causes of fracture in older persons that can be prevented. Public health interventions aimed at helping smokers quit are likely to substantially reduce the number of hip fractures. Although hip fractures carry the greatest costs and risks of mortality and morbidity, other fractures also contribute to these outcomes. Further research is necessary to quantify the risks of these other fractures in smokers.

Table 6.18   Studies on the association between smoking and the risk of hip fractures in men and women used in the 1997 meta-analysis by Law and Hackshaw*

Study	Age at entry (years)	Mean age at fracture (years)	Number of persons (% smokers)	
			With fracture	Without fracture
Cohort studies				
Hemenway et al. 1988	34–59	53	662	68,056 (28)
Meyer et al. 1993	35–49	56	124	20,881 (37)
Holbrook et al. 1988	50–79	75	33	924
Kiel et al. 1992	28–62	75	167 (22)	2,243 (37)
Cummings et al. 1995	65	78	192	9,324 (10)
Forsén et al. 1994	50	78	220 (16)	14,598 (20)
Paganini-Hill et al. 1991	All ages	82	242 (13)	5,558 (13)
Case-control studies				
Wickham et al. 1989	65	88	44	1,375
La Vecchia et al. 1991	29–74	62	158 (11)	1,096 (6)
Williams et al. 1982	50–74	64	160 (60)	567 (53)

*Note: The order of the studies in this table reflects the order of the regression lines in Figure 6.3.
[†]RR = Relative risk.
[‡]CI = Confidence interval.
[§]SD = Standard deviation.
 OR = Odds ratio.
[¶]ERT = Estrogen replacement therapy.

Findings

Compared with nonsmokers, RR† = 0.98 (95% CI‡, 0.84–1.14) for former smokers, 0.95 (95% CI, 0.71–1.20) for current smokers of 1–14 cigarettes∕day, 0.97 (95% CI, 0.79–1.20) for current smokers of 15–24 cigarettes∕day, and 0.99 (95% CI, 0.78–1.25) for current smokers of 25 cigarettes∕day

Compared with never smokers, the age-adjusted RR = 0.81 (95% CI, 0.45–1.46) for former smokers, 1.04 (95% CI, 0.71–1.53) for current smokers of 1–14 cigarettes∕day, and 1.46 (95% CI, 0.81–2.64) for current smokers of 15 cigarettes∕day

RR = 1.1 (not significant) for smokers compared with nonsmokers; adjusted for age, gender, body mass index (BMI), and alcohol use

Compared with never smokers, the age-adjusted RR = 1.08 (95% CI, 0.82–1.42) for ever smokers, 0.97 (95% CI, 0.68–1.39) for former smokers, 1.19 (95% CI, 0.84–1.69) for all current smokers, 1.16 (95% CI, 0.80–1.67) for light smokers (1 pack∕day), and 1.45 (95% CI, 0.66–3.17) for heavy smokers (>1 pack∕day)

Age-adjusted RR = 2.1 (95% CI, 1.4–3.3) for current smokers compared with never smokers

Incidence rates∕1,000 person-years for current smokers compared with nonsmokers for men: 1.3 (SD§ = 0.4) for ages 50–64 years, 3.4 (SD = 1.3) for 65–74 years, 10.3 (SD = 6.4) for 75 years; for women: 2.1 (SD = 1.4) for 50–64 years, 7.8 (SD = 3.5) for 65–74 years, and 23.9 (SD = 16.6) for 75 years

Compared with never smokers, the age-adjusted RR = 1.8 (p <0.001) for current female smokers and 2.2 (p <0.05) for current male smokers

Crude OR = 5.6 (95% CI, 1.8–17.7) for current smokers compared with nonsmokers

Compared with never smokers, RR = 1.7 (95% CI, 1.0–3.0) for former smokers and 1.5 (95% CI, 1.0–2.1) for current smokers; adjusted for age, area of residence, education, BMI, menopausal status, ERT¶, and alcohol use

Age-standardized OR for 1 year of estrogen use compared with obese (based on Ponderal index: height = inches∕cubed root of weight [pounds]; obese = 9.6–12.5, average = 12.6–13.5, thin = 13.6–15.5) never smokers: obese ever smokers = 1.3 (95% CI, 0.4–4.5), average never smokers = 2.1 (95% CI, 0.7–5.9), average ever smokers = 2.1 (95% CI, 0.8–5.8), thin never smokers = 2.7 (95% CI, 0.5–14.0), and thin ever smokers = 6.4 (95% CI, 2.1–19.4)

Table 6.18   Continued

Study	Age at entry (years)	Mean age at fracture (years)	Number of persons (% smokers)	
			With fracture	**Without fracture**
Case-control studies				
Kreiger et al. 1982	45–74	66	98	801
Michaelsson et al. 1995	40–75	68	205 (18)	765 (10)
Kreiger et al. 1992	50–84	74	102 (29)	277 (17)
Grisso et al. 1994	45	75	109 (29)	169 (15)
Paganini-Hill et al. 1981	<80	75	83 (35)	166 (30)
Jaglal et al. 1993	55–84	75	381 (22)	1,138 (16)
Lau et al. 1988	All ages	76	400	800
Cooper et al. 1988	50	78	300 (48)	600 (37)
Cumming and Klineberg 1994	65	82	209	207

¶ERT = Estrogen replacement therapy.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
Source: Law and Hackshaw 1997.

Findings

No OR was given for smoking

Compared with never smokers, OR = 1.50 (95% CI, 1.10–2.05) for ever smokers, 1.17 (95% CI, 0.74–1.86) for former smokers of <20 pack-years**, 1.94 (95% CI, 0.96–3.92) for former smokers of 20 pack-years, 1.91 (95% CI, 1.12–3.26) for current smokers of <20 pack-years, and 1.82 (95% CI, 1.03–3.20) for current smokers of 20 pack-years

OR = 1.73 (95% CI, 0.90–3.32) for current smokers compared with never or former smokers; adjusted for age, dietary calcium, ovariectomy, ERT¶ (months), and Quetelet index (g/cm²)

Compared with never smokers, OR = 1.2 (95% CI, 0.6–2.4) for former smokers, 1.3 (95% CI, 0.7–2.6) for all current smokers, 1.1 (95% CI, 0.5–2.4) for current smokers smoking <1 pack/day, and 2.0 (95% CI, 0.7–6.0) for those smoking 1 pack/day

Compared with never smokers, OR = 1.05 for current smokers of 1–10 cigarettes/day, and 1.96 for 11 cigarettes/day; adjusted for estrogen and ovarian status

Compared with zero pack-years, crude OR for 1–29 pack-years = 1.02 (95% CI, 0.72–1.43), 30–59 pack-years = 1.49 (95% CI, 1.01–2.21) and 60 pack-years = 1.43 (95% CI, 0.73–2.79)

RR = 1.3 (95% CI, 1.0–1.7) for current or former smokers compared with never smokers

RR = 1.7 (95% CI, 1.2–2.3) for ever smokers compared with never smokers

Compared with never smokers, OR for ever smokers = 1.6 (95% CI, 1.0–2.6), former smokers = 1.4 (95% CI, 0.8–2.5), and current smokers = 2.2 (95% CI, 1.1–4.6); adjusted for age, gender, and proxy status (when relevant)

Table 6.19   Studies on the association between smoking and the risk of hip fractures in men and women reported since the 1997 meta-analysis by Law and Hackshaw

Study	Design	Population
Fujiwara et al. 1997	Cohort	1,586 Japanese men, 2,987 Japanese women; mean age 58.5 ± 12.2 years; during and up to the 14-year follow-up, 55 incidents of hip fractures not attributable to traffic accidents were identified
Grisso et al. 1997	Case-control	356 men with radiologically confirmed hip fractures, 402 controls from 20 hospitals in Philadelphia, Pennsylvania, and 14 Kaiser Permanente hospitals in northern California
Clark et al. 1998	Case-control	45 Mexican men and 107 Mexican women with hip fractures, aged 45 years (mean age was 70.2 for men, 73.5 for women); 143 healthy controls (37 men, 106 women) without hip fractures, mean age was 68.9 for men, 71.1 for women
Forsén et al. 1998	Cohort	14,428 Norwegian men, 15,364 Norwegian women aged 50 years; during the 3-year follow-up, 421 new cases of hip fractures were identified
Mussolino et al. 1998	Cohort	2,879 white U.S. men aged 45–74 years; during the 22-year follow-up, 71 cases of hip fractures were identified
Turner et al. 1998	Cross-sectional	2,325 women aged 50 years from the Third National Health and Nutrition Examination Survey were queried about their history of a wrist or hip fracture
Burger et al. 1999	Cohort	2,193 Dutch men, 3,015 Dutch women aged 55 years; during a 4-year follow-up, 47 persons (14 men) experienced their first hip fracture
Cornuz et al. 1999	Cohort	116,229 female nurses (98% white) aged 34–59 years; during a 12-year follow-up, 377 hip fractures occurred because of low or moderate trauma
Høidrup et al. 1999	Cohort	6,159 postmenopausal Danish women; during a 15- to 17-year follow-up, 363 hip fractures were identified and validated
Kanis et al. 1999	Case-control	730 southern European men with hip fractures aged 50 years (mean age 73.9); 1,132 age-stratified controls

*OR = Odds ratio.
†CI = Confidence interval.
‡RR = Relative risk.

Findings

Smoking was not related to a risk for hip fractures

Men in the lowest quintile of body mass had an OR* = 3.8 (95% CI†, 2.3–6.4) compared with the highest quintile

Smoking was not associated with the risk of a hip fracture

Among the persons aged   75 years, the RR‡ of a hip fracture was elevated for current smokers (men = 5.0 [95% CI, 1.5–16.9]; women = 1.9 [95% CI, 1.2–3.1]); for former smokers, including those who had quit smoking >5 years previously, men = 4.4 (95% CI, 1.2–15.3); women = 1.3 (95% CI, 0.6–3.0)

Smoking was not significantly associated with hip fractures

The bivariate analysis showed that the percentage of former smokers in the wrist or hip fracture group was greater than in the nonfracture group; smoking was not associated with fractures in multivariate analyses

When adjusted for age and gender, current smoking was a statistically significant indicator of hip fracture risk (OR = 2.6 [95% CI, 1.4–5.1])

Current smokers experienced higher rates of hip fractures than never smokers; the risk increased with the number of cigarettes smoked daily; the age-adjusted RR of hip fracture was 1.3 (95% CI, 1.0–1.7) for all cigarette smokers and 1.6 (95% CI, 1.1–2.3) for those who smoked   25 cigarettes/day (p = 0.09 for trend); 10 years after quitting, the risk of a fracture was no longer significant

The use of hormone replacement therapy was associated with a lower risk for a hip fracture in former (RR = 0.55 [95% CI, 0.22–1.37]) and current (RR = 0.61 [95% CI, 0.38–0.99]) smokers but not in never smokers (RR = 1.10 [95% CI, 0.60–2.03])

A long history of smoking (>49 years) was associated with a significant increase in the risk of a hip fracture (RR = 1.44 [95% CI, 1.10–1.89]; p <0.01)

Table 6.19 Continued

Study	Design	Population
Melhus et al. 1999	Case-control	247 Swedish women with hip fractures and 873 controls, from a cohort study of 66,651 Swedish women aged 40–76 years
Høidrup et al. 2000	3 population studies in Copenhagen, Denmark	13,393 women and 17,379 men initially examined between 1964 and 1992, followed through 1997
Huopio et al. 2000	Cohort	3,068 Finnish women aged 47–56 years; during 3.6 years of follow-up, 295 (8.4%) sustained a fracture
Kato et al. 2000	Prospective cohort	6,250 postmenopausal women aged 34–65 years at baseline; average 7.6 years follow-up
Baron et al. 2001	Case-control	1,328 cases of postmenopausal women with a mean age of 72.5 years and low trauma hip fractures; 3,262 female controls of a similar age and residence

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Findings

OR for hip fractures among current smokers was 2.1 (95% CI, 1.3–3.2); OR for hip fractures among current smokers with a low intake of vitamin E was 3.0 (95% CI, 1.6–5.4) and of vitamin C, 3.0 (95% CI, 1.6–5.6); OR decreased to 1.1 (95% CI, 0.5–2.4) and 1.4 (95% CI, 0.7–3.0) with high intakes of vitamins E and C, respectively; in current smokers with a low intake of vitamins E and C, OR increased to 4.9 (95% CI, 2.2–11.0)

RR = 1.36 (95% CI, 1.12–1.65) for female and 1.59 (95% CI, 1.04–2.43) for male current smokers compared with nonsmokers; adjusted for body mass index

Smoking was associated with an increased risk of any fracture (RR = 1.8 [95% CI, 1.1–2.7]) independent of low spine or hip bone mineral density, previous fracture history, and 23 chronic illnesses

RR = 71.6 per 105 woman-years (the time from the baseline [first] examination to the date of first post-menopausal fracture) for hip fractures; risks increased with increasing age, body height, and total fat intake, and were lower for obese and African American women

Current smokers had an increased risk for a hip fracture (OR = 1.66 [95% CI, 1.41–1.95]); the OR for a fracture was not significantly higher among former smokers (OR = 1.15 [95% CI, 0.97–1.37])

Table 6.20 Studies on the association between smoking and the risk of fractures at sites other than the hip in men and women

Study	Design	Population
Vertebral fracture		
Aloia et al. 1985	Age-matched case-control	58 cases 58 controls Volunteer women Mean age 64 years United States
Kleerekoper et al. 1989	Case-control	266 cases 263 controls Postmenopausal women who were screened for an osteoporosis trial Aged 45–75 years United States
Cooper et al. 1991	Survey of general practice patients	1,012 women Aged 48–81 years United Kingdom 79 fractures
Santavirta et al. 1992	Population-based survey	27,278 females Aged 15 years Finland 105 fractures
Scane et al. 1999	Case-control	91 men with vertebral fractures 91 age-matched controls Aged 27–79 years (median, 64) United Kingdom
Lau et al. 2000	Cross-sectional	396 community-dwelling Chinese men Aged 70–79 years
Distal forearm fracture		
Williams et al. 1982	Population-based case-control	184 cases 567 controls Aged 50–74 years United States
Kelsey et al. 1992	Cohort	9,704 women Aged 65 years United States 171 fractures over 2.2 years (mean)

*RR = Relative risk.
†CI = Confidence interval.
‡BMI = Body mass index.
§OR = Odds ratio.

Findings

Percentage of smokers (p <0.01)
Cases: 59%
Controls: 30%

Percentage of current smokers (p >0.05)
Cases: 27%
Controls: 20%

Smoking >10 cigarettes/day for >10 years was not related to a risk for fractures

RR* = 1.1 (95% CI[†], 0.6–2.0) for current smokers; adjusted for age, history of trauma, tuberculosis, peptic ulcer, BMI[‡], and occupation

Current smoking was associated with a significantly increased risk of a vertebral fracture (OR[§] = 2.8 [95% CI, 1.2–6.7])

Heavy smoking was a significant risk factor for a vertebral deformity (OR = 6.5 [95% CI, 1.3–32.7])

There was a higher fracture risk in women smokers using estrogen

RR = 1.0 (95% CI, 0.96–1.0) for current smokers (10 cigarettes/day) compared with never smokers

Table 6.20 Continued

Study	Design	Population
Distal forearm fracture		
Kreiger et al. 1992	Hospital case-control	Aged 50–84 years Canada 54 fractures
Mallmin et al. 1994	Population-based case-control	385 cases 385 controls Aged 40–80 years Sweden
Honkanen et al. 1998	Retrospective survey	12,192 women Aged 47–56 years Finland 345 fractures
Kato et al. 2000	Prospective cohort	6,250 postmenopausal women aged 34–65 years at baseline; average 7.6 years follow-up
Proximal humerus fracture		
Kelsey et al. 1992	Cohort	9,704 women Aged 65 years United States 79 fractures over 2.2 years (mean)
Ankle fracture		
Seeley et al. 1996	Cohort	9,704 women Aged 65 years 191 fractures over 5.9 years (mean)
Honkanen et al. 1998	Retrospective survey	12,192 women Aged 47–56 years Finland 210 fractures
Foot fracture		
Seeley et al. 1996	Cohort	9,704 women Aged 65 years 204 fractures over 5.9 years (mean)
Nonhip fracture		
Jacqmin-Gadda et al. 1998	Cohort	3,216 French men and women aged 65 years (mean age 74.8); during a 5-year follow-up, 265 persons (8.2%) reported 1 fracture, 19 (0.6%) reported 2 fractures, and 1 (0.03%) reported 3 fractures

[‡]BMI = Body mass index.

Findings

RR = 1.5 (95% CI, 0.9–2.6) for current smokers compared with former smokers or never smokers; adjusted for age and BMI[‡]

RR = 0.9 (95% CI, 0.5–1.6) for current smokers; adjusted for multiple factors including age, BMI, physical activity, and hormone use

Current smoking: RR = 0.9 (95% CI, 0.6–1.4); any smoking: RR = 0.6 (95% CI, 0.3–1.1), 1–10 cigarettes/day; RR = 1.4 (95% CI, 0.9–2.3), >10 cigarettes/day; adjusted for age, BMI, menopausal status, and chronic health disorders

RR = 334.7 per 10^5 woman-years (the time from the baseline [first] examination to the date of first post-menopausal fracture) for wrist fractures; risks increased with increasing age, body height, and total fat intake, and were lower for obese and African American women

RR = 1.2 (95% CI, 0.9–1.6) for current smokers (10 cigarettes/day)

There was no association with current smoking

Current smoking: RR = 2.2 (95% CI, 1.6–3.2); any smoking: RR = 1.6 (95% CI, 0.9–2.8), 1–10 cigarettes/day; RR = 3.0 (95% CI, 1.9–4.6) for >10 cigarettes/day; adjusted for age, BMI, menopausal status, and chronic health disorders

There was no association with current smoking

Current smoking was associated with a higher risk for nonhip fractures (OR = 1.68 [95% CI, 1.08–2.60]), but not for hip fractures (OR = 0.73 [95% CI, 0.24–2.20])

Dental Diseases

Diseases of the teeth and their supporting structures are a major public health issue with a significant impact on personal well-being. More than $60 billion were spent on oral health care in the United States in 2000, and each year acute oral conditions result in an estimated 1.6 million missed school days and 2.4 million lost workdays. Although there have been tremendous improvements in the oral health of the U.S. public during the past several decades, oral diseases and conditions remain highly prevalent. For example, recent national data indicate that 66 percent of persons aged 12 through 17 years and 94 percent of those aged 18 years and older have experienced dental caries in their permanent teeth (USDHHS 2000).

As the oral cavity is the first part of the human anatomy to be exposed to mainstream smoke in active smokers, researchers have long hypothesized that smoking could have a deleterious effect on the teeth and their supporting structures. However, research on this association was hampered for decades by (1) lack of consensus on case definitions for some diseases; (2) difficulty in measuring oral conditions and consequent use of indices of questionable validity; (3) some incorrect assumptions about disease etiology, pathogenesis, distribution, and natural history; and (4) limited capacity for epidemiologic investigations within the dental research community. As a result, until recently the literature was sparse and findings were not definitive.

Conclusions of Previous Surgeon General's Reports

The previous Surgeon General's reports on smoking and health did not include dental or periodontal effects of smoking, although oral cancer and related premalignant lesions have been addressed. During the past 15 years, however, there has been a substantial amount of research on smoking and oral health, and this topic was addressed in *Oral Health in America: A Report of the Surgeon General* (USDHHS 2000). This section reviews the epidemiologic evidence for smoking as a causal factor for the most common forms of nonmalignant oral disease; cancers of the oral cavity are covered in Chapter 2.

Periodontitis

The periodontium includes those hard and soft tissue structures that support the teeth: the gingiva, the cementum covering the root surfaces of the teeth, the periodontal ligament that attaches the tooth root surfaces to the adjacent alveolar bone supporting each tooth, and the alveolar bone. The gingiva covers the other periodontal structures and comprises attached and free gingiva. The attached gingiva extends from the bottom of the gingival sulcus to the mucogingival junction, where it is contiguous with the mucous membrane of the lip, cheek, and floor of the mouth. The free gingiva extends from the base of the gingival sulcus to the gingival margin.

In a healthy state, the gingival margin is approximately 0.5 to 2.5 mm coronal to the cemento-enamel junction (CEJ) (where the enamel on the crown of the tooth meets the root). The sulcus is 1 to 3 mm in depth and does not bleed when probed. The base of the sulcus is formed by the junctional epithelium, which joins the gingival connective tissue to the tooth surface. Healthy gingiva is usually pink in color, is well adapted to the teeth, has a stippled surface texture, and is tightly bound to the underlying alveolar bone and the roots of the teeth.

Based on the most recent classification system developed by the American Academy of Periodontology, there are at least eight categories of periodontal diseases and conditions (Armitage 1999). Of those, the two most common are gingivitis and chronic periodontitis. Gingivitis is defined as an inflammation of the gingiva in which the junctional epithelium remains on or near the enamel covering the crown of the tooth. It is characterized clinically by redness, gingival bleeding, edema or enlargement, and occasional gingival sensitivity and tenderness (Genco 1990a). Chronic periodontitis (previously called adult periodontitis) is an inflammation of the gingiva and the adjacent attachment apparatus that is characterized by loss of clinical attachment because of destruction of the periodontal ligament and loss of the adjacent supporting bone (Flemmig 1999). Clinical features of chronic periodontitis may include edema, erythema, gingival bleeding upon probing, periodontal pocketing, or suppuration.

The most common forms of both gingivitis and periodontitis involve bacterial infection. Severe forms of periodontitis often are associated with infection by specific bacteria that colonize the subgingival area (Genco 2000). Destruction of soft tissue and alveolar bone is thought to involve toxins and proteases produced by the bacteria as well as hyperresponsiveness and reactivity of various components of the immune system (e.g., the production of cytokines and prostaglandins). Smoking may play a role in the pathogenesis of periodontal diseases by altering immune function and tissue repair.

The understanding of the distribution and natural history of periodontitis has evolved over the past several decades. Previously, it was thought that virtually all persons were susceptible to severe disease if oral hygiene was inadequate. The disease was considered to progress in a linear fashion throughout life from gingivitis to periodontitis to bone loss to tooth loss, generally attacking the entire dentition and was nearly universal among adults (World Health Organization 1961). This concept was driven, in part, by epidemiologic indices that incorporated signs of both gingivitis and periodontitis, analytic methods that aggregated and averaged measurements within persons and populations, and assumptions about disease progression on the part of the early oral epidemiologists. In the current model of periodontal diseases, a small proportion of persons in most populations are considered to have severe periodontitis; periodontitis is usually preceded by gingivitis but few sites with gingivitis later develop periodontitis; periodontal tissues can undergo some degree of self-repair; and generalized forms of periodontitis are uncommon (American Academy of Periodontology 1996; Burt and Eklund 1999).

Based on current concepts of periodontitis, clinical or epidemiologic assessment of the disease involves detailed measurements of various signs of soft tissue or bone destruction at two to six sites per tooth either on all teeth or on selected teeth. Among the most common measurements is probing pocket depth (PPD), which is measured by inserting a calibrated probe into the gingival sulcus and recording the distance in millimeters from the gingival margin to the base of the gingival sulcus (if healthy) or pocket (if diseased). Because the pathogenesis of periodontitis involves destruction of the junctional epithelium at the base of the sulcus, a PPD greater than 4 mm may indicate disease (Genco 1990b). Another common parameter is the clinical attachment level (CAL), which is measured as distance in millimeters from the CEJ to the base of the gingival sulcus or pocket. It is a direct measure of the position of the periodontal epithelial attachment of a tooth relative to its ideal position at the CEJ. Many cross-sectional studies have used the terminology "loss of periodontal attachment" (LPA) to describe this same parameter, although more recent studies tend to reserve the use of the term LPA for longitudinal assessments of change in the CAL between two points in time. The longitudinal change in CAL is sometimes called relative attachment loss, particularly when computer-linked electronic periodontal probes are used to record the measurements from a fixed reference point such as a cusp tip. Examples of all of these parameters and terms are found in the epidemiologic literature on the association between smoking and periodontal destruction. Because periodontal destruction may occur without deep pocket formation, PPD alone will underestimate disease and may not be sufficient as the prime indicator of disease (Goodson 1990). Intraoral radiographs have been used to assess alveolar bone loss from periodontitis, but this approach can have low sensitivity and may underestimate true bone loss (Goodson 1990; Eickholz and Hausmann 2000; Pepelassi et al. 2000). In addition, radiography often is not logistically feasible or acceptable to examinees during large-scale field epidemiologic studies. At this time, change in the CAL is considered the prime indicator of periodontal destruction.

Biologic Basis

Microbiology

It is possible that cigarette smoking affects periodontal health by altering the quantity or composition of bacterial dental plaque. Although some studies found that smokers had more visible bacterial plaque than nonsmokers (Sheiham 1971; Bastiaan and Waite 1978; Lavstedt et al. 1982; Preber and Bergström 1985), many other studies reported no significant differences in mean plaque levels or rates of plaque accumulation (Alexander 1970; Swenson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1998). Cross-sectional differences in plaque levels between smokers and nonsmokers may be due to differences in oral hygiene practices rather than to smoking per se (Preber and Kant 1973; Andrews et al. 1998). However, the presence of specific bacterial species in periodontal plaque may be more important than the quantity of visible plaque and debris on the teeth in the pathogenesis of severe periodontitis (Genco 1996). Some evidence indicates that smokers may be more likely than nonsmokers to harbor specific periodontal pathogens. A study of adults exhibiting a wide range of

periodontal conditions (Zambon et al. 1996) found that subgingival infection with *Bacteroides forsythus* was more common in current smokers even after adjusting for disease severity, with a dose-response relationship between the amount of smoking and infection. Current smokers were also more likely than former or lifetime nonsmokers to have subgingival infection with *Actinobacillus actinomycetemcomitans.* Consistent with those findings, a study of dental clinic patients found that plaque samples from smokers were 11 times more likely than samples from nonsmokers to test positive for one of three periodontal pathogens (Kazor et al. 1999). In a study of young adults with early-onset periodontitis (Kamma et al. 1999), 11 postulated periodontal pathogens were detected more frequently and in greater numbers in the subgingival plaque from smokers than from nonsmokers. Smoking may increase the likelihood of infection with periodontal pathogenic microorganisms even among persons with no clinical signs of disease. In a study of young adults who did not have periodontitis (Shiloah et al. 2000), smokers were 18 times more likely than nonsmokers to have at least one of eight periodontal pathogens in their subgingival plaque. Several studies, however, reported no differences in the plaque bacteria between smokers and nonsmokers (Preber et al. 1992; Stoltenberg et al. 1993). Additional evidence suggests that smoking may act synergistically to potentiate the effects of toxins produced by periodontal pathogenic bacteria (Sayers et al. 1999).

Immune Function

There is substantial evidence that smoking affects both localized and systemic components of the immune system, although the links between these effects and periodontal disease remain to be established. Smoking increases the number but impairs the functions of polymorphonuclear leukocytes (PMNs, or neutrophils), peripheral blood cells that represent the first line of defense against microorganisms (Noble and Penny 1975; Barbour et al. 1997). Either an impairment of the PMN's ability to neutralize periodontal infections or an overstimulation of potentially tissue-destructive processes can lead to periodontal destruction (American Academy of Periodontology 1999). For example, smoking can impair PMN chemotaxis, phagocytosis, and oxidative burst (Eichel and Shahrik 1969; Kenney et al. 1977; Ryder et al. 1998). Impaired phagocytosis has been implicated in refractory periodontitis (MacFarlane et al. 1992). Smoking also

appears to compromise the function of macrophages, which play a vital role in both humoral and cell-mediated immunity, and of B lymphocytes, the major cell type involved in the humoral immune system. Exposure to cigarette smoke also appears to have an immunosuppressive effect on T lymphocytes, which may reduce antibody response to periodontal bacteria (Barbour et al. 1997). Smokers may have a decreased production of antibodies specific to periodontal pathogens, especially IgG2 (Quinn et al. 1998). Recent evidence suggests that levels of cytokines in gingival crevicular fluid, which are secreted by mononuclear cells and are associated with collagen destruction and bone resorption, may be increased in smokers (Boström et al. 1998a,b). Furthermore, there may be a synergistic interaction between smoking and the genotype for a specific cytokine, IL-1, in the development of severe periodontitis (Kornman and di Giovine 1998).

Gingival Blood Flow and Soft Tissue Effects

It has long been hypothesized that the peripheral vasoconstrictive effect of tobacco smoke and nicotine reduces gingival blood flow and thereby impairs the delivery of oxygen and nutrients to gingival tissue. There is some evidence of reduced blood flow in gingival tissues (Clarke et al. 1981; Clarke and Shephard 1984) and reduced size and altered morphology of capillaries in oral mucosa and gingival tissues (Johnson et al. 1989) following exposure to tobacco smoke or nicotine. However, more recent evidence appears contradictory (Baab and Öberg 1987; Johnson et al. 1991). Smokers tend to exhibit less gingival bleeding than nonsmokers, even with control for bacterial plaque levels (Preber and Bergström 1985, 1986; Bergström and Preber 1986; Bergström 1990; Danielsen et al. 1990; Newbrun 1996). However, this reduced gingival bleeding may be related more to the suppression of an inflammatory response than to reduced gingival blood flow.

Nicotine can be stored in and released from periodontal fibroblasts, possibly affecting their morphology and ability to attach to root surfaces (Raulin et al. 1988; Hanes et al. 1991; James et al. 1999). In addition, nicotine may inhibit the growth of gingival fibroblasts and their production of collagen and fibronectin, components of the gingival extracellular matrix involved in the structure and attachment of gingiva (Tipton and Dabbous 1995). Thus, it is possible that smoking impairs the ability of periodontal tissues to repair damaged junctional epithelium. Smoking impairs

wound healing and compromises the prognosis following surgical and nonsurgical periodontal therapy (Preber and Bergström 1990; Ah et al. 1994; Newman et al. 1994; Rosenberg and Cutler 1994; Preber et al. 1995; Tonetti et al. 1995; Grossi et al. 1996, 1997; Kaldahl et al. 1996; Kinane and Radvar 1997; Trombelli and Scabbia 1997; Boström et al. 1998b; Machtei et al. 1998; Renvert et al. 1998; Palmer et al. 1999; Papantonopoulos 1999; Söder et al. 1999). One study that employed statistical modeling of longitudinal changes in the CAL concluded that diminished capacity for repair, rather than direct tissue damage, probably was the major mechanism involved in smoking-associated periodontal destruction (Faddy et al. 2000).

Epidemiologic Evidence

Epidemiologic studies of smoking and periodontitis have employed a variety of case definitions for disease, using various combinations of PPD, CAL or LPA, and alveolar bone loss. Some studies used indices for "periodontal disease" that are no longer considered valid indicators for the prevalence of disease in populations (Burt and Eklund 1999). Other studies employed indices that originally were intended for use in population-based treatment planning and not for etiologic studies, such as the Community Periodontal Index of Treatment Needs (Ainamo et al. 1982). Some studies did not use a case definition for disease, but instead assessed mean levels of one or more clinical parameters among exposed and unexposed groups, or described the proportion of the study population that exceeded various measurement thresholds (e.g., 4 mm LPA). Some studies, primarily conducted before the 1970s, provided no case definition other than diagnosis by the examiner. Despite the numerous problems measuring the disease, published epidemiologic and clinical studies consistently show a moderate to strong degree of association between smoking and periodontitis.

To identify epidemiologic studies of smoking and periodontitis, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000, using the following Medical Subject Headings (MeSH) key words: "smoking," "tobacco," "periodontal diseases," and "periodontitis." These terms also were searched as title words. The smoking and health database maintained by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health

Promotion, CDC, was also searched using those terms as key words. Reference lists from published studies, review articles, and textbooks were examined to identify additional studies.

Tables 6.21 through 6.23 summarize the findings from 6 case-control studies, 52 cross-sectional studies, and 12 cohort studies conducted between 1959 and 2000. The case-control studies consistently found that persons with periodontitis were more likely than controls without periodontitis to be smokers, although not all studies separated current smokers from former smokers in their analyses. These studies generally controlled for potential confounders in either the selection of a control group or in their analyses. Cross-sectional studies that attempted to estimate parameters such as the odds ratio (OR) consistently reported moderate to strong degrees of association between smoking and periodontitis under a wide range of case definitions (Beck et al. 1990; Horning et al. 1992; Haber et al. 1993; Stoltenberg et al. 1993; Grossi et al. 1994, 1995; Sakki et al. 1995; Tomar et al. 1995; Ahlberg et al. 1996; Dolan et al. 1997a; Norderyd and Hugoson 1998; Shizukuishi et al. 1998; Wakai et al. 1999; Tomar and Asma 2000). Consistent with the findings from case-control and cross-sectional studies, cohort studies reported RR estimates for smoking and onset or progression of periodontitis of 1.4 to more than 10, using a wide range of outcome measures. Of the cross-sectional studies that examined the relationship separately for current smokers and former smokers, current smokers were more likely than former smokers to have periodontitis (Haber et al. 1993; Dolan et al. 1997a; Wakai et al. 1999; Tomar and Asma 2000). Two case-control studies (Haber and Kent 1992; Gelskey et al. 1998) and several cross-sectional studies (Grossi et al. 1994, 1995; Norderyd and Hugoson 1998; Wakai et al. 1999; Tomar and Asma 2000) reported a significant dose-response relationship between the number of cigarettes smoked per day and disease status. Two of these studies used cigarette-years[2] or pack-years as the measure for exposure (Grossi et al. 1994, 1995), which combined quantity and duration of smoking to characterize the exposure. One study reported a significant dose-response relationship between the duration of smoking and disease risk (Tomar and Asma 2000). That study also found a significant inverse relationship between the number of years since quitting smoking and the odds of having periodontitis.

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[2]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Nearly all other reviewed studies reported either mean measures of PPD or CAL/LPA or radiographically demonstrated alveolar bone loss by smoking status, or they reported the percentage of persons with some specified number or percentage of sites exceeding some threshold on one or more of these clinical parameters. With only one exception (Preber et al. 1980), all cross-sectional and cohort studies that measured differences in mean CAL/LPA or mean PPD found a worse periodontal status among smokers than among nonsmokers. That 1980 study (Preber et al. 1980), however, was conducted with young military recruits whose duration of smoking must have been relatively short because of their age.

Evidence Synthesis

The available epidemiologic literature is highly consistent in showing a moderate to strong association between cigarette smoking and periodontal destruction. The association is robust across a wide range of case definitions, populations, and study designs. There is also evidence of a dose-response relationship between smoking intensity and risk for periodontitis. Both number of cigarettes smoked and duration of smoking are positively associated with disease risk. The risk of periodontitis appears to decrease after smokers stop smoking, with a decreasing risk as the duration of successful cessation increases. Although only a few prospective cohort studies have been carried out, they consistently found that smokers were more likely than nonsmokers to experience the onset or progression of disease. The association cannot be explained by confounding.

The mechanisms involved in smoking-associated periodontal destruction are still not fully understood. However, available evidence supports several hypotheses. An immune mechanism is plausible because smoking affects many elements of the human immune system. The effects of smoking on local and systemic immune factors may make the smoker more susceptible to bacterial infection. In addition, substantial evidence indicates that smoking impairs the regeneration and repair of periodontal tissues. The evidence is inconsistent in suggesting that smoking quantitatively or qualitatively alters the microflora of subgingival plaque.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

Implications

Smoking intervention should be a major component of prevention and treatment of periodontitis. A recent study (Tomar and Asma 2000) concluded that more than 50 percent of the cases of adult periodontitis in the United States are attributable to cigarette smoking. In light of this conclusion, and because more than one-half of U.S. adult smokers visit a dentist each year (Tomar et al. 1996), the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit. The dental office may also provide an opportune setting for tobacco use prevention efforts among young people (Hovell et al. 1996). Unfortunately, a lack of awareness and inadequate skills may be barriers to further involvement by dentists and dental hygienists (Secker-Walker et al. 1994; Dolan et al. 1997b).

Further research is needed to achieve a greater understanding of the mechanisms involved in smoking-associated periodontitis. In addition, more behavioral research is needed to enhance the willingness and ability of dentists and dental hygienists to intervene in their patients' use of tobacco and to counsel younger patients against tobacco use. Educational research should identify effective methods for training students of dentistry and dental hygiene, as well as licensed clinicians, to become competent at counseling their patients to stop using tobacco and assisting patients who want to quit (Tomar et al. 1996; Barker and Williams 1999; Cabana et al. 1999).

Dental Caries

Dental caries is an infectious, communicable, multifactorial disease in which bacterially produced acids dissolve the hard enamel surface of a tooth (Featherstone 1999). Unchecked, the bacteria may then penetrate the underlying dentin and progress into the soft pulp tissue, which is rich in blood and nerve tissue. Dental caries commonly results in loss of tooth structure and discomfort. Untreated dental caries commonly progresses to incapacitating pain and a bacterial infection that leads to pulpal necrosis, tooth extraction, and loss of dental function, and can progress to an acute systemic infection. The major etiologic factors for this disease are thought to be specific bacteria in dental plaque (particularly *Streptococcus [S.] mutans* and *S. lactobacilli*) on susceptible tooth surfaces and the availability of fermentable carbohydrates.

Most epidemiologic studies conducted during the past 60 years have used some variation of the decayed, missing (due to caries), or filled permanent teeth (DMFT) index (Klein et al. 1938) to measure the frequency of dental caries. Until the mid-1980s the proportion of the population with dental caries was rarely used to estimate disease prevalence in industrialized populations because the disease was nearly universal. The DMFT index is more a measure of disease severity than of disease prevalence; it is simply the sum of the number of permanent teeth (T) that are decayed (D), missing due to dental caries (M), or filled (F). This index, if applied to the number of coronal (i.e., enamel-covered) tooth surfaces (S), is designated the DMFS. The M component is often omitted in adult studies because of the inherent uncertainty as to why a tooth is missing. Thus, some studies report DFT or DFS scores. Other studies report the components of DMFT individually, such as DS, FS, and MS. Nearly all studies aggregate DMF data by reporting the population mean. The number of root surfaces affected by caries is almost always scored and reported separately from coronal caries, and usually is designated as RDFS or RDS (the M component is not reported for root-surface caries).

Biologic Basis

There are several hypothesized mechanisms that may underlie the association between smoking and dental caries. As discussed in the section on smoking and periodontitis, evidence is inconsistent in showing that smoking per se alters either the bacterial profile in the gingivi or the rate of formation of dental plaque (Alexander 1970; Swenson 1979; Bergström 1981, 1990; Feldman et al. 1983; Macgregor et al. 1985; Bergström and Eliasson 1987a,b; Lie et al. 1998). Differences in oral care behavior between smokers and nonsmokers provide an indirect explanation. Perhaps the most consistent explanation is that smokers tend to practice less frequent or less effective oral hygiene and plaque removal (Preber and Kant 1973; Macgregor and Rugg-Gunn 1986; Andrews et al. 1998).

Several studies concluded that smoking might lower the pH or reduce the buffering capacity of saliva (Heintze 1984; Parvinen 1984), impairing the function of saliva as a protective factor against enamel demineralization (Edgar and Higham 1996). In contrast, one review concluded that smoking increases salivary flow rate (Macgregor 1989), raising pH and increasing salivary calcium concentration (ten Cate 1996). These factors would tend to favor enamel remineralization,

but benefit would come only if the flow rate increase were sustained. Another comprehensive review concluded that smoking has a minor effect on saliva flow rate and its chemical composition, at least in terms of factors thought to affect dental cariogenesis (Christen et al. 1991). In sum, an effect of smoking on salivary function does not appear to be a key mechanism in causing dental caries.

The association between smoking and root-surface caries suggested by several studies may be due, in part, to the periodontal effects of smoking. The loss of periodontal attachment and subsequent exposure of root surfaces are necessary conditions for root-surface caries to occur (Burt et al. 1986; Stamm et al. 1990). Persons who experience a loss of periodontal attachment attributable to smoking may also be at greater risk for subsequent root-surface caries.

Epidemiologic Evidence

To identify the epidemiologic studies on smoking and dental caries, the National Library of Medicine's PubMed database was searched for English language publications from 1965–2000. The following MeSH key words were used: "smoking," "tobacco," "dental caries," and "tooth demineralization." These terms also were searched as title words. The smoking and health database maintained by CDC's Office on Smoking and Health was also searched using the same terms as key words. Reference lists from published studies, review articles, and textbooks were sources for additional studies.

Table 6.24 summarizes 12 cross-sectional studies and 3 cohort studies published between 1952 and 1999. Most cross-sectional studies used some variation of the DMF index to measure caries prevalence; all but two (Hart et al. 1995; Tomar and Winn 1999) found that smokers experienced more coronal dental caries than nonsmokers, as measured by mean DS, DFS, DMFS, or DMFT. In general, differences between smokers and nonsmokers in mean DMFT or DMFS were small, even in studies in which the differences were reported to be "statistically significant." The largest differences in numbers of carious lesions were reported in studies that used DMFS (Ludwick and Massler 1952; Ainamo 1971; Zitterbart et al. 1990; Axelsson et al. 1998). None of those studies, however, appeared to limit the "missing" component of DMFS to those tooth surfaces lost due to caries. Consequently, these studies may mix caries caused by smoking with the advanced periodontal destruction that can cause tooth loss in adults.

Few of the studies on the association between smoking and dental caries controlled for potential confounding factors. Although the observed association between smoking and dental caries may reflect a causal relationship, it is also possible that it reflects factors common to both smoking and the risk of dental caries. For example, in industrialized nations both dental caries (USDHHS 2000) and cigarette smoking (Giovino et al. 1995) are more prevalent among groups with lower socioeconomic status (SES) than among higher SES groups. SES is a strong correlate of factors that affect dental caries status, such as diet, use of dental services, and oral hygiene practices (USDHHS 2000). None of the studies adjusted for SES or other potential confounding factors in examining the association between smoking and dental caries. Several literature reviews do suggest that the association between smoking and dental caries may reflect the tendency for smokers to practice less effective dental hygiene and plaque removal (Macgregor 1989; Christen et al. 1991; Kassirer 1994; Andrews et al. 1998).

Few studies adjusted for other notable correlates of both smoking and dental caries in their analyses. The DMF index is a cumulative, irreversible index. As persons experience decayed or filled permanent tooth surfaces or lose teeth over their lifetimes, their DMFT or DMFS scores will increase. Therefore, DMFT and DMFS can be associated strongly with age even if age per se is not a risk factor for incidence of dental caries. Few studies, however, adjusted for age in their analyses. Several studies provided age-specific mean caries scores (Ludwick and Massler 1952; Zitterbart et al. 1990; Axelsson et al. 1998) or age-specific significance testing of differences in means (Hirsch et al. 1991), which revealed an inconsistent association between smoking and caries within age groups. In the one study that used a nationally representative sample of U.S. adults and adjusted for age and race or ethnicity, DFT and DMS were actually slightly lower among male smokers than among those who had never used tobacco (Tomar and Winn 1999).

Two studies attempted to investigate a dose-response relationship between smoking and dental caries (Ludwick and Massler 1952; Ainamo 1971). Although smokers in the highest category of cigarettes smoked per day had experienced slightly higher DMFT, DMFS, or DS than those in the lowest dose categories, the relationship was not consistent. The first study presented age-specific comparisons of mean DMFT and DMFS by the number of cigarettes smoked per day, which showed no clear pattern within age strata. The second study did not present age-stratified or age-adjusted estimates, which potentially could present difficulties in interpreting the association between a disease index that is cumulative with age and an exposure that probably was increasing with age in the study population (aged 18 through 26 years).

Smoking may be associated more with root-surface caries than with coronal caries. Two cohort studies (Ravald et al. 1993; Locker 1996) and two cross-sectional studies (Locker 1992; Tomar and Winn 1999) reported higher mean RDFS or RDS scores among smokers, but in one cohort study (Locker 1996) smoking was not found to be a significant predictor of root-surface caries in multiple logistic regression modeling.

Evidence Synthesis

Few studies have investigated the association between cigarette smoking and dental caries. The available literature is fairly consistent in suggesting that smokers may experience slightly more decayed, missing, or filled coronal tooth surfaces. In addition, smokers generally experienced more decayed or filled root surfaces than nonsmokers. However, many of the published studies did not address potential confounders of these associations. It is therefore possible that the observed associations could reflect in part the presence of other factors associated with both smoking and dental caries. Evidence for a dose-response relationship is sparse and inconsistent. Studies that examined whether quitting smoking reduced the risk of caries development were not identified.

There is little evidence for a biologic mechanism that would explain the role of smoking in the development of coronal dental caries. Methodologic considerations limit the interpretation of findings from epidemiologic studies. The few lines of investigation undertaken have been inconsistent in identifying either bacterial or salivary effects that would be expected to increase this risk.

Some evidence suggests that smoking may indirectly increase the risk for root-surface caries. The mechanism probably involves an increased exposure of root surfaces of teeth secondary to loss of periodontal attachment. This relationship may reflect the impact of smoking on periodontium and the subsequent exposure of tooth root surfaces to the oral environment.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Implications

To better characterize the relationship between cigarette smoking and dental caries, future investigations will need to control for potential confounding factors. These studies should be of the cohort design to allow for assessments of the effect of smoking on carious lesion formation and to determine whether smoking cessation reduces disease incidence. Investigations into an association between smoking and root-surface caries will need to apply indices that take into account the number of root surfaces at risk, such as the Root Caries Index (Katz 1980), or control for root surface exposure in trying to identify whether smoking acts through a direct or indirect mechanism.

The increased risk for root-surface caries may be due to smoking-associated periodontal destruction and subsequent exposure of root surfaces of teeth to the oral environment. Because of the causal relationship between smoking and periodontitis as well as with many other diseases, and because more than one-half of U.S. adult smokers visit a dentist each year, the dental care community has both the opportunity and the professional obligation to counsel patients who smoke to quit.

Table 6.21   Case-control studies on the association between smoking and periodontitis

Study	Number of cases/controls	Case definition	Sources of cases/controls	Findings		
				Smoking status	Odds ratio	95% confidence interval
Preber and Bergström 1986	260/1,769	Moderate to severe peri-odontitis; advanced peri-odontitis (mean PPD* >4.5 mm)	Dental school periodontal clinic/population-based sample	Current smokers Moderate to severe periodontitis	2.1	1.7–2.7
				Advanced periodontitis	2.4	1.7–3.5
Bergström and Eliasson 1987b	134[†]	PPD 4 mm on 1 site	Periodontal patients/population-based sample	Current smokers Men Women Total	2.8[†] 2.1[†] 2.5[†]	NR[‡] NR NR
Haber and Kent 1992	196/209	Moderate periodontitis (20–50% bone loss on 1 surface); advanced periodontitis (>50% bone loss on 1 surface)	Periodontal offices/general dental practices	Never smoked Ever smoked (moderate or advanced disease) Current smokers (moderate or advanced disease) 10 cigarettes/day >10 cigarettes/day 10 years' duration >10 years' duration Moderate disease Advanced disease	1.0 2.6 3.3 1.0 5.4 1.0 4.3 1.8 6.1	1.6–3.9 1.8–5.8 0.4–2.5 2.8–10.6 0.2–6.5 1.6–12.1 0.9–3.7 2.9–12.8
MacFarlane et al. 1992	31/12	Refractory peri-odontitis: persis-tent failure of conventional treatment includ-ing root planing, surgery, and antibiotics	Private periodontal practices and dental school graduate peri-odontal clinics/laboratory personnel	Current smokers (odds ratio estimate calculated from reported raw data by adding 0.5 to each cell; 0 smokers in the control group)	203.6	9.8–4, 242.4

*PPD = Probing pocket depth.
[†]Odds ratio estimates in this study were based on comparisons with smoking prevalence in a general population survey in Stockholm, Sweden. However, periodontal health was not examined in this "control" group.
[‡]NR = Data were not reported.

Table 6.21 Continued

Study	Number of cases/ controls	Case definition	Sources of cases/ controls	Smoking status	Odds ratio	95% confidence interval
					Findings	
Gelskey et al. 1998	205/205	1 tooth with alveolar bone loss >3 mm, or 1 tooth with PPD* 7 mm	Dental school clinic	Never smoked	1.0	NR
				Ever smoked	1.8	1.1–2.9
				Cigarette-years§		
				Aged 35–87 years		
				1–300	1.2	0.7–1.8
				301–500	1.8	0.9–2.7
				>500	3.8	2.9–4.7
				Aged 35–54 years		
				1–300	1.0	0.3–1.7
				301–500	3.2	2.1–4.2
				>500	4.3	6.2–8.5
				Aged 55–87 years		
				1–300	1.7	0.7–3.9
				301–500	1.1	0.01–4.0
				>500	2.2	0.01–7.6
Quinn et al. 1998	270/193	2 mm loss of periodontal attachment on 1 tooth	Clinical Research Center for Periodontal Diseases, Virginia	Blacks		
				Former smokers	1.0	NR
				Current smokers	2.1	0.9–5.1
				Whites		
				Former smokers	1.0	NR
				Current smokers	4.0	2.1–7.6

*PPD = Probing pocket depth.

§Cigarette-years = Number of years of smoking multiplied by the number of cigarettes smoked per day.

 Crude odds ratio estimates were calculated from data reported in the paper.

Table 6.22   Cross-sectional studies on the association between smoking and periodontitis

Study	Population	Findings	Comments
Arno et al. 1959	728 male factory workers and staff Aged 21–45 years Norway	No quantitative results were reported	Mean alveolar bone loss appeared to increase with more cigarettes/day in graphic plots of deviations from the sample mean; the analysis of variance verified with a significant degree of certainty that the difference could not be due to chance (mean and test scores were not reported)
Brandtzaeg and Jamison 1964	206 male army recruits Aged 19–25 years Norway	Mean Periodontal Index score Nonsmokers 0.71 <10 cigarettes/day 0.79 10 cigarettes/day 1.05 Mean Oral Hygiene Index score Nonsmokers 1.22 <10 cigarettes/day 1.45 10 cigarettes/day 1.59	An association between smoking and the Periodontal Index score was not statistically significant in the analysis of covariance
Solomon et al. 1968	2,182 male and 5,009 female dental clinic and hospital patients Aged 20–79 years United States (New York)	Prevalence of periodontal disease was consistently higher among ever smokers than among never smokers for both men and women (e.g., aged 40 years: white men, 75 vs. 50%; white women, 65 vs. 50%)	Periodontal disease included both gingivitis and periodontal disease with or without pocket formation; smoking was strongly associated with periodontal disease in the age-stratified Cochran's test for both men and women
Summers and Oberman 1968	Probability sample of 154 men and 170 women Aged 20 years (mean or range not reported)	Multiple correlation coefficients for cigarette use and the Periodontal Disease Index score by gender Men 0.591 Women 0.551	The Periodontal Disease Index was used to measure periodontal disease; cigarette smoking was measured in packs per day; it is unclear if former smokers were included in this multiple correlation analysis
Ainamo 1971	167 male military recruits Aged 18–26 years Finland	Mean LPA* by daily smoking habit Cigarettes/day LPA 0 0.049 1–9 0.069 10–20 0.072 >20 0.108	LPA was measured clinically on 4 surfaces of all erupted teeth

Note: Unless otherwise defined, current, former, and never refer to smoking status.
*LPA = Loss of periodontal attachment.

Table 6.22   Continued

Study	Population	Findings	Comments
Preber et al. 1980	134 male army conscripts Aged 19–27 years Sweden	There were no significant differences between smokers (n = 81) and nonsmokers (n = 53) in mean bone level or PPD[†]	PPD was clinically assessed on 6 teeth (1st molars, upper right central incisor, lower left central incisor); radiographic assessments were of lower incisors only
Bergström and Floderus-Myrhed 1983	164 twin pairs, selected from twin registry, discordant on smoking Aged 39–78 years Sweden	Mean alveolar bone index High-exposed twins 1.09 Low-exposed twins 0.94 Number of teeth lost High-exposed twins 11.3 Low-exposed twins 9.6	Alveolar bone index was based on a 5-category ordinal scale of radiographic bone loss, with no information on quantity or duration of smoking; the low-exposed group included both nonsmokers and twins with a lifetime exposure to smoking considered to be less than the twin
Feldman et al. 1983	862 men Mean age of nonsmokers = 47.9 years; mean age of smokers = 43.8 years United States	Mean PPD (mm) Smokers 0.73 Nonsmokers 0.56 Mean bone loss Smokers 0.70 Nonsmokers 0.42	Adjusted for age in the analysis of variance; the nonsmoking group included former smokers
Ismail et al. 1983	Population-based sample of 2,948 persons Aged 25–74 years United States	Mean Periodontal Index score by smoking status Current smokers 1.6 Former smokers 1.1 Never smoked 1.0	An association between Periodontal Index scores and current smoking remained significant after adjusting for the Oral Hygiene Index score, race, gender, education, poverty index, frequency of toothbrushing, age, and income in a multiple linear regression model

[†]PPD = Probing pocket depth.

Table 6.22   Continued

Study	Population	Findings		Comments
Markkanen et al. 1985	Population-based sample of 2,019 men and 2,349 women Aged 30 years Finland	Prevalence (%) of PPD[†] 4–6 mm Men Current smokers Nonsmokers Women Current smokers Nonsmokers Total Current smokers Nonsmokers Prevalence of PPD >6 mm Men Current smokers Nonsmokers Women Current smokers Nonsmokers Total Current smokers Nonsmokers	51.6 51.7 50.8 50.8 51.3 51.2 33.1 30.6 20.5 19.3 29.6 24.2	Nonsmokers included former smokers; periodontal status was measured by the Periodontal Treatment Need System (PTNS), classifying each quadrant of the mouth by the highest score within that quadrant and each person according to the highest quadrant score; there were no significant differences between smokers and nonsmokers in periodontal pocketing when stratified by gender; smoking was not a significant correlate of the PTNS score in a log-linear model that also included gender, age, and the number of dentate quadrants
Bergström and Eliasson 1987a	203 male and 32 female professional musicians Aged 21–60 years Sweden	Alveolar bone height (% of root length) Aged 21–40 years Smokers Nonsmokers Aged 41–50 years Smokers Nonsmokers Aged 51–60 years Smokers Nonsmokers Total Smokers Nonsmokers	 84.4 86.3 79.2 83.1 68.0 76.1 77.9 82.3	Radiographically determined alveolar bone height was significantly lower in smokers than in nonsmokers across age groups and plaque index scores; there were no significant differences in plaque levels between smokers and non-smokers; former smokers were excluded from the analysis
Bergström and Eliasson 1987b	208 male and 34 female professional musicians Aged 21–60 years Sweden	Mean number of periodontal pockets 4 mm Aged 21–40 years Smokers Nonsmokers Aged 41–60 years Smokers Nonsmokers Total Smokers Nonsmokers	 27.3 13.4 39.9 31.0 36.0 21.8	The mean number of periodontal pockets was significantly greater in smokers than in nonsmokers across age groups and plaque index scores

[†]PPD = Probing pocket depth.

Table 6.22   Continued

Study	Population	Findings	Comments
Levy et al. 1987	Population-based sample of 477 dentate adults Aged ≥65 years United States (Iowa)	Multiple linear regression coefficient for proportion of teeth that were periodontally healthy by the number of cigarettes smoked Males -0.203 Females -0.088 (not statistically significant)	Periodontally healthy teeth were defined as PPD[†] ≤3 mm with no gingival bleeding; other variables in the models for males were the number of teeth, age, Parkinson's disease, ever smoked a pipe, exercise level, and proportion of teeth with calculus and with recession; for females: the number of teeth; age; and proportion of teeth with coronal decay, calculus, and recession

Beck et al. 1990	Population-based sample of 381 blacks and 308 whites
	Aged ≥65 years
	United States (North Carolina)
		OR[‡] estimates (95% CI[§]) for tobacco use and severe LPA
		Whites
		  Unadjusted 6.7 (3.2–14.0)
		  Adjusted 6.2 (2.6–14.5)
		Blacks
		  Unadjusted 2.8 (1.7–4.7)
		  Adjusted 2.9 (1.6–5.1)
			Severe LPA* was defined as ≥4 periodontal sites with LPA ≥5 mm, and ≥1 of those sites with PPD ≥4 mm; it is unclear if tobacco use included forms other than cigarettes; the prevalence of smoking or other forms of tobacco use was not provided; logistic models for whites included tobacco use, education, dentate status of sibling, most recent dental visit, periodontal plaque bacteria levels, the presence of dental caries, a perceived worsening of finances, and a perceived bother by things in life; for blacks, models included tobacco use, education, reported bleeding gums, most recent dental visit, bacteria levels, socioeconomic status, morning cough, and perceived financial status

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[‡]OR = Odds ratio.
[§]CI = Confidence interval.

Table 6.22   Continued

Study	Population	Findings		Comments
Goultschin et al. 1990	154 male and 190 female hospital workers Aged 17–74 years Israel	Mean number of sextants affected, based on CPITN scores		The mean number of affected sextants did not differ significantly between smokers and nonsmokers for CPITN scores 2 and 4; adjusted for age and gender
		0		
		Smokers	0.32	
		Nonsmokers	0.84	
		1		
		Smokers	0.55	
		Nonsmokers	1.01	
		2		
		Smokers	1.52	
		Nonsmokers	1.32	
		3		
		Smokers	2.46	
		Nonsmokers	1.71	
		4		
		Smokers	0.47	
		Nonsmokers	0.61	
Hansen et al. 1990a	Population-based sample of 156 persons Aged 35 years Norway	Mean number of quadrants with ≥1 site with PPD[†] ≥5 mm		No significant difference in the mean number of quadrants affected
		Smokers	0.397	
		Nonsmokers	0.395	
Bergström et al. 1991	210 female dental hygienists Aged 24–60 years Sweden	Mean alveolar bone loss (mm)		Bone loss was assessed radiographically for interdental septum of right posterior teeth; associations between bone loss and cigarette habits were consistent within age strata; smoking was a significant predictor of bone loss in multiple linear regression models that included age
		Current smokers	1.71	
		Former smokers	1.55	
		Never smoked	1.45	
		Mean alveolar bone loss (mm) in current smokers by cigarettes/day		
		≤10	1.60	
		>10	2.06	
		Mean alveolar bone loss (mm) in current smokers by duration of smoking (years)		
		≤15	1.39	
		>15	1.89	
Horning et al. 1992	1,520 male and 263 female dental patients United States	OR (95% CI) for moderate or advanced periodontitis		This logistic regression model included age, ethnicity, gender, and smoking status; it is unclear if former smokers were included in the analysis
		Smokers	1.8 (1.2–2.7)	

[†]PPD = Probing pocket depth.
 CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22   Continued

Study	Population	Findings	Comments
Locker 1992; Locker and Leake 1993	Population-based sample of 702 dentate adults Aged 50 years Canada (Ontario)	Mean LPA* (mm) Current smokers 3.7 Former smokers 2.9 Never smoked 2.7 Sites (%) with LPA 2 mm Current smokers 84.7 Former smokers 77.6 Never smoked 72.3 Sites (%) with LPA 5 mm Current smokers 30.2 Former smokers 15.9 Never smoked 13.8 Prevalence of severe LPA Current smokers 34.4 Former smokers 20.4 Never smoked 13.1	Severe LPA was defined as the upper 20th percentile of distribution of LPA in the full study population (3.8 mm)
Haber et al. 1993	132 patients with insulin-dependent diabetes mellitus from diabetes clinics; 95 HMO¶ patients	OR (95% CI) of periodontitis by diabetes and smoking status No diabetes Current smokers 8.6 (2.7–27.8) Former smokers 2.1 (1.1–4.2) Never smoked (referent) Diabetes Current smokers 6.9 (2.6–18.5) Former smokers 1.8 (0.8–4.2) Never smoked (referent)	Case definition of periodontitis: 1 site with PPD† 5 mm and LPA 2 mm; Mantel-Haenszel summary OR estimates were adjusted for age
Stoltenberg et al. 1993	63 smokers (mean age 48 years) and 126 nonsmokers (mean age 49 years) matched for age, gender, and plaque and calculus levels HMO patients United States (Minnesota)	Mean PPD (mm) Smokers 3.12 Nonsmokers 2.94 Prevalence (%), OR, and 95% CI for having mean PPD 3.5 mm Smokers 24 5.3 (2.0–13.8) Nonsmokers 6 (referent) Prevalence (%) of 1 site with PPD 3.5 mm Smokers 76.2 Nonsmokers 59.5	It is unclear if former smokers were included in the study; smokers also had a higher prevalence than nonsmokers of 1 site with PPD 4.5 mm or 5.5 mm

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
¶HMO = Health maintenance organization.

Table 6.22 Continued

Study	Population	Findings	Comments
Wouters et al. 1993	Population-based sample of 378 men and 345 women Aged 20 years Sweden	Age-standardized mean inter-proximal alveolar bone height as a percentage of root length, by smoking status Current smokers 77.0 Former smokers 81.5 Never smoked 83.1	Current smoking (but not former smoking) was significantly associated with mean interproximal alveolar bone heights in a multiple linear regression model that included gender, age, urban/rural residence, level of education, frequency of dental and dental hygiene visits, number of tooth surfaces, plaque and calculus scores, and the presence of defective dental restorations
Grossi et al. 1994	Population-based sample of 741 women and 685 men Aged 25–74 years United States (New York)	OR (95% CI) for smoking and LPA* Pack-years** 5.3–15.0 2.05 (1.47–2.87) 15.1–30.0 2.77 (1.91–4.02) 30.1–150.0 4.75 (3.28–6.91)	This stepwise ordinal logistic regression analysis used the mean LPA as a dependent variable (5 ordinal categories), and included age, gender, education, diabetes status, anemia, allergy, and plaque bacteria levels
Linden and Mullally 1994	Random sample of 82 regular dental attenders Aged 20–33 years Northern Ireland	Mean PPD[†] (mm) Current smokers 2.9 Nonsmokers 2.6 Mean number of pockets 4 mm Current smokers 14.6 Nonsmokers 5.8 Mean LPA (mm) Current smokers 1.2 Nonsmokers 0.7 Mean number of LPA sites 2 mm Current smokers 21.8 Nonsmokers 9.3	Nonsmokers included never smokers and those who had quit 2 years before examination

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 6.22   Continued

Study	Population	Findings	Comments

Söder et al. 1994	Population-based sample of 840 men and 841 women Aged 31–40 years Sweden	Prevalence (%) of teeth (1) with PPD[†] 5 mm by smoking status
		  Current smokers 23.1
		  Former smokers 18.7
		  Never smoked 10.1
		
		Mean number (%) of teeth with PPD 5 mm by smoking status
		  Current smokers 1.4 (5.3)
		  Former smokers 0.9 (3.4)
		  Never smoked 0.4 (1.6)
			Smoking was a highly significant correlate of the number of teeth with PPD 5 mm in a multiple linear regression model that also included gender, most recent dental visit, debris and calculus index scores, and the number of teeth

Grossi et al. 1995	Population-based sample of 696 women and 665 men Aged 25–74 years United States (New York)	OR (95% CI) for smoking and alveolar bone loss
		  Pack-years
		    >0–5.2 1.48 (1.02–2.14)
		    5.3–15.0 3.25 (2.33–4.54)
		    15.1–30.0 5.79 (4.08–8.27)
		    30.1–150.0 7.28 (5.09–10.31)
			This stepwise ordinal logistic regression analysis, with mean alveolar bone loss as a dependent variable (4 ordinal categories), also included age, gender, race, education, kidney disease, allergy, and plaque bacteria levels

Martinez-Canut et al. 1995	340 male and 549 female periodontal patients with mild to moderate periodontitis Aged 21–76 years Spain	Mean PPD (mm) by cigarettes/day
		  0 3.36
		  1–10 3.47
		  11–20 3.68
		  21 3.69
		
		Mean GR[††] (mm) by cigarettes/day
		  0 0.48
		  1–10 0.43
		  11–20 0.68
		  21 0.81
		
		Mean LPA (mm) by cigarettes/day
		  0 3.84
		  1–10 3.72
		  11–20 4.36
		  21 4.50
			The number of cigarettes smoked per day was significantly associated with log transformed mean GR, PPD, and LPA* in ANOVA[‡‡] models that also included age and gender

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[††]GR = Gingival recession.
[‡‡]ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments
Sakki et al. 1995	Population-based sample of 266 men and 261 women Aged 55 years Finland	Periodontal sites (%) at risk for PPD[†] 3 mm Never smoked 8.4 Ever smoked 15.3 OR for periodontitis (95% CI) Ever smoked 1.73 (1.11–2.68)	Current and former smokers were not separated; in this multiple logistic regression model, persons with disease were defined as those in the upper one-third of the distribution of the percentage of sites with PPD 3 mm; dietary habits, alcohol intake, and toothbrushing frequency were also included
Schenkein et al. 1995	431 male and 335 female periodontal patients and their family members Aged 5–80 years United States (Virginia)	Prevalence (%) of current smoking by disease classification Localized juvenile periodontitis (LJP) 20 Generalized early-onset periodontitis (GEOP) 43 Adult periodontitis 38 Healthy 16 Mean number of teeth with LPA* 5 mm by disease and smoking status GEOP Current smokers 49.0 Not current 36.8 GEOP (probands) Current smokers 62.7 Not current 49.8 Adult periodontitis Current smokers 16.2 Not current 8.2	Current smoking was determined by serum cotinine analysis; former smoking was not measured; case definitions differed for probands and family members; means were adjusted for age and plaque index scores; among persons with LJP, the mean LPA and mean number of teeth with LPA 2 mm or 5 mm did not differ between smokers and nonsmokers
Söder et al. 1995	85 men and 59 women with at least 1 PPD site 5 mm, selected from population-based sample Aged 31–40 years Sweden	Mean PPD (mm) by smoking status Current smokers 3.0 Nonsmokers 2.8 Number of PPD sites at 5 mm Current smokers 15.4 Nonsmokers 11.6 Mean alveolar bone height (%) Current smokers 76.9 Nonsmokers 80.2	There was no control group; all subjects had disease; response rate was 50% among persons with disease identified in a population-based survey; it is unclear if nonsmokers included former smokers

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.

Table 6.22 Continued

Study	Population	Findings	Comments

Tomar et al. 1995	416 male and 58 female HIV§§-infected military personnel Aged 18–49 years United States	Unadjusted OR (95% CI) for having ≥1 LPA* site ≥5 mm
		  Current smokers 2.6 (1.5–4.8)
		  Former smokers 2.4 (1.2–4.9)
		  Never smoked 1.0 (referent)
		
		Adjusted OR (95% CI) for having ≥1 LPA site ≥5 mm
		  Current smokers 2.0 (1.1–3.5)
		  Former smokers 1.0 (referent)
			This multiple logistic regression model included age, stage of HIV disease, gender, retirement status, gingival cratering or ulceration, AZT‖ use, and the presence of oral candidiasis

Ahlberg et al. 1996	483 male industrial workers Aged 38–65 years Finland	Adjusted OR (95% CI) for having PPD† ≥4 mm Smokers 2.1 (1.3–3.5)	Used the CPITN‡; persons who had quit smoking <6 months before the study were considered smokers; all others were nonsmokers; this logistic regression model included education, access to subsidized dental care, toothbrushing frequency, most recent dental visit, and age

Alpagot et al. 1996	71 female and 46 male dental patients Aged 18–70 years United States (Minnesota)	Pearson correlation coefficients, pack-years
		  Mean LPA (mm) 0.23
		  Mean PPD (mm) 0.27
			An association between pack-years of smoking and the mean LPA or mean PPD was statistically significant in stepwise multiple linear regression models that also included age, enzyme levels in gingival crevicular fluid (β-glucuronidase, neutrophil elastase, myeloperoxidase), and plaque bacteria levels (*Fasibacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis, Eikenella corrodens,* and *Actinobacillus actinomycetemcomitans*)

*LPA = Loss of periodontal attachment.
†PPD = Probing pocket depth.
‡CPITN = Community Periodontal Index of Treatment Needs.
§§HIV = Human immunodeficiency virus.
‖AZT = Azidothymidine or zidovudine, a medication used to treat HIV infections.

Table 6.22   Continued

Study	Population	Findings	Comments
Bridges et al. 1996	118 men with diabetes (46 with type I, 72 with type II) and 115 age-matched men without diabetes, from outpatient clinics Aged 24–78 years United States (Kentucky)	Pearson correlation coefficients for smoking and periodontal parameters Mean PPD[†] (mm) Diabetic 0.23 Nondiabetic 0.25 Mean LPA* (mm) Diabetic 0.34 Nondiabetic NR[¶¶]	The mean PPD and LPA were described as higher among smokers with diabetes than among other groups, but the data were not reported; smoking was reported to be significantly associated with the mean PPD and LPA in a multiple linear regression model, but regression parameters were not reported; smoking included cigarettes, cigars, and pipes; the prevalence of tobacco use was not reported
González et al. 1996	79 persons with established perio-dontitis, including 30 current smokers, 34 former smokers, 15 never smokers Aged 25–64 years United States (New York)	Correlation coefficients between serum cotinine levels and periodontal measures Mean LPA (mm) 0.498 Mean crestal bone height (mm) 0.473	None
Mullally and Linden 1996	100 periodontal patients 50 current smokers (mean age 44 years) and 50 never smokers (mean age 46 years) Northern Ireland	Persons (%) with furcation involvement of 1 molar Current smokers 74 Never smoked 40 Molars with furcation involvement (%) Current smokers 39 Never smoked 16	Maxillary and mandibular 1st and 2nd molars were assessed radiographically; furcation involvement was defined as the area of radiolucency at furcation of the roots of at least 1 molar; molars with fused roots were excluded from the analysis

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[¶¶]NR = Data were not reported.

Table 6.22   Continued

Study	Population	Findings	Comments
Dolan et al. 1997a	Population-based sample of 471 adults Aged ≥45 years United States (Florida)	Prevalence (%) of teeth (≥1) with ≥7 mm LPA* Current smokers 49 Former smokers 33 Never smoked 37 OR (95% CI) for teeth (≥1) with ≥7 mm LPA Current smokers 1.9 (1.2–2.9) Former smokers 1.1 (0.8–1.6) Never smoked (referent) Teeth/person with 4–6 mm LPA (mean %) Current smokers 42 Former smokers 36 Never smoked 35 Teeth/person with ≥7 mm LPA (mean %) Current smokers 21 Former smokers 10 Never smoked 8	Estimates of prevalence and extent of LPA were significantly higher among current smokers but were not adjusted for other factors; OR estimates were adjusted for diabetes status, use of dental care services, tooth-brushing, flossing, and use of toothpicks
Hildebolt et al. 1997	Convenience sample of 155 postmenopausal women Aged 41–71 years United States (Missouri)	Correlation between pack-years and LPA = 0.16 (p <0.07) Parameter estimates for least square linear regression model: Intercept 1.01 Age 0.02 Years menopausal 0.02 Current smokers 2.22 Age*** current smokers -0.04	There was a significant association between age and current smoking status; pack-years of smoking were not significantly associated with the mean LPA among current smokers

*LPA = Loss of periodontal attachment.
***Age was retained in the model because of its interaction with current smokers.

Table 6.22   Continued

Study	Population	Findings		Comments
Imaki et al. 1997	1,611 male factory workers Aged 20–59 years Japan	Persons (%) with PPD[†] 4 mm by plaque bacteria levels, age, smoking status, and cigarettes/day		Used the CPITN ; periodontal pocketing was significantly more prevalent among smokers than nonsmokers, and among persons with high plaque levels
		Low plaque levels		
		Aged 20–39 years		
		Current smokers	15.1	
		1–20	14.3	
		21	16.9	
		Former smokers	12.8	
		Never smoked	17.4	
		Aged 40–59 years		
		Current smokers	43.7	
		1–20	40.5	
		21	47.3	
		Former smokers	31.6	
		Never smoked	32.0	
		High plaque levels		
		Aged 20–39 years		
		Current smokers	49.7	
		1–20	49.3	
		21	50.5	
		Former smokers	43.4	
		Never smoked	29.3	
		Aged 40–59 years		
		Current smokers	84.8	
		1–20	81.3	
		21	88.5	
		Former smokers	82.5	
		Never smoked	72.3	
Taani 1997	Convenience sample of 998 dental patients Aged 20–60 years Jordan	Prevalence (%) of PPD 4 mm by age and smoking status		Nonsmokers included both never smokers and those who had quit 2 years earlier; periodontal status was measured by the CPITN
		Aged 20–34 years		
		Smokers	17.0	
		Nonsmokers	7.5	
		Aged 35–44 years		
		Smokers	21.7	
		Nonsmokers	18.8	
		Aged 45–60 years		
		Smokers	27.9	
		Nonsmokers	25.7	

[†]PPD = Probing pocket depth.
 CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22 Continued

Study	Population	Findings		Comments
Axelsson et al. 1998	Population-based sample of 536 men and 557 women Aged 35, 50, 65, and 75 years Sweden	Mean number of missing teeth		Former smokers were excluded from the analysis; the mean number of missing teeth was significantly higher among smokers for all ages except 35 years; the mean percent of molars with furcation involvement was higher for all age groups except 75 years; the LPA* was measured at mesial surfaces of all teeth
		Aged 35 years		
		Smokers	2.0	
		Nonsmokers	1.6	
		Aged 50 years		
		Smokers	6.3	
		Nonsmokers	4.8	
		Aged 65 years		
		Smokers	13.8	
		Nonsmokers	10.3	
		Aged 75 years		
		Smokers	18.8	
		Nonsmokers	13.0	
		Molars with furcation involvement (mean %)		
		Aged 35 years		
		Smokers	6.3	
		Nonsmokers	2.7	
		Aged 50 years		
		Smokers	28.3	
		Nonsmokers	14.5	
		Aged 65 years		
		Smokers	42.0	
		Nonsmokers	22.3	
		Aged 75 years		
		Smokers	60.0	
		Nonsmokers	33.5	
		Mean LPA (mm)		
		Aged 35 years		
		Smokers	1.1	
		Nonsmokers	0.7	
		Aged 50 years		
		Smokers	2.4	
		Nonsmokers	1.5	
		Aged 65 years		
		Smokers	3.1	
		Nonsmokers	2.3	
		Aged 75 years		
		Smokers	4.0	
		Nonsmokers	2.7	

*LPA = Loss of periodontal attachment.

Table 6.22 Continued

Study	Population	Findings	Comments
Gunsolley et al. 1998	Dental patients 142 nonsmokers and 51 smokers without periodontitis Mean age = 30.9 years United States (Virginia)	Mean LPA* (mm) 　Smokers　　　0.28 　Nonsmokers　　0.17 Teeth with ≥1 LPA site ≥2 mm (mean %) 　Smokers　　　　17.0 　Nonsmokers　　9.9 Teeth with ≥1 LPA site ≥5 mm (mean %) 　Smokers　　　　1.5 　Nonsmokers　　0.4	Analysis of covariance; covariates included age, race, gender, and mean plaque index score
Norderyd and Hugoson 1998	Population-based sample of 283 women and 269 men Aged 20–70 years Sweden	OR (95% CI) for severe generalized periodontitis by cigarettes/day 　1–9　　1.12 (0.19–6.62) 　≥10　11.84 (4.19–33.50)	Severe generalized periodontitis was defined as alveolar bone loss of one-third or more of the root length affecting the majority of teeth; this multiple logistic regression model included age, plaque index score, and the number of cigarettes smoked per day
Persson et al. 1998	416 dental patients Aged 15–94 years United States (Washington)	Smokers were more likely than nonsmokers to have severe vertical alveolar bone defects, and smokers had more vertical defects	Alveolar bone defects were assessed radiographically; χ^2 and ANOVA‡‡ test results were reported, but the prevalence or number of bone defects among smokers and nonsmokers was not reported
Shizukuishi et al. 1998	252 male and 58 female factory workers Aged 20–59 years Japan	OR (95% CI) for moderate or deep periodontal pockets 　Current smokers 2.1 (1.2–3.8)	Miller's modified CPITN† was used to assess periodontal status; disease was defined as the upper 25% of the population distribution; this logistic model included age, gender, alcohol intake, frequency of toothbrushing, and the use of the interdental cleaners; the reference group included former and never smokers

*LPA = Loss of periodontal attachment.
†CPITN = Community Periodontal Index of Treatment Needs.
‡‡ANOVA = Analysis of variance.

Table 6.22 Continued

Study	Population	Findings	Comments

Kamma et al. 1999	40 male and 20 female dental patients with early onset periodontitis Aged 22–35 years Greece	Mean number (%) of periodontal sites with PPD[†] >5 mm
		  Smokers 76.3 (54.1)
		  Nonsmokers 57.5 (39.6)
		
		Mean PPD (mm) per diseased site
		  Smokers 6.9
		  Nonsmokers 5.9
		
		Mean LPA* (mm) per diseased site
		  Smokers 7.6
		  Nonsmokers 6.5
			There was no control group

Liede et al. 1999	Random sample in 1992 and 1993 of 409 male participants in an ongoing cancer preven- tion trial who had 15 teeth and smoked 5 cigarettes/day at baseline (1985–1988) Aged 55–70 years Finland	Mean PPD
		  Current smokers 0.76
		  Former smokers 0.43
		
		Sites (%) with gingival suppuration
		  Current smokers 2.0
		  Former smokers 0.4
		
		Persons (%) with moderate or severe radiographic alveolar bone loss
		  Current smokers 43
		  Former smokers 28
			Former smokers had quit for 6 months before the periodontal examination; gingival suppura- tion and the loss of alveolar bone remained significantly lower among former smokers than among current smokers in multiple logistic regression models

Mullally et al. 1999	21 male and 50 female periodontal patients Aged <35 years; mean age = 28 years (mini- mum age not specified) Northern Ireland	Alveolar bone loss (mean %)
		  Current smokers 31.7
		  Never smoked 25.0
			The early onset of periodontitis was defined as persons with teeth (1) with 30% radio- graphic bone loss, aged <35 years, with no medical condi- tions or drug therapies known to affect periodontium; smoking was not significantly associated with the mean percent of bone loss in this ANOVA[‡‡] model that included age and disease status (generalized vs. localized); there was no control group

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
[‡‡]ANOVA = Analysis of variance.

Table 6.22   Continued

Study	Population	Findings	Comments
Wakai et al. 1999	517 male and 113 female participants in a multiphasic health examination Aged 23–83 years Japan	Adjusted OR (95% CI) for "periodontal disease" by smoking status 　Current smokers (cigarettes/ day) 　　0–19　　　　2.3 (1.2–4.3) 　　20–39　　　3.3 (2.1–5.1) 　　40　　　　　3.6 (2.0–6.7) 　Former smokers 1.4 (0.9–2.1) 　Never smoked　1.0 (referent)	This ordinal logistic regression model with CPITN scores as outcomes was adjusted for age, gender, fasting plasma glucose, and dental debris index; a dose-response relationship was highly significant
Kerdvong-bundit and Wikesjö 2000	77 male and 43 female dental patients (60 current smokers and 60 never smokers) Aged 31–60 years Thailand	Mean PPD[†] (mm) by smoking status 　Current smokers　　5.1 　Never smoked　　　2.1 Mean LPA* (mm) by smoking status 　Current smokers　　4.8 　Never smoked　　　1.5 Persons (%) with PPD　4 mm by smoking status 　Current smokers　　87 　Never smoked　　　20 Persons (%) with LPA　4 mm by smoking status 　Current smokers　　77 　Never smoked　　　19	Mandibular molars buccal sites only
Machuca et al. 2000	304 male military recruits Mean age 19 years Spain	Mean PPD (mm) by smoking status 　Current smokers　　1.68 　Nonsmokers　　　　1.56 Mean LPA (mm) by smoking status and cigarettes/day 　Current smokers　　1.82 　　<5　　　　　　　1.83 　　5–20　　　　　　1.82 　　>20　　　　　　　1.79 　Nonsmokers　　　　1.63	It is unclear if nonsmokers included former smokers

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.
 CPITN = Community Periodontal Index of Treatment Needs.

Table 6.22   Continued

Study	Population	Findings	Comments

Tomar and Asma 2000	Population-based sample of 6,460 men and 7,190 women Aged ≥18 years United States	Adjusted OR for periodontitis and smoking
		Current smokers
		(all) 4.0 (3.2–4.9)
		  Cigarettes/day
		    ≤9 2.8 (1.9–4.1)
		    10–19 3.0 (2.1–4.1)
		    20 4.7 (3.5–6.4)
		    21–30 5.1 (3.5–7.5)
		    ≥31 5.9 (4.0–8.6)
		Former smokers
		(all) 1.7 (1.3–2.2)
		  Years since quitting
		    0–2 3.2 (2.2–4.8)
		    3–5 2.3 (1.3–4.1)
		    6–10 2.0 (1.2–3.2)
		    ≥11 1.2 (0.8–1.6)
		Never smoked 1.0 (referent)
			Periodontitis was defined as 1 or more periodontal sites with both PPD[†] ≥4 mm and LPA* ≥4 mm; there were strong dose-response relationships for current smokers (cigarettes/day and duration) and former smokers (years since quitting)

*LPA = Loss of periodontal attachment.
[†]PPD = Probing pocket depth.

Table 6.23   Cohort studies on the association between smoking and periodontitis

Study	Population	Follow-up (years)	Outcome	Findings
Bolin et al. 1986	170 men and 179 women Aged 18–65 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of root length) by baseline smoking status and cigarettes smoked/day, standardized for plaque level Current 1–9 cigarettes/day 5.1 10–20 cigarettes/day 5.5 >20 cigarettes/day 5.6 Nonsmokers 4.0 Unclear if nonsmokers included former smokers
Feldman et al. 1987	483 men from the Veterans Administration Normative Aging Study United States (Boston)	6	6-year change in mean PPD*, tooth mobility, and radiographic alveolar bone loss	Mean change in PPD by baseline smoking status Smokers 0.167 Nonsmokers -0.079 Mean change in tooth mobility Smokers 0.360 Nonsmokers 0.253 Mean change in alveolar bone level Smokers 0.287 Nonsmokers 0.172
Ismail et al. 1990	167 adults Aged 5–60 years at baseline United States (Michigan)	28	Change in mean LPA† ≥2 mm	OR‡ = 14.2 (95% CI§, 4.1–48.7) for smoking (assessed at baseline); this multiple logistic regression model also included year of birth and amount of tooth mobility
Bolin et al. 1993	170 men and 179 women Aged 18–65 years at baseline Sweden	10	Loss of interproximal alveolar bone	Mean bone loss (% of bone height/root length) by baseline and follow-up smoking status and by baseline cigarettes/day Smokers 6.0 1–9 cigarettes/day 5.2 10–20 cigarettes/day 6.0 >20 cigarettes/day 6.3 Former smokers 4.4 (stopped smoking during the 10-year period) Nonsmokers 3.9

*PPD = Probing pocket depth, measured in millimeters.
†LPA = Loss of periodontal attachment.
‡OR = Odds ratio.
§CI = Confidence interval.

Table 6.23   Continued

Study	Population	Follow-up (years)	Outcome	Findings
Brown et al. 1994	611 community-dwelling persons Aged ≥65 years at baseline United States (North Carolina)	1.5	2 or more sites with incident LPA† ≥3 mm	OR = 3.4 (95% CI, 1.6–7.5) among white adults who smoked cigarettes regularly; this logistic regression model included levels of *Porphyromonas gingivalis*, most recent medical care, and feelings of depression
McGuire and Nunn 1996	100 treated periodontal patients Aged 22–71 years at baseline United States (Texas)	5	5-category clinical prognosis score	OR = 1.9 (95% CI, 1.2–3.1) for smoking and a worsening prognosis
Beck et al. 1997	540 persons Aged ≥65 years at baseline United States (North Carolina)	5	At least 1 periodontal site with LPA ≥3 mm	RR = 1.6 (95% CI, 1.2–2.0); analysis was conducted at the level of the periodontal site; referent group included both never and former smokers; this logistic regression model also included *Porphyromonas gingivalis* status, number of missing teeth, tooth type, periodontal site type, educational attainment, and most recent dental visit

Machtei et al. 1997	44 women and 35 men with established periodontitis Aged 25–66 years at baseline United States (New York)	1	Increased periodontal breakdown (mean bone loss exceeding 2 standard deviations based on radiographic examination)	OR = 5.41 (95% CI, 1.50–19.5) for smoking and increased periodontal breakdown
				
				Sites that experienced loss of clinical attachment (mean %)
				  Smokers 8.35
				  Nonsmokers 6.00
				
				Mean clinical attachment loss (mm)
				  Smokers 0.27
				  Nonsmokers 0.09
				
				Mean bone height loss (mm)
				  Smokers 0.24
				  Nonsmokers 0.12
				
				Sites with bone height loss (mean %)
				  Smokers 15.4
				  Nonsmokers 11.4

†LPA = Loss of periodontal attachment.
 RR = Relative risk.

Table 6.23 Continued

Study	Population	Follow-up (years)	Outcome	Findings
Elter et al. 1999	697 community-dwelling persons Aged 65 years at baseline United States (North Carolina)	7	At least 1 site with incident LPA[†] 3 mm	RR = 1.4 (95% CI, 1.1–1.7) among whites and 1.9 (95% CI, 1.6–2.2) among blacks for current smoking; multivariable Poisson regression models included a number of site-level and person-level variables
Machtei et al. 1999	415 persons with little or no peri-odontal disease Aged 25–75 years at baseline United States (New York)	2–5	Mean LPA 1.95 mm	Mean annual LPA (mm) Smokers 0.19 Nonsmokers 0.10 Sites experiencing LPA (mean %) Smokers 5.28 Nonsmokers 3.75 Smoking also was a strong predictor of annual changes in PPD* in multiple linear regression models
Norderyd et al. 1999	Population-based sample of 357 persons Aged 20, 30, 40, 50, and 60 years at baseline Sweden	17	6 or more sites with radiographic alveolar bone loss >20%	OR = 12.0 (95% CI, 4.5–32.1) for smoking and bone loss
Faddy et al. 2000	456 university staff members Aged 18–65 years Australia	3	4 or more sites with PPD 4 mm	Current smokers had a 28% higher rate of disease regression than non-smokers of the same age and gender; used Markov chain models to model transition probabilities of changes in disease state

*PPD = Probing pocket depth, measured in millimeters.
[†]LPA = Loss of periodontal attachment.

Table 6.24 Cross-sectional and cohort studies on the association between smoking and dental caries

Study	Population	Design	Results
Ludwick and Massler 1952	2,577 male navy enlistees Aged 17–21 years United States	Cross-sectional	Mean DMFS* by mean number of cigarettes/day Cigarettes/day DMFT† DMFS 0 9.5 20.4 5 9.1 20.5 10 9.8 21.7 15 9.75 21.2 20 10.2 23.0 A statistically significant difference was reported in DMFT and DMFS means between those smoking ≤5 cigarettes/day and those smoking ≥15 cigarettes/day
Ainamo 1971	167 army recruits Aged 18–26 years Finland	Cross-sectional	Mean DS‡ and DMFS by cigarettes/day Cigarettes/day DS DMFS 0 13.8 36.4 1–9 20.7 51.7 10–20 19.9 41.5 >20 23.3 58.5 F-test $p < 0.05$ $p < 0.01$
Modéer et al. 1980	232 schoolchildren Aged 13–14 years Sweden	Cross-sectional	The number of cigarettes/day was a significant correlate of the number of decayed tooth surfaces (β = 0.311; $p < 0.01$) and filled tooth surfaces (β = 0.309; $p < 0.05$) in this stepwise multiple linear regression ($R^{2\S} = 0.22$)
Zitterbart et al. 1990	95 male dental patients Aged 18–52 years (34 current smokers and 61 never smokers) United States (Illinois)	Cross-sectional	Mean DS and DMFS by smoking status DS DMFS Current smokers 3.9 24.6 Never smoked 2.4 19.4 In analysis of variance modeling, smoking was significantly associated with the number of untreated decayed tooth surfaces and the number of missing surfaces; dose-response relationships were seen between daily cigarette use and both MS‖ and DMFS; it is unclear if missing tooth surfaces were limited to those lost due to dental caries

*DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
†DMFT = Decayed, missing (due to caries), or filled permanent teeth.
‡DS = Decayed coronal permanent tooth surfaces.
§R² = Prediction values.
‖MS = Missing tooth surfaces.

Table 6.24   Continued

Study	Population	Design	Results
Hirsch et al. 1991	1,122 male and 1,023 female dental patients Aged 14–19 years Sweden	Cross-sectional	Mean DMFT[†] by smoking status (but not adjusted for age) Smokers 9.0 Nonsmokers 7.0 The text suggests that smoking was significantly associated with DMFT across age groups, but data were not presented
Källestål 1991	Population-based sample 283 persons aged 16 years and 287 persons aged 18 years Sweden	Cross-sectional	Among persons aged 18 years, smokers had more DFS[¶] than nonsmokers (p <0.05), but data were not presented
Locker 1992	Population-based sample 907 persons Aged 50 years Canada (Ontario)	Cross-sectional	Mean DS[‡], FS[**], and RDS[††] by smoking status DS FS RDS Current smokers 1.2 18.7 1.2 Former smokers 0.8 22.1 0.6 Never smoked 0.7 25.6 0.6
Jette et al. 1993	Population-based sample of community-dwelling persons Aged 70–96 years United States (New England)	Cross-sectional	Current smokers were significantly more likely than never smokers to have current coronal or root surface decay; prevalence of current decay was not specified
Ravald et al. 1993	27 periodontal patients Aged 47–79 years Sweden	Cohort, 12-year follow-up	Compared with nonsmokers, smokers experienced higher median (8 vs. 1) and mean (14 vs. 7) numbers of new RDS following periodontal treatments
Thomas et al. 1994	Population-based sample 300 persons Aged 60 years India	Cross-sectional	Mean decayed or missing teeth, by smoking status Smokers 16.8 Nonsmokers 13.0
Hart et al. 1995	Convenience sample 200 dental patients Aged 14–88 years United States (Tennessee)	Cross-sectional	No significant difference in mean DMFT between smokers (23.9) and nonsmokers (21.2); not age-adjusted; unclear if missing teeth included only those missing due to dental caries

[†]DMFT = Decayed, missing (due to caries), or filled permanent teeth.
[‡]DS = Decayed coronal permanent tooth surfaces.
[¶]DFS = Decayed or filled coronal permanent tooth surfaces.
[**]FS = Filled coronal permanent tooth surfaces.
[††]RDS = Decayed root surfaces.

Table 6.24   Continued

Study	Population	Design	Results
Locker 1996	Population-based sample 493 persons (of 699 in the baseline survey) Aged 50 years at baseline Canada (Ontario)	Cohort, 3-year follow-up	Mean RDFS[‡‡] and RDS[††] increments by smoking status RDFS RDS Current or former smokers 0.75 0.36 Never smoked 0.47 0.24 Persons (%) experiencing RDFS or RDS increments (1) by smoking status (RDS differences were not statistically significant) RDFS RDS Current or former smokers 31.6 19.0 Never smoked 24.0 12.7 Smoking was not a significant predictor of RDFS or RDS increments in this multiple logistic model
Drake et al. 1997	Noninstitutionalized population-based sample 234 blacks, 218 whites Aged 65 years United States (North Carolina)	Cohort, 3-year follow-up	Blacks who smoked cigarettes or cigars were more likely than black nonsmokers to experience new DFS[¶] (odds ratio = 2.5 [95% confidence interval, 1.1–5.3]) in this stepwise logistic regression model; smoking was not significant among whites

Axelsson et al. 1998	Population-based sample Aged 35 years (n = 155) Aged 50 years (n = 510) Aged 65 years (n = 310) Aged 75 years (n = 310) Sweden	Cross-sectional	Mean DMFS[*] by age and smoking status
			 Aged 35 years
			  Current smokers 48.9
			  Never smoked 38.1
			 Aged 50 years
			  Current smokers 84.4
			  Never smoked 76.7
			 Aged 65 years
			  Current smokers 98.8 (not significant)
			  Never smoked 93.0
			 Aged 75 years
			  Current smokers 114.6
			  Never smoked 100.2
			 Largest difference at ages 50, 65, and 75 years was in the number of MS ; at 35 years, smokers had a higher mean DFS than never smokers (39.3 vs. 31.2); MS were not limited to those missing teeth due to caries

[*]DMFS = Decayed, missing (due to caries), or filled coronal permanent tooth surfaces.
 MS = Missing tooth surfaces.
[¶]DFS = Decayed or filled coronal permanent tooth surfaces.
[††]RDS = Decayed root surfaces.
[‡‡]RDFS = Decayed or filled root surfaces.

Table 6.24   Continued

Study	Population	Design	Results
Tomar and Winn 1999	Population-based sample 6,945 dentate men Aged 18 years United States	Cross-sectional	Mean DFT[§§], DFS[¶], and RDFS[‡‡] by smoking status, adjusted for age, race, and ethnicity DFT DFS RDFS Current smokers 6.3 16.0 2.3 Never smoked 7.0 17.4 1.1 DFT and DFS differences were not statistically significant; current smokers were not significantly more likely than men who had never used tobacco to have 1 RDFS in multiple logistic regression models

[¶]DFS = Decayed or filled coronal permanent tooth surfaces.
[‡‡]RDFS = Decayed or filled root surfaces.
[§§]DFT = Decayed or filled permanent teeth.

Erectile Dysfunction

Erectile dysfunction, defined as the persistent inability to attain and maintain penile erection adequate for satisfactory sexual performance (National Institutes of Health [NIH] Consensus Development Panel on Impotence 1993), has recently received considerable attention as a major medical issue in the United States. Additional emphasis has been given to this condition with increasing recognition of its profound impact on quality of life (Wagner et al. 2000). Epidemiologic data, though sparse, indicate its importance as a public health problem. The prevalence of erectile dysfunction in 1992 was estimated to be 18 percent among men 50 through 59 years of age according to the National Health and Social Life Survey, a United States probability sample of men and women aged 18 through 59 years (Laumann et al. 1999). Among men 40 through 70 years of age, prevalence estimates of complete erectile dysfunction during 1987–1989 exceeded 10 percent and estimates of at least mild erectile dysfunction exceeded 50 percent, according to the Massachusetts Male Aging Study (Feldman et al. 1994). Incidence estimates of erectile dysfunction during 1995–1997, derived from longitudinal results of the Massachusetts Male Aging Study, approach 26 cases per 1,000 men annually (Johannes et al. 2000).

Many conditions have been implicated as causes of erectile dysfunction, including hormonal derangement, psychogenic influences, neurologic disorders, and vascular impairment, which may all interfere with the basic physiologic mechanisms involved in penile erection. Vascular impairment, which commonly refers to disease states that hamper penile blood flow, warrants particular attention for several reasons. Most importantly, vascular diseases are commonly associated with presentations of erectile dysfunction. Objectively demonstrable erectile dysfunction has been found in patients with myocardial infarction, coronary bypass surgery, cerebral vascular accidents, peripheral vascular disease, and hypertension (Melman and Gingell 1999). Furthermore, reports of patients with vasculogenic erectile dysfunction have suggested predisposing vasculopathic risk factors, which include cigarette smoking, fatty diets, adverse serum lipid levels, hypertension, physical inactivity, and obesity (Goldstein and Hatzichristou 1994). Several large epidemiologic studies have explored the extent to which these factors impair erectile function (Feldman et al. 1994; Derby et al. 2000b; Feldman et al. 2000; Johannes et al. 2000). The results of these studies also imply that

modifications of risk factors may reduce the occurrence of erectile dysfunction.

Among widespread concerns about adverse health effects associated with cigarette smoking is the growing belief that this activity adversely affects sexual health and, in particular, erectile function. It is plausible that cigarette smoking exerts atherogenic effects on penile circulation relevant to erectile function, akin to effects on coronary circulation associated with heart disease (Fried et al. 1986; Raichlen et al. 1986). Furthermore, cigarette smoking cessation may afford a preventive strategy for reducing erectile dysfunction rates. However, each of these hypotheses requires a critical examination of the evidence regarding the effects of smoking on penile erection. This chapter summarizes and evaluates current observational and experimental data linking cigarette smoking and tobacco use with erectile dysfunction, including the pathophysiologic concepts.

Conclusions of Previous Surgeon General's Reports

This topic has received some coverage in prior Surgeon General's reports. The 1964 report (U.S. Department of Health, Education, and Welfare [USDHEW] 1964) included a discussion on masculinity in relation to COPD. The discussion drew from an investigation that defined the "element of masculinity as indicated by external morphologic features," and contended that "weakness of the masculine component is significantly more frequent in smokers than in nonsmokers, and most frequent in heavier smokers" (USDHEW 1964, pp. 383–4). This vaguely described element merely relates to the theme of male sexual prowess, as erectile ability or lack thereof was not directly assessed. The Advisory Committee to the Surgeon General recognized the tentative nature of the conclusions and the need for further confirmation. The 1990 report carried out a comprehensive review of sexual activity and performance, and sperm density and quality (USDHHS 1990). This review did not lead to specific conclusions, reflecting limitations of the available data and their inconsistency. This section reviews the issue of male sexual function, examining the influence of cigarette smoking on penile erection, one specific component of male sexual function.

Biologic Basis

Direct biologic evidence establishing plausible mechanisms for the effects of cigarette smoking on penile erection certainly would strengthen the premise that cigarette smoking constitutes a risk factor for erectile dysfunction. One possible mechanism is smoking-induced endothelial dysfunction of the penile vasculature. This hypothesis is supported by recent investigations into the physiology of penile erection affirming that the endothelium of the blood vessels supplying the penis, as well as that lining the lacunar spaces within the penis, releases vasoactive substances that contribute to the control of penile smooth muscle relaxation required for penile erection (Lue and Tanagho 1987).

Saenz de Tejada and colleagues (1989) probed whether smoking affects penile vasculature endothelium as part of an investigation of the consequences of diabetes mellitus on endothelial function in the penis in men with erectile dysfunction. Using isolated strips of human corpora cavernosa of the penis, the investigators compared isometric tension results from men with and without diabetes who were smokers (having at least a five pack-year history of cigarette smoking) or nonsmokers. The findings indicate that a history of smoking was not associated with a worsened impairment of endothelium-mediated relaxation responses. The study did not assess responses of tissue from smokers independently while controlling for other possible erectile dysfunction risk factors, nor did it carry out a subset analysis of responses from smokers specified to have had large amounts of cigarette smoke exposure. These limitations restrict the conclusions that can be drawn concerning the effects of smoking on endothelial function in the penis.

In a study of rats, Xie and colleagues (1997) examined the long-term effects of smoking on the endothelial synthesis of nitric oxide in the penis. Nitric oxide is now known to be the principal vasoactive mediator of penile erection (Burnett 1997). Nitric oxide is released by endothelial cells in response to direct cholinergic stimulation and in response to dynamic factors of changing penile blood flow. In the study, rats were passively exposed to cigarette smoke in 60-minute sessions once per day, five days per week, for eight weeks. Immunoblot analyses of the protein expression of endothelial nitric oxide synthase (eNOS) in penile tissue from the exposed rats did not reveal any diminution of eNOS expression compared with tissue from control rats. However, these investigators confirmed that overall nitric oxide synthase enzymatic activity (which combines neuronal and endothelial

sources) and specifically the protein expression of the neuronal form of nitric oxide synthase in the penis were both markedly reduced following passive exposure to cigarette smoke in rats as compared with rats not exposed to smoke. Their findings mainly suggest that smoking selectively impairs neuronal mechanisms, in particular the neuronally based nitric oxide signal transduction pathway associated with penile erection. But the relevance of the rat model for humans is uncertain.

The investigation by Saenz de Tejada and colleagues (1989) also evaluated whether smoking affects the neurogenic mechanisms responsible for penile erection. The overall finding was that the impairment of neurogenically mediated relaxation of penile smooth muscle from smokers (combining results from men with and without diabetes) was not different from the impairment observed in nonsmokers (both men with and without diabetes). However, these conclusions have the same limitations as those concerning endothelial effects observed in this study (see above). An in vitro investigation of neuromuscular transmission in human corpus cavernosum also studied nicotine and found that the actions of this agent are both contractile and relaxant (Adaikan and Ratnam 1988). If erectile dysfunction results from exogenously administered nicotine during cigarette smoking, it may be due to the acute vasoactive modulatory effects of this agent on the penile vasculature.

Epidemiologic Evidence

Observational Data

This section explores the association between cigarette smoking, as well as other forms of tobacco use, and the occurrence of erectile dysfunction based on a review of available observational data. A literature search was conducted using the National Library of Medicine's PubMed system and was supplemented with professional knowledge of other resources. The critical feature of the observational data is the necessary reliance on self-reporting and other subjective instruments (e.g., logs, questionnaires, and sexual function inventories) to determine tobacco exposure and erectile performance, rather than quantitative measurements of these variables. A single-item assessment (e.g., "Do you experience difficulty getting and/or maintaining an erection that is rigid enough for satisfactory sexual intercourse?") has gained prominence particularly for population-based epidemiologic studies (Derby et al. 2000a). This assessment has been

useful as a single, direct practical tool to ascertain the presence of erectile dysfunction, whereas clinical questions are impractical (Derby et al. 2000a). This data collection methodology does introduce the possibility of information bias, probably toward underreporting. Differential underreporting by smoking status would bias estimates of the effects of smoking; however, the findings do prove insightful as to its probable significance within the general population. Furthermore, aspects of compromised sexual function are fundamentally issues of a subjective nature, wherein patient self-reporting may accurately serve as the main, or even the sole, criterion for establishing the existence and severity of the problem.

Case Series

Cigarette smoking has been linked to erectile dysfunction in several clinical reports, most qualifying as observational case series. As such, they are limited by not having true comparison groups, but they are reviewed here because they are often cited and data from more formal studies are limited. Wabrek and colleagues (1983) found that approximately 50 percent of 120 men referred for evaluation and management of erectile dysfunction to a hospital-based medical sexology program were smokers, counting users of cigarettes, cigars, or pipes. Virag and colleagues (1985) confirmed a 64 percent rate of cigarette smoking, defined as tobacco use exceeding 15 cigarettes per day for at least 15 years, among 440 men referred for clinical evaluation of erectile dysfunction. Bornman and Du Plessis (1986) similarly observed a 62 percent cigarette smoking rate, based on approximately 25 cigarettes per day for more than 20 years among 300 men screened at an andrology clinic. An attempt to provide comparative information was made by Condra and colleagues (1986), who studied 178 men with erectile dysfunction referred for clinical evaluation and found that 51.4 percent were current smokers and 81 percent were current or former cigarette smokers. These rates exceeded the 38.6 percent and 58.3 percent rates, respectively, ascertained in the general population using concurrent survey data. A recently published meta-analysis of smoking prevalence in men with erectile dysfunction also included a comparative assessment that controlled for age distribution, time period, and geographic location (Tengs and Osgood 2001). This meta-analysis, which consisted of 19 clinical studies published in the last 20 years with data on current smoking, revealed that 40 percent of the combined total of 3,819 men with erectile dysfunction were current smokers compared with 20 percent of men in the general population (Tengs and Osgood 2001).

Population-Based Studies

More valid appraisals of the effects of cigarette smoking on erectile dysfunction have been obtained through cross-sectional, random surveys of a sample population (Table 6.25). The Vietnam Experience Study of 1985–1986, which surveyed 4,462 U.S. Army Vietnam-era veterans aged 31 through 49 years, found erectile dysfunction prevalence rates of 2.2 percent among nonsmokers, 2.0 percent among former smokers, and 3.7 percent among current smokers (p = 0.005). The association (OR = 1.5 [95 percent CI, 1.0–2.2]) was maintained even after adjustments for comorbidity factors including vascular disease, psychiatric problems, hormonal factors, substance abuse, marital status, race, and age (Mannino et al. 1994).

Additional recent studies support the direct association between cigarette smoking and erectile dysfunction. A cross-sectional study assessing the prevalence of erectile dysfunction in 2,010 men aged over 18 years in Italy in 1996–1997 showed that smoking was associated with an increased risk of the condition (Parazzini et al. 2000). Although the study was controlled for multiple variables including age, marital status, SES, and chronic diseases, it found an increased risk of erectile dysfunction for current smokers (OR = 1.7 [95 percent CI, 1.2–2.4], p <0.05) and for former smokers (OR = 1.6 [95 percent CI, 1.1–2.3], p <0.05) in comparison with lifetime nonsmokers (Parazzini et al. 2000). The Krimpen Study, a community-based study conducted in Rotterdam, the Netherlands, between 1995 and 1998 that surveyed 1,688 men aged 50 to 78 years, also confirmed that smokers professed significant erectile dysfunction (adjusted OR = 1.6 [95 percent CI, 1.1–2.3], p <0.05) to a greater extent than nonsmokers (Blanker et al. 2001). A cross-sectional study of erectile dysfunction prevalence conducted in Spain in 1998–1999, consisting of 2,476 men aged 25 to 75 years, demonstrated that cigarette smoking was significantly associated with erectile dysfunction (adjusted OR = 2.5 [95 percent CI, 1.64–3.80], p <0.05) (Martin-Morales et al. 2001).

Another recent study supports the direct association between cigarette smoking and erectile dysfunction (Bacon et al. 2001). The Health Professionals Follow-up Study, a prospective cohort study of heart disease and cancer among U.S. male health professionals (Rimm et al. 1991; Ascherio et al. 1996), surveyed 34,282 men aged 53 through 90 years in 2000. The study showed an increased probability of erectile dysfunction among current smokers compared with nonsmokers (OR = 1.3 [95 percent CI, 1.1–1.6], p <0.05), while controlling for age, marital status, and chronic diseases (Bacon et al. 2001).

Table 6.25 Cross-sectional studies on the association between smoking and the risk of erectile dysfunction (ED)

Study	Population	Smoking status	ED rate (%)	p value
Feldman et al. 1994*	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1989	Never and former smokers Current smokers	9.3 11.0	>0.200
Mannino et al. 1994*	U.S. veterans aged 31–49 years; studied during 1985–1986	Never smokers Current smokers Former smokers	2.2 3.7 2.0	0.005[†]
Feldman et al. 2000[‡]	Boston, Massachusetts, residents aged 40–70 years; studied during 1987–1996	Never and former smokers Current smokers	14 24	0.010
Parazzini et al. 2000*	Italian men aged 18 years; studied during 1996–1997	Never smokers Current smokers Former smokers	24.2 35.6 40.2	NR[§]
Bacon et al. 2001*	U.S. male health professionals aged 53–90 years; data gathered in 2000	Never smokers Current smokers Former smokers	22.4 27.9 26.2	NR
Blanker et al. 2001*	Dutch men aged 50–78 years; studied during 1995–1998	Never and former smokers Current smokers	NR NR	NR
Martin-Morales et al. 2001*	Spanish men aged 25–95 years; studied during 1998–1999	Never and former smokers Current smokers	NR NR	NR

*Prevalence study.
[†]Significant results.
[‡]Incidence study.
[§]NR = Data were not reported.

Evidence against an independent association between cigarette smoking and erectile dysfunction comes from the baseline phase of the Massachusetts Male Aging Study, a community-based survey conducted from 1987–1989 of 1,290 men aged 40 through 70 years living in the Boston, Massachusetts, area (Feldman et al. 1994). The probabilities of complete erectile dysfunction were 11 percent in smokers and 9.3 percent in nonsmokers, including both former smokers and those who had never smoked (p >0.20) (Feldman et al. 1994). However, the longitudinal phase of the Massachusetts Male Aging Study, extending over a nine-year median interval, showed the comorbidity-adjusted rate of incident erectile dysfunction to be significantly higher among cigarette smokers (24 percent) than nonsmokers (14 percent) (OR = 1.97 [95 percent CI, 1.07–3.63], p = 0.03) (Feldman et al. 2000). The classification of erectile dysfunction was based on an algorithm derived by the discriminant analysis of 13 questions.

Kleinman and colleagues (2000) reanalyzed the baseline data from the Massachusetts study using new methods for classifying erectile dysfunction. One method corresponded to the approach used by Feldman and colleagues (2000), based on responses from men attending a urology clinic to an original

questionnaire and to an additional global question for self-rating erectile dysfunction. Another analysis was based on responses to an expanded follow-up questionnaire. Cross-sectional analyses of predictors of erectile dysfunction were carried out in the 1987–1989 baseline data. With the clinic-based method for classification, current smoking was not associated with erectile dysfunction (OR = 0.95 [95 percent CI, 0.72–1.22]) while with the study-based method it was (OR = 1.39 [95 percent CI, 1.07–1.80]).

Disease Correlates

Type of Tobacco Exposure. The prospective analysis of the Massachusetts Male Aging Study examined various types of tobacco exposures to identify associations with erectile dysfunction. The odds of incident erectile dysfunction were more than doubled both for passive exposure to cigarette smoke, if present both at home and at work (adjusted OR = 2.07 [95 percent CI, 1.04–4.13]) (p = 0.04), and for cigar smoking (adjusted OR = 2.45 [95 percent CI, 1.09–5.50]) (p = 0.03). Passive exposure at home or at work alone did not increase the odds of incident erectile dysfunction in nonsmokers, but each increment of exposure did increase the estimated likelihood of erectile dysfunction in smokers (Feldman et al. 2000).

Dose-Response. The relationship between the amount of tobacco exposure and the extent of erectile dysfunction has been subjected preliminarily to epidemiologic analyses. Several population-based studies further explored the effects of measures of exposure on erectile dysfunction. The Vietnam Experience Study did not show any relationship between the number of cigarettes smoked daily or the number of years smoked and erectile dysfunction among currently smoking veterans (Mannino et al. 1994). Similarly, the baseline phase of the population-based Massachusetts Male Aging Study did not reveal any dependence of packs per day or lifetime pack-years smoked on reported erectile dysfunction among current smokers (Feldman et al. 1994). By contrast, an Italian cross-sectional study showed an increased erectile dysfunction risk with duration of the behavior, based on an OR of 1.6 (95 percent CI, 1.1–2.3) for men smoking 20 or more years and an OR of 1.2 (95 percent CI, 1.0–2.4) for men smoking less than 20 years (Parazzini et al. 2000).

Risk Factor Covariates and Effects of Medication. The combined effects (i.e., synergistic or additive interactions) of cigarette smoking and other risk factors in the development of erectile dysfunction have been analyzed. Goldstein and colleagues (1984) examined clinical characteristics in 19 potent patients who underwent pelvic irradiation for prostate cancer, finding that 14 out of 15 who displayed diminished erectile capacity were cigarette smokers, whereas only 1 out of 4 who preserved erectile capacity was a cigarette smoker. The strong association of cigarette smoking with erectile impairment in this study led the investigators to propose a synergistic role of smoking, and conceivably other vasculopathic risk factors, with the radiation effects associated with radiation-induced erectile dysfunction (Goldstein et al. 1984). In the baseline phase of the Massachusetts Male Aging Study, Feldman and colleagues (1994) found that cigarette smoking did not constitute an independent risk factor for erectile dysfunction; however, in that same study, the association of erectile dysfunction with certain risk factors was greatly amplified in current cigarette smokers. This amplification was demonstrated for persons having erectile dysfunction with treated heart disease (from 21 percent for current nonsmokers to 56 percent for current smokers), treated hypertension (from 8.5 to 20 percent), and untreated arthritis (from 9.4 to 20 percent), and for those persons receiving various medications including cardiac drugs (from 14 to 41 percent), antihypertensive medications (from 7.5 to 21 percent), and vasodilators (from 21 to 52 percent). Similarly, in an Italian cross-sectional study, smoking increased the adjusted ORs for erectile dysfunction associated with diabetes by 13 percent and with hypertension by 39 percent (Parazzini et al. 2000).

Effects of Smoking Cessation. The hypothesis that cigarette smoking adversely affects erectile function would seemingly be strengthened by epidemiologic evidence demonstrating that smoking cessation leads to erectile function recovery. Forsberg and colleagues (1979) presented the case reports of two cigarette smokers aged 20 and 27 years with erectile dysfunction whose erectile function returned in concordance with improved penile vascular testing results following smoking cessation. Elist and colleagues (1984) determined that 8 (40 percent) out of 20 men with erectile dysfunction who had smoked one to two packs of cigarettes per day for at least 15 years recovered functional erections after abstaining from cigarette smoking for six weeks. In this study, seven responders (35 percent) were confirmed by objective testing criteria to have recovered normal erectile activity from baseline abnormal levels.

Population-based reports add additional perspectives to the premise that modifying cigarette smoking behavior affects the occurrence of erectile dysfunction. One study in this regard is the Vietnam Experience Study of 1985–1986, which determined that the prevalence of erectile dysfunction among former smokers was comparable to that among nonsmokers, and the prevalence rates were significantly lower than those found in current smokers (Mannino et al. 1994). Similarly, the longitudinal phase of the Massachusetts Male Aging Study determined that incident erectile dysfunction was no more likely among former smokers than among nonsmokers, in contrast to current smokers (Feldman et al. 2000). Results from the Health Professionals Follow-up Study also suggest that former smokers carry a lower risk of erectile dysfunction than current smokers, although this risk for former smokers still exceeds that of nonsmokers (Bacon et al. 2001).

From these population-based study results, one might further conclude that the discontinuation of smoking results in a recovery of functional erection status. However, this simple conclusion is challenged by recent results from the prospective evaluation of men participating in the Massachusetts Male Aging Study who discontinued smoking during the almost nine-year follow-up period of this study. This latter analysis found that the covariate-adjusted incidence of erectile dysfunction was not significantly reduced after smoking discontinuation (p = 0.28). Important considerations of this investigation are that the men who quit smoking had begun smoking at an early age (mean age 16.6 years) and had accumulated a high lifetime exposure to tobacco smoke before quitting (mean pack-years 39.4). The data provide a refined understanding of the effects of cigarette smoking cessation on erectile dysfunction: smoking cessation in middle age after a significant lifetime exposure to cigarette smoke may fail to modify erectile dysfunction occurrence, because long-term vascular effects of smoking conceivably persist after smoking cessation (Derby et al. 2000b).

Clinical Data

This section examines the link between tobacco exposure and erectile dysfunction based on objective clinical criteria. The erectile dysfunction specialty has developed quantitative measurements that serve as indices of erectile function, including physiologic and anatomic descriptions of the physical state of the penis. Numerous investigations have applied these methodologies to ascertain the effects of cigarette smoking and other forms of tobacco use on penile erection.

Penile Tumescence Studies

Nocturnal penile tumescence (NPT) monitoring provides a noninvasive diagnostic technique to quantify erection physiology objectively during the naturally occurring cycle of sleep-related penile erections. These spontaneous episodes of tumescence normally accompany rapid eye movement (REM) sleep and are diminished in men with presumably organic erectile dysfunction (Karacan et al. 1978; Allen and Brendler 1992). Several early investigations of the objective basis for vasculogenic erectile dysfunction applied NPT monitoring. Elist and colleagues (1984) confirmed NPT-monitored abnormalities in 20 smokers with erectile dysfunction, among whom 7 (35 percent) displayed normal NPT-monitored results after six weeks of smoking cessation. Virag and colleagues (1985) determined that smokers comprised 72 percent of patients with abnormal NPT results but only 32 percent of patients with normal NPT results. In a study of 168 men who smoked one or more packs per day (heavy smokers) and 632 men who smoked less than one pack per day (light smokers), Karacan and colleagues (1988) found that sleep-related penile erection rigidity was significantly lower at each decade of life after 30 years of age in heavy smokers compared with light smokers, and the duration of maximal tumescence was significantly lower for heavy smokers aged less than 30 years and 51 through 60 years compared with age-equivalent light smokers. In an investigation of 314 smokers with erectile dysfunction, Hirshkowitz and colleagues (1992) confirmed a significant inverse correlation between sleep-related penile erection rigidity and the number of cigarettes smoked per day (r = -0.12; p = 0.04). These investigators also showed that the duration of maximal tumescence was significantly shorter at the penile base (p 0.05), and the duration of detumescence (which refers to the decline from full erection to penile flaccidity) was also shorter (p = 0.06) among men who smoked 40 or more cigarettes per day compared with men who smoked 1 to 19 per day and 20 to 39 per day (p = 0.14).

Penile Vascular Hemodynamics

Impaired blood flow to the penis can be assessed using various measurement techniques. One widely used early technique to assess arterial vascular competence within the penis was the Doppler ultrasound of arterial pulsations in the flaccid, unstimulated organ. Although this method is no longer applied, the findings of these studies may still be relevant with respect to the pathogenesis of smoking-related vascular

disease of the penis. With the values obtained, the penile-brachial index (PBI) can be calculated (the PBI refers to the ratio of penile to brachial systolic blood pressures). Reduced PBI values have been associated with impairment of the erectile process (Kempczinski 1979). Using this technique, Wabrek and colleagues (1983) did not find a significant association between cigarette smoking and abnormal PBI values. Virag and colleagues (1985) also did not find an independent smoking effect on PBI, although a synergistic effect was observed with smoking in combination with other arterial risk factors such as diabetes, hyperlipidemia, and hypertension. In contrast, Condra and colleagues (1986) demonstrated significantly lower PBI values among smokers than among nonsmokers. This same study also noted that the amount of time smoked correlated with abnormal PBI values: smokers with normal PBI values had smoked for a mean duration of 19.95 years while those with abnormal PBI values had smoked for a mean duration of 26.55 years. DePalma and colleagues (1987) likewise found that cigarette smoking carried a significantly higher probability of abnormal (49 percent) than normal (28 percent) vascular laboratory findings including PBI, which was not observed for age, hypertension, diabetes, or prior myocardial infarction. Hirshkowitz and colleagues (1992) confirmed consistent PBI reductions among 314 cigarette smokers with erectile dysfunction, finding significant correlations between the number of cigarettes smoked per day and the magnitude of these reductions for the left dorsal artery ($r = -0.14$; $p = 0.01$) and right cavernosal artery ($r = -0.13$; $p = 0.03$) of the penis.

The vascular evaluation of the penis has more recently employed a pharmacologic stimulus in combination with penile duplex ultrasonography to characterize the penile arteries. This application followed the discovery that a pharmacologic stimulus to induce an artificial erection provides an improved assessment of the physiologic responsiveness of these arteries over that provided during the resting state (Abber et al. 1986). Using this technique and applying a combined set of ultrasonographic parameters to establish normal vascular findings, Shabsigh and colleagues (1991) showed a consistent, nearly statistically significant difference in vascular impairment in smokers compared with nonsmokers. Kadioğlu and colleagues (1995) also observed that penile vascular parameters were abnormal to a greater extent among smokers than among nonsmokers, although the differences were not statistically significant.

In summary, PBI testing suggests deleterious effects of smoking on the "resting state" circulation of the penis, and sonographic evaluation of the penis following pharmacostimulation additionally demonstrates apparent deleterious effects of smoking on dynamic blood flow changes in the penis.

Penile Vascular Morphology

Arteriographic studies have been conducted in patients with erectile dysfunction to characterize the vascular anatomy of the penis. Investigations have been carried out among cigarette smokers to confirm the presence and location of arteriographic lesions. Virag and colleagues (1985) calculated a 67.8 percent rate of arteriographic abnormalities among patients in whom organic erectile dysfunction had been established by NPT monitoring, of whom 86 percent were smokers. Bähren and colleagues (1988) similarly showed that 82 percent of their patient group with arteriographically proven peripheral arteriosclerotic lesions were heavy smokers. In a study by Forsberg and colleagues (1989), men with erectile dysfunction underwent screening studies of penile blood flow to identify abnormalities. Using both pharmacostimulation and angiography in 17 men, this study found significant distal penile vessel lesions; 14 (82 percent) of the men were identified as smokers. Rosen and colleagues (1991) carried out a comprehensive evaluation of penile circulation in cigarette smokers with erectile dysfunction, finding that smoking represented a significant independent risk factor in the development of atherosclerotic lesions in the internal pudendal and common penile arteries. These investigators also determined that the number of pack-years smoked was independently associated with hemodynamically significant atherosclerotic disease in the hypogastric cavernous arterial bed supplying the penis (for each 10 pack-years smoked, $RR = 1.31$ [95 percent CI, 1.05–1.64]).

Histopathology

The effects of cigarette smoking on erectile tissue were investigated by Mersdorf and colleagues (1991), who confirmed degenerative tissue changes (including a decrease in smooth muscle content, sinusoidal endothelium, nerve fibers, and capillaries, and an increase in collagen density) in erectile tissue of smokers. These tissue alterations are consistent with tissue alterations seen in other vascular diseases.

Experimental Data

This section reviews experiments carried out to test the effects of cigarette smoking on erectile function (Table 6.26). These experimental approaches controlled cigarette smoking exposures and provided the possibility for a rigorous evaluation of the consequences for erectile ability. The value of the information was enhanced when experiments involved robust scientific methodology (e.g., a random allocation of people to experimental and control groups, the use of different control groups, and the application of blinding procedures to reduce bias).

Human Studies

Perhaps the first reported study to experimentally evaluate the hypothesized association between cigarette smoking and erectile dysfunction was performed by Gilbert and colleagues (1986), who made polygraphic recordings of penile erection responses in smokers during the viewing of erotic videos. Several aspects of this study are noteworthy: (1) the study population consisted of 42 male self-reported heterosexual cigarette smokers in good health, aged 18 through 44 years; (2) participants were assigned to high-nicotine exposure (0.9 mg nicotine per cigarette smoked), low-nicotine exposure (0.002 mg nicotine per cigarette smoked), or control (sucking on a hard mint candy) groups randomly selected and unknown to the experimenter; (3) at enrollment, a counterdemand was issued to the effect that nicotine enhanced sexual potency, to militate against contaminating hypotheses held by the participants about the effects of smoking on erections; (4) smoking abstention was required for two hours before the experiment; (5) baseline erotic videos were shown for participant acclimation; and (6) concomitant measures of cardiovascular response were obtained. The study found that smoking two, but not one, high-nicotine cigarettes significantly decreased the rate of penile diameter increase compared with the other conditions during the erectile stimulus (p < 0.001). It also determined that high-nicotine cigarettes caused significantly more vasoconstriction and heart rate increase than did low-nicotine cigarettes, which did not differ from control conditions (p < 0.001).

In another experiment undertaken to assess the acute effects of cigarette smoking exposure on penile erection, Glina and colleagues (1988) studied the interference of smoking on vasoactive drug-induced erectile responses monitored by intracavernous pressure recording. Study design features were as follows: (1) 12 chronic cigarette smokers, aged 22 through 65 years, were enrolled; (2) subjectively reported erectile

function status of the participants at enrollment was not stated; (3) smoking was prohibited on test days; (4) each participant underwent pharmacostimulation consisting of intracavernous injection of 100 mg papaverine hydrochloride at baseline (without smoking) and one week later immediately after nicotine exposure (smoking two cigarettes containing 1.3 mg nicotine per cigarette); and (5) intracavernous pressure measurements were performed 20 minutes following pharmacostimulation by the same experimenter. The study found that all men obtained an erection by clinical judgment at baseline compared with only four (33 percent) after smoking, corresponding to a significant decrease in mean intracavernous pressures from 85.83 mm Hg at baseline to 53.50 mm Hg after smoking. As part of an earlier, larger investigation of the use of papaverine injections to test diagnostically for erectile dysfunction, Abber and colleagues (1986) described a similar experiment involving a chronic smoker with erectile dysfunction who displayed an acutely worsened erectile response immediately following smoking a cigarette compared with his baseline results.

In a visual depiction of the effects of cigarette smoking on arterial flow to the penis, Levine and Gerber (1990) described their pelvic arteriographic study of a 38-year-old man with a 25 pack-per-year smoking history who presented for evaluation of erectile dysfunction. Whereas a complete baseline evaluation including pelvic arteriographic studies showed no abnormalities, repeat pelvic arteriography immediately after the patient smoked two cigarettes revealed a decrease in the caliber of the entire pudendal artery and nonvisualization of the deep penile artery. The investigators suggested that acute vasospasm was responsible for the observed effects.

Further experimental evidence of the deleterious effects of cigarette smoking on erectile function was recently documented in an acute smoking cessation study by Guay and associates (1998). Ten men, 32 to 62 years of age who had at least a current 30 pack-year smoking history and were smoking one pack of cigarettes or more per day, were enrolled in a study monitoring NPT and rigidity by a home RigiScan® technique. The study required monitoring of sleep-related penile erections on two successive nights, the first night following a usual day of smoking and the second night following discontinuation of smoking for one 24-hour interval. An additional component of the study involved repeat monitoring in four men who did not smoke for one month although they were administered transdermal nicotine patches (21 mg) during this time. The study results show that erectile parameters improved to a statistically significant degree in men who

Table 6.26 Experimental studies on the association between smoking and erectile dysfunction

Study	Population	Study design	Stimulus	Outcome
Human studies				
Gilbert et al. 1986	42 smokers aged 18–44 years	Randomized controlled trial	Visual sexual stimulation	High-nicotine cigarettes reduced the amount of penile diameter increase
Glina et al. 1988	12 smokers aged 22–65 years	Acute experiment	Erection pharmaco-stimulation	Two cigarettes reduced intracavernous pressure measurements
Guay et al. 1998	10 smokers aged 32–62 years	Acute experiment	Sleep-related erections	Cigarette smoking discontinuation improved erectile parameters
Animal studies				
Juenemann et al. 1987	Dogs	Acute experiment	Cavernous nerve electrostimulation	Cigarette smoke inhalation reduced erectile parameters
Xie et al. 1997	Rats	Chronic experiment	Cavernous nerve electrostimulation	Cigarette smoke inhalation did not alter erection parameters

had stopped smoking for 24 hours, with further observed improvements in those not smoking and wearing nicotine patches for one month. The investigators concluded that eliminating cigarette smoking improves erectile function although factors contained in cigarette smoke other than nicotine primarily exert the damaging effects.

Animal Studies

Animal models have provided another useful approach for investigating the association between cigarette smoking and erectile dysfunction. The study by Juenemann and colleagues (1987) using an in vivo canine model represents a comprehensive, well-controlled investigation that combined stimulatory and monitoring techniques relevant to the physiology of erection. The methodology involved monitoring arterial inflow, intracavernous pressure, and venous outflow of the penis during cavernous nerve stimulation of erection alone, and with regulated penile perfusion before and after acute inhalation of cigarette smoke (1.4 mg nicotine per cigarette). Following smoking exposure (one to six cigarettes), compared with

nonsmoking baseline conditions, peak arterial inflow was significantly diminished, peak intracavernous pressure was significantly diminished and could not be maintained, and venous outflow was not significantly restricted. Measurable serum nicotine and cotinine levels, obtained in the dogs following smoking exposure and used as markers, were consistent with concentrations found in human smokers, whereas no changes in arterial blood gases or systemic blood pressure were observed throughout the investigation. The investigators concluded that smoking exerts a localized deleterious effect on the neurovascular mechanisms required for penile erection, with a particular impairment of the veno-occlusive mechanism associated with maintenance of penile erections.

In a rat model, Xie and colleagues (1997) evaluated the long-term effects of cigarette smoking on penile erection. The methodology involved monitoring in vivo neurostimulated erections after exposing rats to a constant influx of cigarette smoke in an enclosed cage for a 60-minute session once per day, five days per week, for eight weeks. The investigation surprisingly found increases in intracavernous pressures in

smoke-exposed rats compared with controls. However, the rats exposed to cigarette smoke also developed systemic hypertension. Intracavernous pressures standardized to systemic blood pressures in rats exposed to cigarette smoke did not differ from intracavernous pressures found in controls. The investigators explained their findings on the basis of tobacco smoke–associated vasoconstriction, and they conceded that vascular damage commonly associated with long-term cigarette smoking is inappreciable in the rat model, which is resistant to atherosclerosis.

Evidence Synthesis

Available evidence indicates that cigarette smoking constitutes a risk factor for erectile dysfunction. However, the causal basis for this relationship must be carefully evaluated. With regard to the consistency of the relationship, both case series and population-based studies evaluating rates of erectile dysfunction among smokers provide support. The population-based studies afford a more accurate observational basis for this assessment than do uncontrolled case series, although the paucity of these studies hampers reaching a definitive conclusion. The strength of the relationship also rests on limited available information, but is similarly supported by observational evidence showing that a variety of tobacco exposures (including active and passive cigarette smoking and cigar smoking) is associated with erectile dysfunction. Consideration of a dose-response relationship is supported by a few observational and experimental investigations that have shown an increased risk of erectile dysfunction associated with increased exposures to cigarette smoking. The temporality of the relationship seems likely, with a few observational studies showing some evidence of erectile dysfunction following exposure to tobacco smoke. Intriguingly, preliminary observational findings demonstrate that cigarette smoking cessation apparently leads to a recovery of erectile function only if the discontinuation occurs after a limited extent of lifetime smoking.

Coherence of the relationship is supported by several biologic studies that have proposed plausible mechanisms for the deleterious effects of cigarette smoking on erections. The acute deleterious effects of smoking on erectile function result at least in part from nicotine carried in cigarette smoke. The nicotine pharmacologically induces vasospasm of penile arteries, and hence alters the dynamics of local blood flow required for penile erection. The chronic deleterious effects of smoking on erectile function result from impaired vascular physiology of the erectile tissue, as evidenced by degenerative morphologic changes in tissue of smokers. Although the exact mechanism of the impairment remains unclear, early studies in animals point to damaging effects on tissue-dependent erection regulatory factors. In sum, several lines of evidence contribute toward the inference of a causal relationship between cigarette smoking and erectile dysfunction. However, because the scope of observational and experimental evidence remains limited and incomplete, it seems reasonable to consider the evidence to be suggestive but insufficient to establish a causal relationship at this time.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Implications

The clinical studies and basic scientific research summarized in this section suggest a relationship between cigarette smoking and erectile dysfunction. A strong inference that smoking causes erectile dysfunction requires more evidence to confirm initial findings and to fill in gaps in the knowledge base. Additional observational studies of sufficient size and with well-validated outcome measures are needed. More basic scientific studies to identify biologic mechanisms for the deleterious effects of smoking on penile erections also are necessary. In the meantime, current knowledge about the problem still prompts recommendations for smoking cessation and avoidance to limit the risk of erectile dysfunction. Promoting nonsmoking to prevent erectile dysfunction seems clinically appropriate. There may be significant public health benefits by reducing morbidity rates of this increasingly recognized, widespread condition.

Eye Diseases

Diseases of the visual system, and possible subsequent visual loss, represent substantial social and economic concerns to the U.S. public. In the last three decades, Gallup polls have consistently indicated that blindness is second only to mental incapacity as the disability Americans fear most (National Advisory Eye Council [NAEC] 1998). There is ample reason for concern. An estimated 3.4 million Americans aged 40 years and older have visual impairment and 1 million of these people are legally blind. Because most vision loss results from eye disease associated with advancing age, and the "baby boom" population in the United States is aging, the public health impact of this problem is projected to double by 2030 (Prevent Blindness America 2002).

The economic consequences of eye disease for the U.S. population are huge. For example, sight-restoring cataract surgery was the most frequently performed surgical procedure among Medicare beneficiaries, at an estimated annual cost of $3.4 billion in 1991 (Steinberg et al. 1993). Altogether, the economic impact of visual disabilities and disorders was estimated at more than $38.4 billion in 1995 (NAEC 1998). Thus, substantial contributions to the social and economic welfare of the public are possible by finding and controlling the causes of these eye diseases, particularly the factors that present the opportunity to prevent the disease or loss of sight.

Conclusions of Previous Surgeon General's Reports

Epidemiologic investigation into risk factors for eye disease did not begin in earnest until the 1970s, bolstered by the establishment of the National Eye Institute (NEI) in 1968. Reports of the Surgeon General on smoking and health published before 2001 did not include eye disease as a topic simply because there were scant data indicating that smoking was related to ocular morbidity, although a compelling biologic basis did exist for postulating such associations. At least two of the three leading causes of visual loss worldwide, cataract and age-related macular degeneration (AMD), probably are due, at least in part, to smoking.

Cataract

Cataract is the leading cause of blindness worldwide and a leading cause of visual loss in the United States (Thylefors et al. 1995; Muñoz et al. 2000). Currently, the most common and effective means of restoring vision is through surgical removal of the opacified lens and insertion of an artificial lens into the eye. According to NEI, about 1.35 million cataract operations are performed annually in the United States for Medicare beneficiaries (NAEC 1998), at an estimated cost of $3.4 billion in 1991 (Steinberg et al. 1993). If risk factors that either delay the onset or slow the progression of cataracts could be identified, major socioeconomic gains would be realized. The research findings that link cigarette smoking to cataract, specifically nuclear cataract, have identified one of the few modifiable risk factors for cataract.

The ocular lens is a normally transparent organ having a purely optical function. The lens, situated behind the pupil, focuses radiant energy on the retina to produce an image, much like the lens of a camera. The shape of the lens changes, or accommodates, in response to the distance of the viewed object to focus a sharp image onto the retina.

The transparency of the lens is a function of its peculiar characteristics. The lens itself is composed of a central core, or nucleus, of inert, protein-filled, former epithelial cells. The interior proteins are highly structured to ensure transparency. The lens grows by the constant addition of protein-filled, elongated, former epithelial cells that have differentiated into lens fibers that do not have a nucleus or other organelles. Of interest in this process is that the lens contains every fiber cell ever incorporated into it, including cells formed in the embryo stage through those formed very recently. These cells must maintain transparency throughout the life of an individual to ensure visual clarity, yet this central core is metabolically inert and cannot renew itself. Thus, the central lens is severely restricted in its ability to repair damage. The outermost layer of the lens is composed of a layer of epithelial cells, which are responsible for most of the metabolic activity of the lens. These cells are the source of new cells, as the old cells differentiate into fiber cells and are displaced toward the nucleus. These newest lens fibers make up the lens cortex, which surrounds the nucleus.

The loss of lens transparency is termed lens opacity, and lens opacification becomes increasingly common with advancing age. When the opacity becomes sufficiently dense or extensive or both so as to interfere with vision, the lens opacity is called a cataract. There are three main types of lens opacity or cataract, which are distinct in terms of risk factors, location in the lens, and epidemiologic pattern: nuclear, cortical, and posterior subcapsular lens opacity (West and Valmadrid 1995). The different types of opacities also can occur together in the lens, resulting in a "mixed" opacity.

The frequency of each type of lens opacity in the population increases with age and varies by racial or ethnic group. In one population-based study of 2,520 older Americans (West et al. 1998), aged 65 to 69 years, 32 percent of whites had nuclear, 15 percent had cortical, and 8 percent had posterior subcapsular cataract in at least one eye; comparable figures for African Americans were 20 percent, 42 percent, and 4 percent, respectively. At least 4 percent of the study participants in that age group had undergone cataract surgery as well.

Biologic Basis

Several hypotheses have been advanced to explain a possible association of smoking and cataract. Given the plethora of aromatic compounds and trace metals in cigarette smoke that are capable of damaging lens proteins, it is difficult to know which mechanism is likely to be the most important. Harding (1995) has postulated that cadmium, lead, thiocyanate, and aldehydes from cigarette smoke lead to lens damage. Investigators analyzing blood and lenses from cataract surgery patients have shown significant accumulations of cadmium in the blood and lenses of smokers compared with lenses of nonsmokers, with cadmium in lenses proportional to the amount smoked (Ramakrishnan et al. 1995; Cekic 1998).

Harding (1991) also has suggested that the damage to the lens may be from thiocyanate, which can cause carbamylation of crystallins (lens proteins) and enzymes. Smokers do have elevated thiocyanate levels in their blood, but levels in lenses have not been measured.

Others suggest that smoking may cause cataract through an indirect route, by lowering antioxidants (Taylor et al. 1995). However, the role of antioxidants in protecting against cataractogenesis still is controversial. Few studies have determined the level of antioxidants in the lens and the relationship between lens levels and blood or serum levels. One of the better

studied antioxidants is vitamin C, which appears to be concentrated in the lens, and ocular levels of vitamin C are sensitive to plasma levels of this vitamin (Taylor et al. 1997). A review of research linking vitamin C and cataract found studies that reported a protective effect of vitamin C, an increased risk with serum levels of vitamin C, and no association at all; the conflicting results do not provide evidence of an association (West and Valmadrid 1995). In one study, smokers compared with nonsmokers had lower serum values of vitamin C, and in another, both smokers and nonsmokers had similar blood and lens levels of vitamin C (Kallner et al. 1981; Ramakrishnan et al. 1995). At present, the antioxidant pathway for lens damage from smoking requires more corroborative research.

Epidemiologic Evidence

The relevant articles for this section on eye diseases were identified initially through a search in PubMed from 1966 through 2000 by using the following search terms: "lens opacity," "cataract," "lens," "nuclear lens opacity," "cortical lens opacity," "posterior subcapsular lens opacity," "age-related macular degeneration," "senile macular degeneration," "age related maculopathy," "choroidal neovascularization," "drusen," "geographic atrophy," "atrophic macular degeneration," "diabetic retinopathy," "diabetic eye disease," "glaucoma," "intraocular pressure," "Graves' ophthalmopathy," "thyroidopathy," "eye pathology," and "eye disease." These terms were searched with the Boolean operator "and" followed by the terms "cigarette," "smoking," and "tobacco" in appropriate combinations. All articles were reviewed, and their bibliographies were reviewed for relevant articles not captured by the search strategy. The final selection of articles for citation in this section was made in consideration of the adequacy of the research or review and the relevance to the topic. The selection of eye diseases for review was based on the public health importance of the disease and the availability of research relevant to an association with smoking.

Several key methodologic issues should be addressed in any research on risk factors for cataract. First, there are different types of cataract, with largely unique risk factors for each type. Early research on risk factors often did not differentiate cataract type, making interpretation difficult because the mix of cataract types was unknown. For example, a surgical series of cataract patients is likely to be heavily weighted for posterior subcapsular cataract, whereas a population-based series will have few posterior subcapsular cataract cases. Surgical notes, or ophthalmologist

notes, of the cataract type may lead to misclassification, as only the major cataract type usually is recorded. Ideally, studies on cataractogenesis would use one of several reliable, valid grading schemes for documentation of the presence and severity of lens opacity types.

The second methodologic issue is that each type of lens opacity has a different impact on the visual system. Research that defines cataract to include a visual acuity criterion effectively excludes asymptomatic, early lens changes or may include substantial numbers of persons with lens opacity not yet affecting acuity in the control group. Such research is less desirable from an etiologic standpoint.

Finally, issues of bias and confounding must be addressed with any research. Selection bias in clinic-based, case-control studies of cataract can be problematic, because controls sometimes have eye problems that may share risk factors in common with cataract. In population-based studies, patients with bilateral cataract surgery often are excluded from the analyses, because the type of cataract or date of surgery may be unknown. If the risk factor of interest drives progression of cataract, the exclusion of bilateral surgical cases will result in an underestimation of the risk. Potential confounders for the relationship of smoking and nuclear or posterior subcapsular cataract include age, race, gender, steroid use, and possibly alcohol use.

Ten epidemiologic studies reviewed have found an association between smoking and nuclear opacity and four found an association between smoking and posterior subcapsular opacity (Table 6.27). The studies reporting an association between nuclear cataract and smoking were carried out in diverse populations using different methodologies and different lens grading systems (Flaye et al. 1989; West et al. 1989a, 1995; Leske et al. 1991, 1998; Christen et al. 1992; Hankinson et al. 1992; Klein et al. 1993b; Cumming and Mitchell 1997; Hiller et al. 1997). The association with smoking generally was consistent (with most RRs ranging between 2 and 3); a dose-response relationship with the amount smoked was found. Four prospective cohort studies have found an association with smoking at baseline and subsequent risk of developing new nuclear opacities, surgery for nuclear opacities, or progression of existing nuclear opacities (Christen et al. 1992; West et al. 1995; Hiller et al. 1997; Leske et al. 1998).

Smoking has been less consistently associated with an increased risk of posterior subcapsular opacity. Two prospective cohort studies have found an increased risk, between 2.5- and 3-fold, associated with heavy smoking (smoking 20 or more cigarettes per day and smokers of 65 or more pack-years) (Christen et al. 1992; Hankinson et al. 1992). Two cross-sectional, population-based studies found a weaker association, and one reported an association only among men (Klein et al. 1993b; Cumming and Mitchell 1997). Two other population-based surveys did not find any association with posterior subcapsular cataract (Flaye et al. 1989; Hiller et al. 1997).

One limitation of population-based studies of risk factors for posterior subcapsular cataract is the rarity of that cataract type, making it difficult to acquire enough cases to precisely characterize risk. Another limitation is that posterior subcapsular cataract is highly visually disabling, and generally progresses quickly, so while it is overrepresented in surgical series it may be underrepresented in population-based studies because affected persons already have had cataract surgery (West et al. 1998). Thus, prospective cohort studies on posterior subcapsular cataract in populations are likely to provide more compelling data about the association.

The three studies that found no association between smoking and cataract deserve comment. The case-control study in India (Mohan et al. 1989) was hospital-based and relied on patients from one center. The possibility of selection bias, especially in terms of cases with vision loss and controls without vision loss and their COPDs, must be considered. The case-control study in Italy (Italian-American Cataract Study Group 1991) had a design similar to the study in India but used cases and controls from three clinics covering the population in Parma, Italy. This broader coverage reduced the possibility for selection bias. However, the recruitment rates of cases of posterior subcapsular cataract and nuclear cataract were lower than expected; the smoking data were not shown for this study, so an assessment of the power to detect an increased risk associated with smoking could not be done. The third study (Bochow et al. 1989), a case-control study of risk factors for posterior subcapsular cataract, did not evaluate the association of smoking with other cataract types. The controls included patients with nuclear cataract alone or with AMD, which may have increased the prevalence of smoking in the comparison group. Thus, the three studies that did not find an association between smoking and cataract have limitations that may have introduced bias toward the null.

There are no clinical trials of smoking cessation and determinations of either reduced risk of onset or progression of lens opacities. Six studies examined

the risk in former smokers, and the data in general support a lower risk of progression or development of cataract after cessation. The mechanism is likely to be a reduction in the smoking-related dose of injurious agents to the lens rather than any reversal of the cataractogenic process. A cross-sectional survey looked in detail at time since smoking cessation and reported that cessation of 10 or more years reduces the risk of nuclear opacity (West et al. 1989a). In two large prospective cohort studies, former smokers at baseline had no increased risk of new nuclear opacities (Christen et al. 1992) or new cataract surgery (Hankinson et al. 1992). The 13-year follow-up study among male physicians of self-reported development of visually significant cataract found a lower risk among former smokers compared with current smokers (Christen et al. 2000). The prospective data are compatible with previous work showing that ongoing smoking drives progression. Other researchers who found similar risks for former smokers as for current smokers did not evaluate risk by years since cessation (Cumming and Mitchell 1997; Hiller et al. 1997). Studies of risk for cataract among smokers using low-yield cigarettes or low-tar products have not been reported.

Evidence Synthesis

Substantial evidence based on cross-sectional and prospective cohort studies now has accrued linking nuclear, and possibly posterior subcapsular, cataract to cigarette smoking. There is a dose-response relationship and evidence that former smokers have a lower risk of cataract and of progression of cataract compared with current smokers. On the basis of the epidemiologic studies, researchers now are investigating the mechanisms by which smoking may damage the lens, by using animal and lens cell culture models. The laboratory data are not yet sufficiently mature to inform the discussion of smoking and cataract, in part because there are few animal models of age-related cataract; most require an external insult to initiate the cataractogenic process. However, smokers are exposed to a number of agents that may cumulatively damage the lens, which lacks reparative capacity.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.

2. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

Implications

There is moderate evidence to suggest that smoking also may be associated with an increased risk of posterior subcapsular opacities as well, but more research is needed before a causal association can be inferred for this cataract type. The difficulty the lens has in repairing damage suggests that opacification at the time of smoking cessation is likely to be irreversible. Studies of cataract in clinical trials of smoking cessation would provide more definitive evidence for any protective effect, although feasibility would be constrained by the need for large populations.

Age-Related Macular Degeneration

AMD is the leading cause of blindness in whites aged 65 years and older in the United States (Sommer et al. 1991; Muñoz et al. 2000). There currently is no well accepted treatment to prevent or halt the progression of atrophic AMD, the most common form of AMD. Treatment to halt vision loss from the less common, severe form of AMD, exudative (neovascular) AMD, often is short lived, as neovascularization (new blood vessel formation) often recurs. A recent large-scale clinical trial has provided evidence that antioxidant supplements plus zinc may delay the progression of some signs of AMD (Age-Related Eye Disease Study Research Group 2001). Otherwise, no preventive therapy for AMD is available, so considerable attention has focused on identifying risk factors for this disease.

The macula is a component of the retina at the center of the optical axis; it contains the fovea, a highly specialized area of the retina responsible for high-resolution vision. The retina consists of neural tissues, including the photoreceptors that convert energy from visible light into electrical signals sent on to the brain for processing. The photoreceptors—rods and cones—have high metabolic requirements and replace their outer segments daily. The metabolic functions of the retina are supported by the retinal pigment epithelium, which phagocytizes an estimated 2,000 outer segment membranes daily. This high rate of activity is made possible by the exchange of nutrients (and removal of waste) through the retinal blood supply, the choriocapillaris. There is a blood retinal barrier to this exchange, which is formed by both the retinal pigment epithelium and its anchor, Bruch's membrane (lamina basalis choroideae). Thus, the complex of the retinal pigment epithelium, Bruch's membrane, and the choriocapillaris serve as the nutritional source for the

sensory retina. Changes in each of the tissues in this complex have been hypothesized to result in AMD. However, the pathogenesis of AMD, indeed the differentiation of changes in early AMD from those of normal aging, is uncertain (Sarks and Sarks 1994).

AMD is an umbrella designation for a variety of degenerative changes in the macula. The degeneration is characterized in its early stages by pigmentary disturbances and atrophic changes. The late stages of AMD are characterized by widespread atrophy of the retinal pigment epithelium, loss of photoreceptors (atrophic AMD), and, less commonly, exudative AMD. With exudative AMD, new, unstable blood vessels develop in the choroid and grow under or through the retinal pigment epithelium via breaks in Bruch's membrane. Leakage from these neovascular membranes may lead to detachment of the retinal pigment epithelium, hemorrhage, and formation of a disciform scar. The late stages are associated with vision loss, classically loss of central vision, the part of vision responsible for activities such as reading and close work.

Morphologic changes associated with AMD include basal laminar deposits at the level of the retinal pigment epithelium, thickening of Bruch's membrane, and drusen. Drusen are deposits of extracellular material thought to be accumulations or "garbage bags" of waste products from the retinal pigment epithelium. At least two types of drusen are recognized clinically on the basis of their appearance: small, hard drusen, which are a common feature of aging; and larger, soft drusen, which also are common with aging but are a likely risk factor for developing severe AMD. The presence of drusen in the fundus, thought to be the hallmark of early AMD, is being challenged as a marker by observations that drusen can appear and disappear over time (Bressler et al. 1995; Klein et al. 1997), that most people with large, soft drusen do not develop advanced AMD (Klein et al. 1997), and that epidemiologic patterns associated with advanced AMD are different from those for drusen-defined early AMD. This debate has relevance in evaluating the evidence for an association of smoking and early versus advanced AMD.

Biologic Basis

Of the postulated mechanisms underlying the retinal changes in AMD, three have bearing on the hypothesis that smoking is associated with AMD. The first can be characterized as oxidative stress leading to changes in the ability of the retinal pigment epithelium to phagocytize cellular products, which in turn leads to accumulations of debris that interfere with the nutrient exchange between the retinal pigment epithelium and the choriocapillaris. Oxidative stress can result from free-radical damage to proteins, lipids, and possibly, mitochondrial DNA. The stress is considered to contribute to malfunctions of the retinal pigment epithelium. The macula is a particularly likely target for oxidative stress because of the macula's high exposure to light, high metabolic rate, and high concentrations of fatty acids. But the macula also is very rich in antioxidative, protective mechanisms, including an array of antioxidant nutrients and enzymes, as well as melanin. Smoking, through its actions on reducing plasma levels of antioxidants in addition to reducing macular pigment, is hypothesized to increase the oxidative stress on the macula by robbing it of its defenses (Hammond et al. 1996).

The second hypothesis for the pathogenesis of AMD proposes that the degradation of Bruch's membrane, as manifested by thickening and changes in the composition, leads to interference with nutrient exchange between the retinal pigment epithelium and its blood supply. Vascular endothelial growth factor (VEGF) has been reported in the retinal pigment epithelium cells; these cells may liberate VEGF in response to the interference in nutrient exchange. Investigators are working on the role of VEGF, released in connection with hypoxia, in the pathogenesis of AMD, particularly for the neovascular type (Mousa et al. 1999). Smoking has been associated with an increase in plasma immunoreactive VEGF, at least acutely, operating likely through its ability to cause tissue hypoxia (Wasada et al. 1998).

The third hypothesis for the pathogenesis, or at least a possible contributing cause, of AMD is vascular insufficiency. Changes in the choroidal circulation may impair the ability of the retinal pigment epithelium to dispose of waste substances, leading to the accumulation of waste material. The rate and volume of blood flow through the choriocapillaris are high in response to the demands of the pigmented epithelium and the photoreceptors. Smoking has been shown to alter choroidal blood flow (Bettman et al. 1958). Smoking also affects the vasculature through platelet adhesions and hypoxia from elevated levels of carboxyhemoglobin, which might add to the stimulation of new vessel growth.

It is likely that multiple pathways are responsible for the degenerative changes in the macula with age, and a reasonable basis exists for presuming that smoking may operate through one or more of these pathways.

Table 6.27   Studies on the association between smoking and cataracts

Study	Population	Design
	Association found	
Clayton et al. 1982	931 cataract surgery patients; 325 controls	Case-control
Klein et al. 1985	1,370 persons with diabetes	Cross-sectional
Harding and Van Heyningen 1988	300 cataract surgery patients; 609 controls	Case-control
Flaye et al. 1989	983 volunteers with complete data	Cross-sectional
West et al. 1989a	838 male fishermen	Cross-sectional
Leske et al. 1991	945 clinic cases; 435 controls	Case-control
Christen et al. 1992	17,824 male physicians without self-reported cataracts at baseline	5-year prospective

*Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
†OR = Odds ratio.
‡CI = Confidence interval.
§RR = Relative risk.

Cataract assessment	Results
No type specified; surgical cases	Heavy smoking was twice as common in cases; no data were reported; confounding was not addressed
Clinical exam for cataract type	Smoking was associated with cataracts (cataract type not stated, smoking not characterized)
No type specified; surgical cases	Heavy smoking (>75 pack-years*) was associated with cataracts, OR[†] = 1.97 (95% CI[‡], 1.05–3.67); confounding was not addressed
Clinical exam for nuclear, cortical, and posterior subcapsular opacities	Nuclear opacity was associated with current smoking: OR = 2.5 for light smokers (95% CI, 1.6–4.0), 2.7 for moderate (95% CI, 1.6–4.3), and 2.9 for heavy (95% CI, 1.4–5.9); also related to past heavy smoking, OR = 2.6 (95% CI, 1.4–5.0); there were no associations with past light to moderate smoking or with other cataract types
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	There was an association between cumulative pack-years and risk of nuclear opacities, p <0.004 (too few posterior subcapsular opacities to analyze); risk declined if participants had stopped smoking for 10 years; adjusted for age and gender
Photographs for nuclear, cortical, and posterior subcapsular cataracts; Lens Opacities Classification System II used	Nuclear cataracts were associated with current smoking, OR = 1.68 (95% CI, 1.03–2.75); there were no associations with other cataract types or any analyses of former smokers; adjusted for confounders
Self-reported development of cataracts; medical records for date of diagnosis, date of extraction, type, and loss of vision	For current smokers of 20 cigarettes/day, RR[§] = 2.24 for nuclear (95% CI, 1.47–3.41) and 3.17 (95% CI, 1.81–5.53) for posterior subcapsular cataracts; there was no association with <20 cigarettes/day; former smokers had no increased risk of nuclear or posterior subcapsular cataracts; adjusted for confounders

Table 6.27 Continued

Study	Population	Design
Association found		
Hankinson et al. 1992	50,828 female nurses without self-reported cataracts at baseline	Approximately 8-year prospective
Klein et al. 1993b	Population-based sample of 4,926 adults	Cross-sectional
West et al. 1995	442 male fishermen with photographs 5 years apart	5-year prospective for incidence and progression
Cumming and Mitchell 1997	Population-based sample of 3,654 adults	Cross-sectional
Hiller et al. 1997	660 members of Framingham Eye Study with no lens opacities	12.5-year prospective
Leske et al. 1998	764 of 1,380 participants in a case-control study	4-year prospective of cases and controls
Christen et al. 2000	20,907 male physicians with no cataracts at baseline	13-year prospective

Cataract assessment	Results
Self-reported cataract extractions; medical records for type	Smokers of 65 pack-years had increased risks for nuclear cataracts, RR = 1.79 (95% CI, 0.83–3.88), and posterior subcapsular cataracts, RR = 2.59 (95% CI, 1.59–4.50) (few current smokers, few cases of nuclear cataracts); former smokers had no increased risk unless they had smoked 35 cigarettes/day; adjusted for confounders
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wisconsin grading system used	Smoking was associated with nuclear opacity, OR = 1.09 for 10 pack-years (95% CI, 1.04–1.16), and with posterior subcapsular cataracts among men, OR = 1.05 (95% CI, 1.00–1.11), and women, OR = 1.06 (95% CI, 0.98–1.14); former smokers were not studied; adjusted for confounders
Photographs for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	OR for current smokers = 2.45 (95% CI, 1.00–6.04) for progression of nuclear opacity, which was associated with interim 5-year smoking, OR = 1.18 (95% CI, 1.06–1.32) for pack-years in 1 pack-year increments; adjusted for baseline severity and age; there was no association with incident nuclear opacity
Photographs of nuclear, cortical, and posterior subcapsular opacities; Wisconsin cataract system used	Ever smokers had increased ORs for nuclear opacity, OR = 1.3 (95% CI, 1.1–1.6), and posterior subcapsular opacity, OR = 1.5 (95% CI, 1.1–2.1); there was no risk for cortical opacity; former smokers (no time since quitting was specified) had similar risks
Clinical exam for nuclear, cortical, and posterior subcapsular opacities; Wilmer grading system used	Light smoking at baseline was associated with incident nuclear opacity, OR = 1.68 (95% CI, 1.14–2.49), as was heavy smoking, OR = 2.37 (95% CI, 1.43–3.93); former smokers (but could be interim smokers) had an increased risk of incident nuclear opacity, OR = 2.02 (95% CI, 1.14–3.57); there was no association with other cataract types
Photographs for nuclear, cortical, and posterior subcapsular opacities; Lens Opacities Classification System III used	There was an increase in nuclear opacity with smoking at baseline, RR = 1.58 (95% CI, 1.06–2.35); interim smoking, quitting smoking, and other opacities were not studied
Self-reported development of cataracts; medical records with dates of diagnosis and extraction, and loss of vision (type not specified)	Former smokers had a lower risk of cataracts (type not specified) compared with current smokers, and a lower risk of cataract surgery, adjusting for number of cigarettes smoked and other confounders, RR = 0.79 (95% CI, 0.67–0.92)

Table 6.27   Continued

Study	Population	Design
No association found		
Bochow et al. 1989	Posterior subcapsular cataract cases and controls	Case-control
Italian-American Cataract Study Group 1991	1,008 clinic cases; 469 controls	Case-control
Mohan et al. 1989	1,441 patients in India with cataracts; 549 controls	Case-control

Epidemiologic Evidence

Two methodologic issues add to the complexity of assessing the relationship between AMD and smoking. The first issue is that advanced, or severe, AMD mostly occurs in the very old. About 7 percent of the white population aged 75 years and older will have advanced AMD (Klein et al. 1992). The second issue is that life expectancy of smokers is less than that of nonsmokers, so selective survival of smokers to even develop AMD is an issue. Together, the relatively low incidence of AMD and the low prevalence of smoking in very elderly populations diminish the power to detect associations in all but the largest studies, which is evident in the population-based studies of AMD that have low numbers of cases of severe AMD.

One way to circumvent the problem is to study the association of smoking in precursor lesions or early AMD; however, there is no uniform agreement on the clinical signs of early AMD. Many of the signs currently in use are common in the population and can be so unstable as to be almost uninformative about who will develop advanced AMD. Data are accumulating on predictors of advanced AMD, the presence of very large drusen, and the retinal area covered by drusen. In part, the difficulty of determining the relevant early signs may be due to the limitations of photographic systems to detect such changes in, for example, Bruch's membrane; for research purposes, however, no alternative detection systems are available for accurately detecting early changes.

With these caveats in mind, the research findings to date suggest a strong likelihood that smoking is related to advanced or severe AMD, particularly exudative AMD, but there is scant evidence that smoking is related to the apparent early signs of AMD (Table 6.28). One cross-sectional, population-based study (Smith et al. 1996) found increased odds of early AMD among smokers compared with nonsmokers (OR = 1.89 [95 percent CI, 1.25–2.84]). However, two others, using identical grading methods, found no increased odds (Klein et al. 1993c; Delcourt et al. 1998). In another cross-sectional survey of fishermen who were heavy smokers, a paradoxical protective effect was seen for smoking and the odds of early AMD, primarily cases of moderate drusen (West et al. 1989b). A prospective cohort study of the risk of developing early signs of AMD found an increased risk of developing large (>250 µm) drusen among smokers compared with lifetime nonsmokers; the RR was 3.21 (95 percent CI, 1.09–9.45) among men and 2.20 (95 percent CI, 1.04–4.66) among women. No other early sign was associated with smoking (Klein et al. 1998). The lack of association with presumed early AMD may be due to the imprecision of the signs chosen to represent early AMD, thus biasing the results toward the null. Further work on improving this classification is warranted. It is also possible that smoking is related to progression of AMD to the exudative form but not to the onset of early lesions.

Gender differences appear in the findings as well. In one case-control study of severe AMD, the relationship with smoking was observed in men only (Hyman et al. 1983). In one prospective cohort study in a population having primarily early AMD, progression of AMD among smokers was observed with a dose-response pattern only among men (Klein et al. 1998).

Cataract assessment	Results
Chart reviews for and absence of posterior subcapsular cataracts	Current and former smoking were not related to posterior subcapsular cataracts
Slit lamp exam for nuclear, cortical, and posterior subcapsular cataracts; Lens Opacities Classification System I used	Compared never, former, and current smokers among cases and controls; no differences were reported (data were not shown)
Nuclear, cortical, and posterior subcapsular cataracts on clinical exam; no grading scheme described	Compared never, former, and current smokers among cases and controls; no differences were reported (data were not shown)

A prospective cohort study of exudative AMD among men found a benefit of quitting smoking after 20 years of cessation (Christen et al. 1996), but a similar study among women found no benefit after 15 or more years of cessation (Seddon et al. 1996). There are not evident explanations for these differences, except that the significantly lower prevalences of smoking among women may reduce the power to detect associations with AMD, especially if heavy smoking is the risk-determining factor.

The strongest and most consistent association seen in the literature is the association of current smoking and risk of severe AMD, especially exudative AMD. Because several studies tended to combine atrophic and exudative AMD into "late" or "severe" AMD, it is difficult to know whether to attribute the association to either one or both, unless specified. Four case-control studies have been reported to date. A large case-control study of exudative disease (Eye Disease Case-Control Study Group 1992) found an increased OR with current and past smoking of 2.2 (95 percent CI, 1.4–3.5) and 1.5 (95 percent CI, 1.2–2.1), respectively. Three other case-control studies also found an increased risk for severe AMD in smokers, with estimated ORs between 2 and 3 (Hyman et al. 1983; Macular Photocoagulation Study Group 1986; Tamakoshi et al. 1997). Four cross-sectional, population studies found increased odds of exudative AMD among current smokers, with ORs between 1.5 and 3.6; two of the four studies found a dose-response relationship. Two of the four cross-sectional studies found increased odds of atrophic AMD with current smoking (Vinding et al. 1992; Smith et al. 1996), but the other two did not

(Klein et al. 1993c; Vingerling et al. 1996). Two prospective studies found a significant association with either exudative disease or severe AMD in current heavy smokers (20 or more cigarettes per day) (Christen et al. 1996; Seddon et al. 1996). Former smokers also had an increased risk of AMD, although lower than that for current heavy smokers. Quitting more than 20 years previously appeared to decrease the risk in two cross-sectional studies (Vingerling et al. 1996; Delcourt et al. 1998), as well as in a prospective cohort study in men (Christen et al. 1996). In the prospective study in women (Seddon et al. 1996), however, quitting 15 or more years prior did not decrease the risk of severe AMD.

The data from cross-sectional studies suggest that passive smoking is not related to early or late AMD (Klein et al. 1993c; Smith et al. 1996). There are no corroborating data from animal models. Although animal models of induced retinal damage exist, no good animal models present the spectrum of features of AMD.

Evidence Synthesis

These data provide evidence that current smoking is associated with exudative AMD and possibly atrophic AMD. Dose-response relationships with the amount of smoking have been described. Maintaining smoking cessation at least 20 years decreased the risk of severe AMD and exudative AMD. The possibility that smoking is associated with the neovascular form of AMD is further bolstered by the findings from a study of ocular histoplasmosis (Ganley 1973), where

neovascularization can result from the infection. In that study, smokers were twice as likely as nonsmokers to develop disciform scars. Moreover, in a clinical trial of photocoagulation to halt progression of neovascularization, smokers were more likely than nonsmokers to have recurrent neovascularization over time (Macular Photocoagulation Study Group 1986). However, smoking did not predict development of neovascularization in the previously unaffected companion eyes of the eyes with neovascularization (Macular Photocoagulation Study Group 1997).

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

Implications

There is a need for more research into gender differences, dose-response relationships, and a possible threshold effect. Further research is also needed to determine the effect of smoking cessation on the risk of neovascular AMD.

Diabetic Retinopathy

Diabetic retinopathy is a serious ocular complication of diabetes associated primarily with long-term duration of diabetes and poor control in both type 1 and type 2 diseases. The retinopathy is likely the result of vascular changes occurring in the retinal circulation that feeds the inner layers of the retina. Diabetic retinopathy in the early stages (mild, nonproliferative retinopathy) is characterized by excessive permeability of the vasculature, with ballooning of the retinal capillaries to form microaneurysms, dot hemorrhages, and hard and soft exudates. Preproliferative retinopathy includes, in addition to the aforementioned features, vascular occlusion and dilation and/or venous beading. Proliferative diabetic retinopathy is characterized by new vessel growth or fibrous proliferation or both. Vitreous hemorrhage secondary

to the neovascularization also may be seen. Clinically significant macular edema, the result of extensive vessel leakage, can be a feature of chronic diabetic eye disease that may occur at any stage of the process. The prevalence of diabetic retinopathy increases with duration of diabetes, and most persons with diabetes have signs after 10 years' duration. Moreover, diabetic retinopathy is an important cause of vision loss. Although photocoagulation is an effective means of treating proliferative diabetic retinopathy, too often the retinopathy is not diagnosed at an early stage when treatment can be maximally effective.

Biologic Basis

Several investigators have postulated that smoking may contribute to the onset of diabetic retinopathy and/or drive progression of existing retinopathy through its effect on the retinal circulation (Morgado et al. 1994). If such relationships exist, one mechanism of action is likely to be hypoxia from chronic exposure to carbon monoxide, which may be toxic to retinal vasculature. Carbon monoxide also is associated with separation of arterial endothelial cells, causing edema, which also is a feature of diabetic retinopathy. Nicotine exposure increases levels of plasma vasoconstrictors, such as angiotensin and vasopressin, which have binding sites on retinal blood vessels. In addition, nicotine exposure increases platelet adhesiveness, and persons with diabetic retinopathy are more likely to have increased platelet aggregation compared with persons with diabetes but without retinopathy. Although there is a reasonable biologic basis to the hypothesis that smoking is related to diabetic retinopathy, the data suggest otherwise.

Epidemiologic Evidence

Many studies have examined the association between smoking and diabetic retinopathy (Table 6.29), and the data from several studies do not support the proposed association. The well-controlled studies, including prospective cohort studies in large populations of persons with diabetes, found no association between smoking and the amount smoked and the prevalence, incidence, or progression of diabetic retinopathy (Klein et al. 1983; Moss et al. 1991, 1996). Studies that found an association in general did not adjust for level of control of diabetes, a major risk factor for diabetic retinopathy. One study did adjust for level of control and other risk factors and found an

association between smoking and a six-year progression of diabetic retinopathy (Mühlhauser et al. 1996). However, progression was defined as any progression, from onset of diabetic retinopathy to becoming blind, if proliferative diabetic retinopathy was present at baseline. There were no data shown on whether smokers tended to have worse retinopathy at baseline, but the analyses should have adjusted for baseline status of diabetic retinopathy as a risk factor for progression. When the progression was confined to the subgroup with no retinopathy at baseline, smoking was not significantly associated with either the incidence or progression of diabetic retinopathy.

Evidence Synthesis

Although smoking might plausibly worsen diabetic retinopathy, the evidence is inconsistent. The strongest studies, the prospective cohort studies, do not show an association. The level of diabetes control is a potential major confounder that has not been considered in a number of the studies.

Conclusion

1. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

Implication

As research on diabetes continues, possible effects of smoking should be reassessed.

Glaucoma

Glaucoma is the third leading cause of blindness worldwide (Thylefors et al. 1995). In the United States, African Americans and Hispanics are more affected than other groups. Glaucoma is a disease characterized by loss of retinal ganglion cells, probably through a variety of mechanisms. The two main types of primary glaucoma are primary open-angle glaucoma and angle closure glaucoma. The angle refers to the angle between the iris and trabecular meshwork in the anterior chamber, which if shallow or closed impedes outflow of aqueous fluid and causes a rise in pressure. There are distinct differences between the two types of glaucoma, and their distribution differs in populations. In the United States, primary open-angle glaucoma is the more common type.

Biologic Basis

There is no evident basis for proposing that smoking might predispose a person to either developing glaucoma or having more severe glaucoma. Investigators have proposed that factors that diminish perfusion of the optic nerve head with blood may be associated with glaucoma. Because smoking affects the retinal circulation (although any direct effect of smoking on the optic nerve head is unknown), several investigators have examined the association of glaucoma with smoking. However, the effects of smoking on blood flow in ocular circulation are difficult to measure, in part because studies often do not consider separating acute effects in smokers and nonsmokers from the chronic effects that result from repeated exposures. The role of smoking in altering intraocular pressure also is variable. In one study (Shephard et al. 1978), smoking (including cumulative consumption) was not associated with intraocular pressure differences.

Evidence Synthesis

The few epidemiologic studies conducted (Table 6.30) do not indicate any relationship between smoking and glaucoma. Three cross-sectional studies found no association between smoking and glaucoma (Klein et al. 1993a; Ponte et al. 1994; Leske et al. 1995), and one prospective cohort study found no increased risk of glaucomatous field loss among persons with ocular hypertension who smoked compared with those who did not smoke (Quigley et al. 1994). The association has not been evaluated in angle closure glaucoma, but there is little biologic basis for proposing such a relationship.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

Implication

As further studies of glaucoma are undertaken, the role of smoking should remain under investigation.

Table 6.28   Studies on the association between smoking and age-related macular degeneration (AMD)

Study	Population	Design
Paetkau et al. 1978	114 cases of exudative AMD from 1 clinic	Cross-sectional
Maltzman et al. 1979	30 persons with AMD and 30 normal controls from 1 clinic matched for age, gender, and race	Case-control
Hyman et al. 1983	162 persons with AMD and 175 controls from 34 practices matched for age and gender	Case-control
Blumenkranz et al. 1986	26 persons with exudative AMD compared with 23 controls matched for age and gender (spouses or partners)	Case-control
Macular Photocoagulation Study Group 1986	119 eyes with neovascular AMD assigned to argon laser photocoagulation	3-year prospective
West et al. 1989b	838 male fishermen, 96 with early AMD (large drusen, confluence, and hyperpigmentation)	Cross-sectional
Eye Disease Case-Control Study Group 1992	421 persons with neovascular AMD from 5 centers; 615 controls (control group matched for age, gender, race, and center)	Case-control
Vinding et al. 1992	Population-based sample of 773 participants in Copenhagen aged 60 years; 88 cases of atrophic AMD and 24 of exudative AMD	Cross-sectional
Klein et al. 1993c	Population-based sample of 4,771 participants aged 43 years; 41 cases of exudative AMD and 29 of atrophic AMD	Cross-sectional

*OR = Odds ratio.

†CI = Confidence interval.

‡RR = Relative risk.

AMD assessment/type studied	Results
Fluorescein angiography	Current smokers had an earlier age of onset of vision loss (64 years) compared with nonsmokers (71 years), p <0.001
Data were not reported	10 persons with AMD reported smoking at some point, compared with 7 controls; no association was concluded
Diagnosis of drusen and/or macular degeneration confirmed by fundus photographs	Male smokers (not defined) had an increased risk of AMD: OR* = 2.6 (95% CI†, 1.2–5.8); there was no dose-response pattern
Fundus photographs to determine cases and controls without AMD	Smokers were not significantly more likely to have exudative AMD, OR = 1.3 (95% CI, 0.3–4.4)
Angiograms showing choroidal neovascularization within 200–2,500 μm of the fovea; outcome: recurrence of choroidal neovascularization on photographs	Current smokers of 10 cigarettes/day had greater rates of choroidal neovascularization recurrences, RR‡ = 1.8 (p <0.02); dose-response was not studied
Fundus photographs to diagnose AMD	Ever smokers had a lower risk than never smokers of AMD, OR = 0.54 (95% CI, 0.30–0.95); there was no dose-response relationship after adjusting for confounders
Physician-diagnosed AMD with visual loss, drusen, and 1 of several signs of choroidal neovascularization; verification by fundus photographs	Current smoking was associated with neovascular AMD, OR = 2.2 (95% CI, 1.4–3.5); former smokers also had an increased risk, OR = 1.5 (95% CI, 1.2–2.1); dose-response was not studied
Physician-diagnosed atrophic and exudative AMD, with visual loss	Both atrophic OR = 2.5 (p <0.01) and exudative OR = 1.5 (p >0.05, small sample size) AMD cases were more likely to be found in smokers than in nonsmokers
Fundus photographs; Wisconsin grading scheme used for early and late AMD	There was no relationship of early AMD (drusen characteristics, pigmentary disturbances) to smoking status, dose, or passive smoking; current smokers had a higher frequency of exudative AMD, OR = 2.50 (95% CI, 1.01–6.20) among women and 3.29 (95% CI, 1.03–10.5) among men; it was not associated with passive smoking; a dose-response pattern was reported only for women; there was no association with atrophic AMD

Table 6.28   Continued

Study	Population	Design
Christen et al. 1996	21,157 male physicians aged 40 years with no AMD at baseline, followed for 7 years; 268 had AMD with vision loss and 64 had exudative AMD	Prospective
Seddon et al. 1996	31,843 female nurses aged 50 years with no AMD at baseline, followed for 2–12 years; 215 had AMD with vision loss and 77 had exudative AMD	Prospective
Smith et al. 1996	Population-based study of 3,654 participants aged 49 years; 50 cases of exudative AMD and 22 of atrophic AMD	Cross-sectional
Vingerling et al. 1996	Population-based study of 6,251 participants aged 55 years; 65 cases of neovascular AMD and 36 of atrophic AMD	Cross-sectional
Tamakoshi et al. 1997	56 cases of exudative AMD among Japanese men aged 50–69 years in 5 hospitals; 82 male controls with no macular changes (coming for physical exam)	Case-control

[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

AMD assessment/type studied	Results
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist	Current smokers of 20 cigarettes/day had an increased risk of AMD with vision loss, RR = 2.57 (95% CI, 1.70–3.90); there was no increased risk with smoking <20 cigarettes/day, RR = 1.18 (95% CI, 0.57–2.42); former smokers had an increased risk, RR = 1.30 (95% CI, 1.01–1.69); dose-response relationship was present; quitting for 20 years decreased the risk; current smokers (no dose was given) had an increased risk of exudative AMD, RR = 1.95 (95% CI, 0.89–4.24); no increased risk with former smoking; cases of AMD without vision loss had no association with smoking
Self-reports with vision loss of 20/30 or worse; chart review by ophthalmologist/optometrist; subset validated by fundus photographs	Current smokers had an increased risk of AMD with vision loss, RR = 1.7 (95% CI, 1.2–2.5), greatest in those smoking 25 cigarettes/day, RR = 2.4 (95% CI, 1.4–4.0); former smokers had an increased risk, RR = 1.8 (95% CI, 1.3–2.5); dose-response relationship was present; former smokers had RRs similar to current smokers with no evidence of effects from quitting even after 15 years; a dose-response relationship was also seen with exudative AMD
Fundus photographs graded according to Wisconsin grading scheme for early and late AMD	Current smokers had a higher prevalence of neovascular AMD, OR = 3.26 (95% CI, 1.45–7.33); atrophic AMD, OR = 4.94 (95% CI, 1.29–18.82); and early AMD, OR = 1.89 (95% CI, 1.25–2.84); ORs were elevated for neovascular and atrophic AMD, but not significantly for men; passive smoking was not associated with any AMD; there were no associations between late or early AMD and pack-years[§]
Fundus photographs graded according to Wisconsin grading system	Current smokers aged <85 years had an increased prevalence of neovascular AMD, OR = 3.6 (95% CI, 1.8–7.4); no increase in atrophic AMD; there was a dose-response relationship with 10 pack-years, OR = 9.1 (95% CI, 3.2–25.9); stopping smoking for 20 years decreased the risk of neovascular AMD among nonsmokers
Fundus photographs and fluorescein angiography	Neovascular AMD was associated with current smoking, OR = 3.07 (95% CI, 1.09–8.63), and former smoking, OR = 2.09 (95% CI, 0.71–6.13); a dose-response relationship was present, with a high risk for those who started smoking before 20 years of age, OR = 3.41 (95% CI, 1.20–9.73)

Table 6.28 Continued

Study	Population	Design
Delcourt et al. 1998	2,196 participants aged 60 years in a population-based survey; 41 cases of late AMD (neovascularization or geographic atrophy)	Cross-sectional
Klein et al. 1998	3,583 participants aged 43 years in a longitudinal, population-based study (reported low incidence of atrophic and exudative AMD)	5-year prospective

AMD assessment/type studied	Results
Fundus photographs graded according to Wisconsin grading system	Current smoking, OR = 3.5 (95% CI, 1.0–12.2), and former smoking, OR = 2.8 (95% CI, 1.1–6.9), were associated with late AMD (not further separated into atrophic vs. neovascular AMD); dose-response relationship was present; those who stopped smoking within 20 years had the same risk as current smokers; there were no associations with early AMD
Fundus photographs graded according to Wisconsin grading system	Current smokers were more likely to develop large (>250 μm) drusen compared with never smokers, RR = 3.21 (95% CI, 1.09–9.45) among men and 2.20 (95% CI, 1.04–4.66) among women; dose-response relationship was present; no other sign was associated; male (not female) current smokers progressed to age-related maculopathy in a dose-response pattern

Table 6.29   Studies on the association between smoking and diabetic retinopathy (DR)

Study	Population	Design
Paetkau et al. 1977	150 cases of diabetes	Cross-sectional; compared PDR* cases with DR cases
Christiansen 1978	180 patients with insulin-dependent juvenile-onset diabetes of different durations	Cross-sectional
West et al. 1980	973 Native Americans with adult-onset diabetes	Cross-sectional
Gray et al. 1982	194 patients with type 1 diabetes with varying levels of DR	Cross-sectional
Klein et al. 1983	467 patients with younger-onset (diagnosed before 30 years of age and taking insulin) and 1,039 with adult-onset diabetes	Cross-sectional
Telmer et al. 1984	688 patients with insulin-dependent diabetes with a duration of 12–40 years	Cross-sectional
Rand et al. 1985	111 patients with insulin-dependent diabetes with PDR and 81 patients with diabetes with no or minimal DR	Case-control, matched for duration of diabetes
Sjolie 1985	577 insulin-treated patients with diabetes aged 10–70 years	Cross-sectional
Walker et al. 1985	193 diabetic patients	Cross-sectional
Ballard et al. 1986	Population-based group of 1,031 patients with adult-onset diabetes	Prospective, up to 20 years
Mühlhauser et al. 1986	192 smokers and 192 nonsmokers with type 1 diabetes	Matched case-control
Borch-Johnsen et al. 1987	184 survivors of long-term insulin-dependent diabetes participating in a prospective study	Cross-sectional
Kingsley et al. 1988	754 patients with insulin-dependent diabetes	Cross-sectional

*PDR = Proliferative diabetic retinopathy.
†NR = Data were not reported.
‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
§OR = Odds ratio.

Diabetes/DR assessment	Results
NR[†]	Smoking was associated with PDR in patients with a long duration of diabetes; there was no adjustment for level of control of diabetes
Standard exam/clinical observer of DR	Smoking was not associated with DR or PDR
Standard exam/clinical exam for DR	Smoking was not associated with DR or PDR
Standard exam/not stated	Patients with DR were more likely to be smokers, likely explained by level of diabetes control; no dose-response pattern was noted
Fasting glucose/fundus photographs graded according to the modified Arlie House Classification	There were no associations between smoking, pack-years[‡], and DR or severity of DR
Clinic records/clinical exam and fluorescein angiogram for PDR	Smoking, smoking dose, and former smoking were not associated with PDR
Standard exam/PDR on stereo fundus photographs graded according to the modified Arlie House Classification	Smoking was not associated with PDR
Clinic reports/clinical exam for DR	There was an increased risk of any DR with smoking, OR[§] = 1.9; not adjusted for control of diabetes
Clinic records/clinical exam for DR	Smoking was related to DR in men, not in women; not adjusted for level of control of diabetes
Standard exam/DR by clinical exam	Smoking was not associated with incidence of DR or PDR
Clinic records/DR assessed by ophthalmologist	Smokers had more PDR compared with nonsmokers (12.5 vs. 6.8%); no increased risk of all DR; not adjusted for level of control of diabetes
Clinic records/clinical exam, DR graded in nonstandard fashion	Smoking was not associated with DR or PDR
Standard exam/58 patients had angiography, otherwise self-reported	There were no differences in percentages for smokers with and without severe retinopathy; there were no adjustments for other factors

Table 6.29   Continued

Study	Population	Design
Moss et al. 1991	668 patients with early-onset and 1,379 with adult-onset diabetes	4-year prospective for incidence and progression of DR
Marshall et al. 1993	277 patients with type 1 diabetes with durations of 5 years	Prospective for 1 years (mean follow-up = 2.7 years)
Klein et al. 1995	765 patients with younger-onset (diagnosed under 30 years of age and taking insulin) and 533 with older-onset diabetes with a 10-year follow-up	10-year prospective
Moss et al. 1996	708 persons with early-onset and 987 with adult-onset diabetes	10-year prospective for progression of DR
Mühlhauser et al. 1996	636 patients with type 1 diabetes	6-year prospective for progression of DR
Sinha et al. 1997	100 patients with insulin-dependent diabetes (53 smokers)	Prospective for up to 6 years

*PDR = Proliferative diabetic retinopathy.

Diabetes/DR assessment	Results
Fasting glucose/fundus photographs graded according to modified Arlie system	Smoking was not associated with incidence or progression in either group with diabetes
Not stated/DR by fundus photographs graded according to modified Arlie classification	Smoking was not associated with a transition to DR in a consistent manner
Fasting glucose/fundus photographs graded according to modified Arlie system	10-year incidence of diabetic macular edema was not related to smoking history
Fasting glucose/fundus photographs graded according to modified Arlie system	Pack-years, pack-years while diabetic, and smoking status were not associated with incidence and progression of DR or progression to PDR*
Standard exam for diabetes/DR by clinical exam and photographs; grading system not described	Pack-years smoked while diabetic were associated with any progression; not adjusted for baseline status: OR = 1.44/10 pack-years (95% confidence interval, 1.10–1.88); there were no associations of smoking variables with incidence of or progression to PDR in the group with no DR at baseline; adjusted for level of control and duration of diabetes
NR	Smokers had more DR at baseline and follow-up; no adjustment for level of control of diabetes

Table 6.30   Studies on the association between smoking and glaucoma

Study	Population	Design	Glaucoma assessment	Results
Morgan and Drance 1975	Cases of glaucoma diagnosed by multiple ophthalmologists; neighborhood controls	Case-control	Data were not reported	Smoking was not related to glaucoma
Wilson et al. 1987	83 cases, 237 controls matched for age and gender	Case-control	Visual fields, cup and optic disc, and intra-ocular pressure on chart; controls without glaucoma	Smoking was related to glaucoma, odds ratio = 2.9 (95% confidence interval, 1.3–6.6)
Klein et al. 1993a	Population-based survey of 4,926 whites aged 43 years (104 cases of glaucoma)	Cross-sectional	Visual fields, intraocular pressure, and cup-to-disc ratio on photo-graphs	Smoking was not related to glaucoma
Ponte et al. 1994	44 cases of glaucoma or elevated intra-ocular pressure (24 mm Hg); 220 controls with intraocular pressure <21 mm Hg	Cross-sectional	Visual fields and elevated intraocular pressure	Smoking was not related to glaucoma
Quigley et al. 1994	647 persons with ocular hypertension, followed for 1–12 years	Prospective	Intraocular pressure >21 mm Hg (ocular hyper-tension); visual field loss at follow-up	Smoking was not related to incident visual field loss
Leske et al. 1995	Population-based study of 4,314 Barba-dian blacks (302 glaucoma cases)	Cross-sectional	Visual fields and optic disc	Smoking was not related to glaucoma

Other Eye Diseases: Graves' Ophthalmopathy

Several other eye diseases have been investigated for an association with smoking. Most were not reviewed for this report, however, because the data are insufficient to reach any conclusions. The one exception is an uncommon condition—Graves' ophthalmopathy, an ocular complication of Graves' disease.

Graves' disease is thought to be an autoimmune disease of the thyroid. It is likely that both genetic and environmental factors are related to the risk of the disease. Among its clinical manifestations, the ophthalmologic complications appear to be related to smoking. Graves' ophthalmopathy is characterized by proptosis (protrusion of the eyeball), diplopia (double vision), optic neuropathy, and conjunctival and periorbital inflammation. The pathogenesis of Graves' ophthalmopathy is not completely understood, but it appears to involve the orbital fibroblasts that are stimulated to release glycosaminoglycans, which in turn are related to the orbital edema seen with the ocular complications. Recent data suggest an autoimmune basis for Graves' ophthalmopathy as well (Bahn 2000).

Biologic Basis

The mechanism by which smoking may cause or aggravate Graves' ophthalmopathy is unknown. Orbital hypoxia and effects of thiocyanate have been postulated, and other research has investigated the effect of smoke constituents on orbital fibroblast activity. Researchers investigating the role of hypoxia in muscular inflammation have found stimulation of protein synthesis and proliferation of extra-ocular, muscle-derived fibroblasts under hypoxic conditions (Metcalfe and Weetman 1994). Smoking does not appear to affect serum concentrations of proinflammatory cytokines in Graves' disease, even among persons with ocular complications (Salvi et al. 2000).

Epidemiologic Evidence

Seven studies (Table 6.31) found an increased risk associated with smoking of developing the ophthalmologic complications of Graves' disease (Hägg and Asplund 1987; Shine et al. 1990; Tellez et al. 1992; Prummel and Wiersinga 1993; Winsa et al. 1993; Pfeilschifter and Ziegler 1996; Bartalena et al. 1998); three found a dose-response relationship with the number of cigarettes smoked (Shine et al. 1990; Tellez et al. 1992; Pfeilschifter and Ziegler 1996). The studies, while consistent, are limited in number and the sample sizes of some are small. The severity of the ophthalmopathy was associated with smoking in two studies (Prummel and Wiersinga 1993; Winsa et al. 1993). Estimates of the OR varied between 2 and 10, depending on the control population selected. The effect of quitting smoking on Graves' ophthalmopathy has not been well studied and would provide convincing evidence of a causal relationship. On the basis of the findings of the epidemiologic studies, several investigators are studying the effect of smoking on the thyroid gland and the extra-ocular, muscle-derived fibroblasts.

Evidence Synthesis

Although there are suggestive epidemiologic findings, the biologic basis for a role of smoking in Graves' ophthalmopathy is unclear. The epidemiologic data are still limited, although consistent in indicating an increased risk in smokers. Dose-response is not well documented.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Implication

Data on the role of smoking cessation in preventing or lessening the severity of the ophthalmopathy would be important to understanding the relationship between Graves' disease and smoking.

Table 6.31   Studies on the association between smoking and Graves' ophthalmopathy

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Hägg and Asplund 1987	12 persons with Graves' ophthalmopathy, 24 controls with Graves' disease and no ophthalmopathy, 48 population controls	Case-control	Clinical exam	Smoking increased the OR* of ophthalmopathy compared with no ophthalmopathy among persons with Graves' disease, OR = 10.0 (95% CI[†], 1.4–74.3), and with population controls, OR = 20.2 (95% CI, 2.8–144.8)
Shine et al. 1990	85 patients with ophthalmopathy, 62 with Graves' disease, 81 controls without Graves' disease	Case-control	Clinical exam	Cases of ophthalmopathy were more likely to be smokers than healthy controls or controls without ophthalmopathy; dose-response pattern was reported
Tellez et al. 1992	155 patients with newly diagnosed Graves' disease	Cross-sectional	Clinical exam, using American Thyroid Association Classification system	Ophthalmopathy prevalence was higher in smokers and in former smokers, OR = 2.4 (95% CI, 1.1–5.2); there was a dose-response pattern with cigarette-years[‡]
Prummel and Wiersinga 1993	100 cases of Graves' ophthalmopathy, 100 cases of Graves' disease without ophthalmopathy, 175 cases of goiter, 75 cases of hyperthyroidism, 400 controls	Case-control	Clinical exam	Graves' ophthalmopathy cases and severe cases (classified by total eye score) were adjusted for gender, age, and education, and were more likely to be smokers, OR = 6.5 (95% CI, 3.8–11.2), compared with controls; there was no dose-response pattern with an increasing severity of eye disease; smoking was not associated with other thyroid diseases
Winsa et al. 1993	208 patients with newly diagnosed Graves' disease and 72 cases of Graves' with ophthalmopathy	Cross-sectional	Clinical exam	Patients with ophthalmopathy were more likely to be current and former smokers compared with patients without ophthalmopathy, 63 vs. 45%; there was an increased prevalence of smoking with an increase in the severity of ophthalmopathy

*OR = Odds ratio.
[†]CI = Confidence interval.
[‡]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Table 6.31   Continued

Study	Population	Design	Diagnosis of ophthalmopathy	Results
Pfeilschifter and Ziegler 1996	253 patients with recent onset of Graves' disease	1 year prospective	Clinical exam/patient report of double vision (diplopia) and exophthalmometer readings >20 mm (proptosis)	Current smoking was associated with incidence of symptomatic ophthalmopathy, OR = 1.3 (95% CI, 1.1–1.6), proptosis, OR = 2.6 (95% CI, 1.8–3.9), and diplopia, OR = 3.1 (95% CI, 1.7–6.0); there was a dose-response relationship; former smokers had no increased risk
Bartalena et al. 1998	300 patients with mild ophthalmopathy receiving 1 of 2 treatments, 150 patients with severe ophthalmopathy	Prospective, for risk of progression	Degree of ophthalmopathy assessed by clinical exam, masked to smoking status	Mild ophthalmopathy was more likely to progress among smokers and less likely to improve with treatment; severe ophthalmopathy was less likely to respond to treatment among smokers

Peptic Ulcer Disease

In the early 1990s, the central role played by the bacterium *Helicobacter pylori* (*H. pylori*) in both the incidence and recurrence of peptic ulcer disease was recognized (Kuipers et al. 1995). This section reviews the evidence of an association between smoking and peptic ulcer disease in light of this new understanding of the pathogenesis of ulcer disease. Relevant articles were identified through a MEDLINE search from 1985 through June 2000 using the following terms: "ulcer and smoking and pylori" and "smoking and pylori and eradication." A further search was performed for the years 1998 through June 2000, using the terms "ulcer and smoking" to identify any major studies that were not included in the previous Surgeon General's report (USDHHS 2001), even though the studies had not evaluated *H. pylori*.

Conclusions of Previous Surgeon General's Reports

Numerous studies have demonstrated an association between smoking and the occurrence of peptic ulcer disease. This evidence was reviewed in the 1964, 1971, and 1972 Surgeon General's reports on smoking and health (USDHEW 1964, 1971, 1972). The 1979 report concluded that cigarette smoking was significantly associated with both the incidence and an increased risk of dying from peptic ulcer disease: "the association between smoking and peptic ulcer disease is significant enough to suggest a causal relationship" (USDHEW 1979, p. 1-23). In addition, that report concluded that there was highly suggestive evidence that smoking also retards ulcer healing. The 1990 report concluded that smokers had an increased risk of developing both duodenal and gastric ulcers, and smoking cessation reduced that risk (USDHHS 1990). That report also found that among smokers ulcer disease was more severe, duodenal ulcers were less likely to heal, and both duodenal and gastric ulcers were more likely to recur. Ulcer patients who stopped smoking, however, were found to have an improved clinical course compared with continuing smokers. Although much of this previous evidence was based largely on studies of men, the more recent Surgeon General's report on women and smoking (USDHHS 2001) concluded that women who smoked also had an increased risk of peptic ulcer disease.

Biologic Basis

In the decades since the 1964 Surgeon General's report, explanations of the pathogenesis of peptic ulcer disease have changed dramatically with the identification of the gastric bacterium *H. pylori* in a high proportion of patients with peptic ulcers (Marshall and Warren 1984). Up to 100 percent of duodenal ulcers and 70 to 90 percent of gastric ulcers are now associated with *H. pylori* infection (Kuipers et al. 1995). Most ulcers in persons without *H. pylori* infection were linked to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Borody et al. 1991, 1992a). Other causes of peptic ulcers, although rarer, include Crohn's disease and Zollinger-Ellison syndrome.

Normally, the gastrointestinal mucosa is protected from injury by, among other factors, a layer of mucus and the secretion of bicarbonate by gastric and duodenal epithelial cells to neutralize gastric acid. If these protective mechanisms are impaired, or if there is an increase in levels of damaging factors, then ulceration may occur.

Effects of Smoking on Gastrointestinal Physiology

The 1990 Surgeon General's report (USDHHS 1990) reviewed the effects of cigarette smoking on aspects of human gastrointestinal physiology relevant to peptic ulcer disease. Likely mechanisms whereby smoking could promote the development of peptic ulcer disease included the potential for tobacco smoke and/or nicotine to increase maximal gastric acid output and duodenogastric reflux and to decrease alkaline pancreatic secretion and prostaglandin synthesis.

Two subsequent reviews (Endoh and Leung 1994; Eastwood 1997) evaluating the potential effects of cigarette smoke and nicotine as injurious and protective factors that could play a role in peptic ulcer formation came to similar conclusions. Data on the effects of smoking on gastric acid secretion in humans have been highly inconsistent; multiple reports found that smoking and/or nicotine variously stimulated, inhibited, or had no effect on gastric acid secretion. However, there was more consistent evidence that smoking promotes reflux of duodenal contents into the stomach, and increases production of free radicals and the release of vasopressin, a potent vasoconstrictor. Protective mechanisms consistently affected by smoking were the chronic inhibition of gastric mucus secretion,

cytoprotective prostaglandin production, pancreatic and duodenal mucosal bicarbonate secretion, and a decrease in mucosal blood flow.

The mucosal protection mechanism most clearly affected by smoking is the pancreatic secretion of bicarbonate. A transient reduction in secretion is seen immediately after smoking, leading to a drop in pH in the duodenal bulb (Eastwood 1997). Acidity in the duodenal bulb appears to be the most important determinant for the development of gastric metaplasia in the duodenum, thus paving the way for duodenal colonization by *H. pylori* (Tytgat et al. 1993).

Results from studies evaluating mucosal blood flow among smokers and nonsmokers have been more varied, possibly because of a variation in the measurement methods. Taha and colleagues (1993) demonstrated that both gastric and duodenal mucosal blood flow were reduced in chronic NSAID users. However, after allowing for NSAID use, significantly reduced duodenal blood flow was seen only in *H. pylori*-positive smokers. There was no additional effect of either *H. pylori* infection or smoking on gastric mucosal blood flow.

Finally, some strains of *H. pylori* produce a vacuolating toxin that may be important in determining the virulence of the organism. This toxin induces vacuolation of HeLa cells in vitro, as does nicotine alone, but the addition of nicotine to *H. pylori* potentiates the vacuolating effect of the toxin (Cover et al. 1992).

In summary, studies document that smoking appears to have a multitude of effects on gastroduodenal physiology, and through a number of mechanisms it could promote peptic ulceration. These effects are, however, largely transient, and the affected physiologic measures return to normal within minutes or hours after smoking cessation (Eastwood 1997). These same studies also indicate that smoking could particularly increase the likelihood of ulceration in *H. pylori*-positive persons.

Smoking and *Helicobacter pylori* Infection

Both *H. pylori* infection (Malaty et al. 1992; EUROGAST Study Group 1993) and smoking (Bergen and Caporaso 1999) are more common among groups of lower SES. Cross-sectional studies that have evaluated the association between *H. pylori* infection and smoking in healthy volunteers consistently have reported higher infection rates in smokers (current or former) than in nonsmokers. In a study of 485 volunteers in the United States, current and former smokers were more likely to be seropositive for *H. pylori* than nonsmokers (among blacks, rates were 73 percent

among current smokers, 85 percent among former smokers, and 61 percent among nonsmokers; and among whites, rates were 40 percent, 48 percent, and 25 percent, respectively) (Graham et al. 1991). Infection also was slightly more common among 3,496 adult smokers in Northern Ireland (65 percent among former smokers, 57 percent among smokers of fewer than 20 cigarettes, and 64 percent among smokers of 20 or more cigarettes per day compared with 53 percent among people who had never smoked) (Murray et al. 1997). Similar findings were seen in a group of 273 adults from Melbourne, Australia, among current and former smokers (45 percent and 44 percent, respectively, compared with 31 percent in people who had never smoked) (Lin et al. 1998) and among 1,064 adult heavy smokers in New Zealand (38 percent in smokers of more than 20 cigarettes per day compared with 23 percent in smokers of less than 20 cigarettes per day and nonsmokers) (Collett et al. 1999). Similar patterns have been reported in adults visiting general practitioners in Germany (Brenner et al. 1997) and in patients receiving an endoscopic examination in the United Kingdom (Bateson 1993) and Malaysia (Goh 1997).

In some of these studies, the association between *H. pylori* and smoking was attenuated after adjusting for other factors, including age and SES. In both developed and developing countries, *H. pylori* infection is believed to occur during childhood (Xia and Talley 1997), and thus it is unlikely that smoking influences the risk of initial *H. pylori* infection to any great extent. It is unclear whether smoking could be a risk factor for the acquisition or persistence of *H. pylori* infection in adulthood or if low SES is a common, more distal risk factor for both *H. pylori* and smoking. These variables do not, however, alter the fact that smokers are more likely than nonsmokers to be infected with *H. pylori*. The link between *H. pylori* and peptic ulcer disease is well established; thus, it is important to consider whether smoking also is a risk factor or if some or all of the observed associations between smoking and peptic ulcer disease could be due to confounding by *H. pylori* infection status.

Trends in Peptic Ulcer Disease

During the past several decades, rates of hospitalization for and mortality from peptic ulcer disease in the United States have declined dramatically. Using hospitalization rates from the computerized database of the U.S. Department of Veterans Affairs, El-Serag and Sonnenberg (1998) showed that although gastric ulcers accounted for 67.6 and duodenal ulcers

for 168.8 out of every 10,000 hospitalizations of veterans from 1970–1974, comparable figures for 1990–1995 were 49.6 per 10,000 and 52.5 per 10,000, respectively. Similarly, using vital statistics data from CDC's National Center for Health Statistics, these two authors showed that mortality from gastric ulcer disease had fallen from 17.4 per million per year in 1968–1972 to 7.7 per million per year in 1988–1992, with a comparable drop in mortality for duodenal ulcer disease from 19.6 to 8.4 per million per year (El-Serag and Sonnenberg 1998). However, peptic ulcer disease still is a leading cause of morbidity. In 1989, the National Health Interview Survey included a special questionnaire on digestive diseases. Among approximately 42,000 adult respondents, 10 percent reported that they had ever had a physician-diagnosed peptic ulcer, one-third of whom also reported having a new or recurring ulcer in the past 12 months (Sonnenberg and Everhart 1996). Among the 50 percent who reported the site of their ulcer, gastric and duodenal ulcers were equally common overall, although nonwhites reported gastric ulcers more frequently and duodenal ulcers less frequently than whites. When recurrent ulcers (defined as a relapse in the past 12 months of a previously diagnosed ulcer) were excluded, the incidence of new peptic ulcers in 1989 was an estimated 52.7 per 10,000 (Everhart et al. 1998). Among those respondents who specified the site of the ulcer, the incidence of gastric ulcers (17.0 per 10,000) was about three times that of duodenal ulcers (6.1 per 10,000). This finding suggests that the incidence of new duodenal ulcers may have fallen more rapidly over time than that of gastric ulcers.

A large part of the decrease in peptic ulcer rates over the last few decades in the United States has been attributed to lower smoking rates (Kurata et al. 1986), although the same pattern was not seen in the United Kingdom (Sonnenberg 1986). However, the prevalence of *H. pylori* infection in developed countries also is believed to have declined over a similar time period (Banatvala et al. 1993; Kosunen et al. 1997), and it is this decline, rather than falling smoking rates, that may explain some or all of the reductions in ulcer rates.

Epidemiologic Evidence

Smoking and Development of Peptic Ulcer

Studies that evaluated the relationship between tobacco smoking and the development of peptic ulcer disease repeatedly have shown an increased risk of both duodenal and gastric ulcers among smokers (USDHEW 1979; USDHHS 1990). In some studies, this risk also has been observed to increase with increasing levels of smoking. During a 149,291 person-years follow-up of a cohort of 7,624 Japanese men in Hawaii, the age-adjusted incidence of gastric and duodenal ulcers increased with increasing levels of smoking at baseline (RR among nonsmokers and smokers of less than 24, 24 through 40, and greater than 40 pack-years: 1.0, 1.5, 3.1, and 3.8 [P_{trend} <0.01], respectively, for gastric ulcers and 1.0, 1.8, 2.4, and 3.3 [P_{trend} <0.01], respectively, for duodenal ulcers [Kato et al. 1992]). In contrast, an analysis of self-reported ulcer history, using data from the 1989 National Health Interview Survey in the United States, suggested that smoking may be a stronger risk factor for chronic ulceration than for the development of new ulcers (Everhart et al. 1998). Although these data show a strong relation between smoking and age-standardized prevalence of chronic active ulcers (1.8 percent, 3.0 percent, 3.9 percent, and 5.3 percent among nonsmokers and smokers of <20, 20, and >20 cigarettes per day, respectively), there was no association between smoking and the incidence of new ulcers.

Helicobacter pylori, *Smoking, and Peptic Ulcer*

Only a few studies have considered both smoking and *H. pylori* infection in relation to the incidence of peptic ulcer disease (Table 6.32). These studies largely have been cross-sectional surveys of patients referred for upper gastrointestinal endoscopy using variable definitions of smoking, and rarely presenting results that distinguished between smokers with and without *H. pylori* infection. No studies have separately evaluated the risk of peptic ulcers in former smokers after allowing for *H. pylori* infection.

Four of these studies were conducted with groups receiving endoscopic examinations. Martin and colleagues (1989) found no duodenal ulcers in 47 *H. pylori*-negative persons although 4 of them, all of whom were taking NSAIDs, had a gastric ulcer. Among the 60 *H. pylori*-positive persons, peptic ulcers were significantly more common in smokers than in nonsmokers. Similarly, Talamini and colleagues (1997) reported a significant association between duodenal ulcers and smoking after adjusting for *H. pylori* infection. In a Swiss study, smoking also appeared to be associated with an increased risk of duodenal ulcers, particularly among *H. pylori*-positive persons (Halter and Brignoli 1998). The lack of a single reference group in this study, however, makes comparisons with other studies difficult. In contrast, Schubert and colleagues (1993) reported no significant differences between the

proportion of smokers in patients with and without ulcers and, as a consequence, did not include smoking status in their multivariable models adjusting for *H. pylori*. It is possible, however, that the very broad definition of smoking used in this last study may have led to very light or occasional smokers being inappropriately classified as smokers, thus masking differences between patients with and without ulcers.

Two other studies used groups of company employees. Wang and colleagues (1996) conducted a case-control study in a factory in Shanghai, China. To prevent confounding by SES and gender, data were analyzed separately for men and women, drivers and workers (lower SES), and staff (higher SES). Among male workers and drivers (304 cases and 263 controls), current smoking was associated with a significantly elevated risk of peptic ulcer disease that increased with the amount of cigarettes smoked. A similar pattern was seen for duodenal ulcer disease alone. There was only one female employee smoker, and too few former smokers to evaluate risks in those groups. Although smoking status was assessed after the development of ulcers, smoking rates were high and few workers reported having stopped smoking. It is therefore unlikely that many employees changed their smoking behavior following ulcer diagnosis.

Schlemper and colleagues (1996) conducted parallel studies in companies in Japan and the Netherlands. Men and women with verifiable ulcer disease who had not been treated with *H. pylori* eradication therapy were compared with those without ulcers or prior gastric surgery. After adjusting for potential confounders, researchers found that daily smoking was associated with a nonsignificant increased risk of peptic ulcer disease only in the Dutch population. In this study, the majority of ulcers had been diagnosed a median of six years before smoking data were collected, and it is possible that employees with peptic ulcer disease may have changed their smoking behaviors over time.

There is a potential for bias in any of these studies if participants altered their smoking behaviors because of ulcer symptoms or if they misreported their smoking patterns. If ulcer patients tend to stop or reduce their smoking because of symptoms, or if they systematically underreport the amount they smoke, then the true associations between smoking and ulcers could be greater than those reported. Conversely, if ulcer patients actually increase their smoking in response to ulcer symptoms or if they systematically overreport the amount they smoke, then the observed associations could exaggerate the true effect. This latter situation would seem less likely than the former.

Nonsteroidal Anti-Inflammatory Drugs, Smoking, and Peptic Ulcer

The main cause of ulcers in persons negative for *H. pylori* infection, at least in developed countries, is the use of NSAIDs (Borody et al. 1991, 1992a). In the 1990 Surgeon General's report (USDHHS 1990), smoking was associated with peptic ulcer disease and acute gastric erosions in three studies of NSAID users. Since then, three more studies have evaluated the relationship between smoking and peptic ulcers in NSAID users, with conflicting results.

Hansen and colleagues (1996) compared 94 NSAID users admitted to a hospital with complications of peptic ulcers (predominantly bleeding or perforated ulcers) with 324 controls selected at random from all assumed NSAID users. Overall, cases were no more likely than controls to be smokers (44 percent and 41 percent, respectively), but after adjusting for age, gender, ulcer history, and duration of NSAID use, current smoking was associated with an almost twofold increased risk of ulcer complications (OR = 1.9 [95 percent CI, 1.0–3.6]).

In contrast, Aalykke and colleagues (1999) compared 132 current NSAID users diagnosed with bleeding peptic ulcers with 136 ulcer-free NSAID users selected from a rheumatology clinic and geriatrics department. Smokers were not at an increased risk of developing bleeding ulcers compared with controls (OR, adjusted for age, gender, ulcer history, *H. pylori* infection status, and NSAID dose = 0.91 [95 percent CI, 0.48–1.71]). Similarly, in a large case-control study in the United Kingdom, Weil and colleagues (2000) compared 1,121 patients diagnosed with bleeding peptic ulcers with 989 community controls. Information on *H. pylori* infection status was not available, but among NSAID users the risk for bleeding peptic ulcers (compared with nonsmokers who did not use NSAIDs) did not differ appreciably between current smokers (OR = 4.0 [95 percent CI, 2.9–5.5]) and nonsmokers (OR = 3.6 [95 percent CI, 2.9–4.5]).

Mortality from Peptic Ulcer

Large-scale cohort studies consistently have shown that smokers are at a greater risk of dying from peptic ulcer disease than nonsmokers (USDHHS 1990). Follow-up of the U.S. Veterans Study now has been extended to 26 years, with a total of 5.4 million person-years. Smoking information was collected only at baseline. To allow for the fact that many current smokers at baseline subsequently would have stopped smoking, the analysis was restricted to people who never smoked (who were unlikely to have started

Table 6.32 **Studies on the association between smoking and peptic ulcer disease, allowing for**
Helicobacter pylori (_H. pylori_) infection

Study/location	Population	Definition of smoking
Martin et al. 1989 United States	107 patients referred for endoscopy, including 14 with duodenal ulcers, 14 with gastric ulcers, and 19 healthy volunteers	>10 cigarettes/day
Schubert et al. 1993 United States	1,088 patients referred for endoscopy, including 107 with duodenal ulcer, 97 with gastric ulcer, and 5 with both duodenal and gastric ulcers	At least 1 cigarette 4 weeks before endoscopy
Schlemper et al. 1996 Japan and the Netherlands	215 Japanese and 493 Dutch employees in companies with periodic health screening, including 57 with past peptic ulcers (median 6 years since diagnosis) and 4 with current peptic ulcers	Daily smoking at time of interview
Wang et al. 1996 China	Factory employees: 500 (422 men) with any peptic ulcer within previous 2 years and 500 (396 men) ulcer-free employees	Current (15 and >15 cigarettes/day); former smokers excluded
Talamini et al. 1997 Italy	495 patients referred for endoscopy, including 69 with duodenal ulcers and 23 with gastric ulcers	1–10 or >10 cigarettes/day
Halter and Brignoli 1998 Switzerland	282 patients referred for endoscopy, including 24 with duodenal ulcers and 5 with gastric ulcers	Data were not reported

*OR = Odds ratio.
†CI = Confidence interval.

Results

Prevalence of peptic ulcers among *H. pylori*-positive patients:

Smokers	73%
Nonsmokers	27% (p <0.01)

No significant association was found between smoking and peptic ulcer: prevalence of smoking was 36.7% among ulcer-free group, 42.9% among duodenal ulcer group, and 34.0% among gastric ulcer group (no adjusted estimates provided)

OR (95% CI) adjusted for age, *H. pylori* infection, family history of peptic ulcers, and occupation, smokers vs. nonsmokers:

Netherlands (men only)	1.6 (0.5–4.9)
Japan (men and women)	0.8 (0.3–1.8)
	0.2 (0.1–0.9), duodenal ulcer only

OR* (95% CI[†]) adjusted for age, *H. pylori* infection, and family history of peptic ulcer among smokers vs. never smokers, by occupation group (men only):

	Workers/drivers	Staff
Any peptic ulcer		
15 cigarettes/day	3.85 (2.29–6.48)	1.24 (0.65–2.39)
>15 cigarettes/day	5.30 (3.10–9.05)	1.47 (0.66–3.27)
Duodenal ulcer		
15 cigarettes/day	3.38 (1.97–5.79)	1.36 (0.68–2.72)
>15 cigarettes/day	4.34 (2.49–7.57)	1.36 (0.57–3.22)

Percentage of those with duodenal ulcer: nonsmokers, 10.8%; smokers 1–10 cigarettes/day, 15.4%; and >10 cigarettes/day, 25.6%; p <0.001

OR (95% CI) adjusted for gender and *H. pylori* infection, smokers vs. nonsmokers:

Duodenal ulcer vs. rest (including gastric ulcer)

1–10 cigarettes/day	1.35 (0.57–1.38)
>10 cigarettes/day	2.53 (1.35–4.74)

Crude OR (95% CI) vs. for each group vs. other 3 groups combined:

Duodenal ulcer vs. rest (including gastric ulcer)

H. pylori-negative nonsmokers	0.13 (0.02–0.93)
H. pylori-negative smokers	0.37 (not reported)
H. pylori-positive nonsmokers	0.94 (not reported)
H. pylori-positive smokers	5.53 (1.97–15.53)

smoking) and to former smokers at baseline. Former smokers had elevated risks for mortality from both duodenal ulcer disease (OR = 1.8 [95 percent CI, 1.3–2.4]) and gastric ulcer disease (1.6 [1.1–2.2]) (NIH 1997). During follow-up of the British doctors cohort, information about smoking behaviors was collected at baseline in 1951 and again in 1957, 1966, 1972, 1978, and 1990. After 40 years, mortality from peptic ulcer disease was 8 per 100,000 per year among men who had never smoked cigarettes; 12 per 100,000 per year among former smokers; and 11, 33, and 34 per 100,000 per year among current smokers of 1 to 14, 15 to 24, and 25 or more cigarettes per day, respectively (p <0.001) (Doll et al. 1994). None of these studies, however, could explore possible confounding of this association by *H. pylori* infection.

Effect of Smoking on Ulcer Severity

Ulcers may be more severe and complications may occur more frequently among continuing smokers (USDHHS 1990). Hasebe and colleagues (1998) compared 35 patients with deep gastric ulcers (ulceration beyond the muscularis propria) and 33 patients with shallow and intermediate depth ulcers (ulceration in submucosa and muscularis propria) in Japan. They found that patients with deep ulcers were more likely to be heavy smokers, defined as smoking 20 or more cigarettes per day, than patients with shallower ulcers (81 percent versus 55 percent, p <0.05). However, patients with deep ulcers also were significantly more likely to drink alcohol on a daily basis (40 percent versus 27 percent, p <0.05) and to have *H. pylori* infections (97 percent versus 79 percent, p <0.01), so it is possible that these differences could explain some or all of the associations with smoking.

Smoking and Peptic Ulcer Complications

Svanes and colleagues (1997) compared patients diagnosed with perforated peptic ulcers with population controls (90 percent response rate) in Norway. Analyses of smoking were restricted to cases (36 gastric perforation and 73 duodenal perforation) and controls (n = 4,270) aged 15 through 74 years because smoking was rare in older patients. After adjusting for age and gender, the risk of perforated ulcers in current smokers increased significantly with the number of cigarettes smoked per day. The ORs were 7.3 (95 percent CI, 4.0–18.1) for smokers of 1 to 9 cigarettes per day, 8.7 (95 percent CI, 5.5–14.4) for smokers of 10 to 19 cigarettes per day, and 11.2 (95 percent CI, 6.3–27.5) for smokers of 20 or more cigarettes per day (p

<0.001) compared with people who had never smoked. The risk among former smokers was no greater than that among those who had never smoked (OR = 0.8 [95 percent CI, 0.2–2.2]). Smokers were less likely than nonsmokers to have used NSAIDs or other ulcerogenic drugs. Thus, variation in NSAID use could not explain the relationship with smoking. The high alcohol consumption, however, which was significantly more common among current smokers (25 percent versus 4 percent among nonsmokers), could possibly explain some of the strong associations between smoking and perforated ulcers. *H. pylori* infection was not assessed, but among the cases, 87 percent of smokers and 96 percent of nonsmokers reported previous "ulcer dyspepsia," suggesting that infection rates probably were high in both groups.

Lanas and colleagues (1997) conducted a similar study in Spain, comparing 76 patients with gastrointestinal perforation (including 31 with duodenal ulcers and 28 with gastric ulcers) with matched hospital and community controls. After adjusting for the use of NSAIDs and alcohol and histories of ulcers and arthritis, smoking was again associated with a significantly increased risk of perforated ulcers (p = 0.003). In Italy, Labenz and colleagues (1999) compared 72 patients admitted with bleeding peptic ulcers with matched hospital controls. After adjusting for *H. pylori* infection status, NSAID use, and alcohol intake, smoking was associated with a nonsignificant 40 percent increased risk of bleeding ulcers (OR = 1.4 [95 percent CI, 0.5–3.6]).

In the large case-control study conducted by Weil and colleagues (2000) in the United Kingdom, overall current smoking was associated with a 60 percent increased risk of bleeding peptic ulcers (OR = 1.6 [95 percent CI, 1.2–2.0]). This risk appeared to differ, however, between users and nonusers of NSAIDs. Among NSAID nonusers, smoking was associated with an almost twofold increased risk of bleeding ulcers (OR = 1.9 [95 percent CI, 1.4–2.4]). In contrast, the risk for peptic ulcers in NSAID users did not differ appreciably between current and nonsmokers as described above.

Effect of Smoking on Ulcer Healing and Recurrence

Ulcer Healing

Many studies have shown that smoking adversely affects healing of duodenal ulcers by acid-reducing agents (Lam 1990; USDHHS 1990). It does not appear, however, to have the same adverse effect

on healing by other agents, including sucralfate (Lam 1991) or colloidal bismuth subcitrate (Lam 1991; Lambert 1991). In a meta-analysis, data from six studies of sucralfate were combined, giving overall healing rates of 78 percent among 301 smokers and 78 percent among 272 nonsmokers (Lam 1991). In the same analysis, data also were pooled from three studies of colloidal bismuth subcitrate, giving healing rates of 82 percent among 55 smokers and 76 percent among 38 nonsmokers. Less consistent results were reported for the effects of smoking on gastric ulcer healing, although studies evaluating the benefits of smoking cessation have suggested that ulcer patients who stop smoking do better than patients who continue to smoke (USDHHS 1990).

Rates of ulcer healing are significantly higher (Hentschel et al. 1993; Labenz and Börsch 1994) and recurrence rates significantly lower (Rauws and Tytgat 1995) among patients with ulcers (gastric or duodenal) who received *H. pylori* eradication therapy, which now is the recommended treatment for patients with *H. pylori* infection (NIH 1997). The combined effects of smoking and *H. pylori* eradication on ulcer healing in the short term have not been directly evaluated; however, in three studies of ulcer patients treated with *H. pylori* eradication therapy, there were no significant differences in ulcer healing rates between smokers and nonsmokers (O'Connor et al. 1995; Bardhan et al. 1997; Kadayifçi and Simsek 1997). O'Connor and colleagues (1995) reported healing rates for gastric and duodenal ulcers of 83 percent for smokers compared with 92 percent for nonsmokers (p = 0.3); the *H. pylori* eradication rate also was slightly lower among smokers (83 percent versus 94 percent, p = 0.2), possibly explaining the slightly different healing rates. Bardhan and colleagues (1997) reported duodenal ulcer healing in 96 percent of smokers compared with 94 percent of nonsmokers (p = 0.6), whereas rates of *H. pylori* eradication were slightly higher for nonsmokers (77 percent versus 71 percent, p = 0.5). Kadayifçi and Simsek (1997) reported duodenal ulcer healing in 82 percent and 83 percent of heavy (more than 20 cigarettes per day) and mild (1 to 20 cigarettes per day) smokers, respectively, compared with 85 percent of nonsmokers (p = 0.9). In this study, *H. pylori* eradication rates were slightly higher for nonsmokers (68 percent versus 66 percent among mild and 59 percent among heavy smokers). These reports suggest that ulcer healing rates are high in patients treated with *H. pylori* eradication therapy, regardless of their smoking status.

Duodenal Ulcer Recurrence

In studies comparing duodenal ulcer recurrence rates for smokers and nonsmokers before the introduction of *H. pylori* eradication therapy, higher relapse rates consistently were reported for smokers (USDHHS 1990). However, ulcers rarely, if ever, recur in patients who remain free of *H. pylori*, regardless of their smoking status. George and colleagues (1990) observed no recurrence of duodenal ulcers among 71 patients (31 current and 12 former smokers, and 28 lifetime nonsmokers) whose ulcers had healed, whose *H. pylori* had been eradicated, and who remained free of *H. pylori* during the four years they were followed. In an Australian study, 197 patients successfully treated for *H. pylori*-positive duodenal ulcers had their infections eradicated and their ulcers cured. They then were followed for 12 to 73 months (Borody et al. 1992b). There was no recurrence of *H. pylori* or duodenal ulcers among the groups of 80 current smokers (smoking 5 to 40 cigarettes per day), 38 former smokers (who gave up smoking during follow-up or up to 20 years earlier), and 79 patients who had never smoked. In the Netherlands, Van Der Hulst and colleagues (1997) also found no recurrences in 141 duodenal ulcer patients whose ulcers had been cured and who had been treated successfully for *H. pylori* infection; they remained free of infection during nine years of follow-up. In Greece, there was no recurrence of duodenal ulcers during 12 to 72 months of follow-up in 141 patients who remained *H. pylori* negative, regardless of their smoking status; there were seven recurrences (six in smokers) among 24 patients (unknown number of smokers) who became reinfected with *H. pylori* (Archimandritis et al. 1999).

Although other authors have documented low ulcer recurrence rates in patients whose *H. pylori* infection was eradicated, ulcer recurrence commonly is associated with either reinfection with *H. pylori* (Bayerdörffer et al. 1993) or NSAID use (Chen et al. 1999). Furthermore, recurrence rates have not varied between smokers and nonsmokers. A study in Hong Kong followed patients for 10 to 18 months who had been successfully treated for *H. pylori* infection and whose duodenal ulcers had healed (Chan et al. 1997). The authors documented two recurrences (2.9 percent, both *H. pylori* negative) among 68 smokers (10 cigarettes per day) and four recurrences (2.1 percent, three *H. pylori* negative) among 188 persons who had never smoked or were former smokers. The study concluded that smoking did not influence ulcer recurrence after *H. pylori* eradication.

Patients treated for *H. pylori*-positive duodenal ulcers in a multicenter study (Canada, Ireland, United Kingdom, and United States) were followed for six months (Bardhan et al. 1997). All patients had healed ulcers, but *H. pylori* was eradicated in only 77 percent of nonsmokers and 71 percent of smokers. Ulcers recurred in 22 percent of 118 smokers and 16 percent of 117 nonsmokers (p = 0.32). The slightly higher rate seen in smokers could be a result of the slightly lower *H. pylori* eradication rate for this group. Recurrence rates in this study among patients who apparently remained free of *H. pylori* during follow-up were an unusually high 12 percent (<6 percent in three of the centers) for both smokers and nonsmokers.

In summary, smoking does not appear to affect duodenal ulcer recurrence rates in patients whose *H. pylori* infection has been eradicated. Among those who remain *H. pylori* positive, smoking may increase the risk of relapse, although no good data support or refute this possible association.

Gastric Ulcer Recurrence

A similar pattern is seen for *H. pylori*-positive gastric ulcers, which also rarely recur after successful *H. pylori* eradication therapy in the absence of NSAID use (Labenz and Börsch 1994). There were no relapses of gastric ulcers in 45 patients who remained *H. pylori* negative during 10 years of follow-up (Van Der Hulst et al. 1997). Chan and colleagues (1997) observed one recurrence of gastric ulcer accompanied by the reappearance of *H. pylori* in 15 smokers and no recurrences in 16 nonsmokers followed for up to 18 months after *H. pylori* eradication and successful ulcer healing.

These data suggest that for both gastric and duodenal ulcers, the main predictor of successful ulcer healing with no recurrence is *H. pylori* infection status. If smoking has any effect on the healing or recurrence of ulcers, it is therefore likely to be through an effect on the process of *H. pylori* eradication.

Smoking and Helicobacter pylori Eradication

A number of studies have evaluated the effects of smoking on *H. pylori* eradication. Results of studies that included more than 50 participants and presented separate eradication rates for smokers and nonsmokers are shown in Table 6.33. (Because three other studies [Fraser et al. 1996; Harris et al. 1996; Georgopoulos et al. 2000] simply reported that smoking was not significantly associated with eradication without presenting eradication rates, it is not possible to tell if there

were nonsignificant differences between smokers and nonsmokers.) Although the definition of smoking in these studies often is unclear, and a range of different drug combinations was used to treat the infections, a fairly consistent pattern of lower eradication rates is seen in groups defined as smokers.

Other factors known to be strongly predictive of *H. pylori* eradication are compliance with therapy (Graham et al. 1992; Cutler and Schubert 1993; Labenz et al. 1994) and the prevalence of metronidazole resistance (O'Riordan et al. 1990). Although some studies have reported poorer compliance among smokers (Unge et al. 1993), others have found similarly high compliance rates between smokers and nonsmokers (O'Connor et al. 1995; Bardhan et al. 1997; Kamada et al. 1999). In a logistic regression model also adjusting for therapy duration and omeprazole pretreatment, Labenz and colleagues (1994) found both lack of compliance (OR = 74.72 [95% CI, 24.17–205.51]) and smoking (OR = 2.75 [95% CI, 1.56–4.86]) to be independent risk factors for treatment failure. Witteman and colleagues (1993) found that metronidazole resistance developed more readily in smokers following therapy with bismuth and metronidazole after allowing for variations in compliance (p = 0.01). However, poorer eradication rates in smokers also are seen with regimens that do not contain this class of drug. Therefore, it seems unlikely that the lower eradication rates for smokers can be attributed to either poorer compliance or an increase in metronidazole resistance. It has been suggested that smoking may adversely affect eradication by increasing acid output or by decreasing gastric blood flow, thereby reducing drug delivery to the gastric mucosa, but little evidence supports either of these hypotheses.

Evidence Synthesis

Incidence of Peptic Ulcer

Many studies have reported strong and significant associations between smoking and peptic ulcer disease. Only six studies, however, have allowed for the effects of *H. pylori* infection when evaluating this association. Three of those studies reported significantly increased risks of ulcer disease in smokers after adjusting for *H. pylori* infection; in each study, the majority (80 to 90 percent) of ulcer patients were *H. pylori* positive (Wang et al. 1996; Talamini et al. 1997; Halter and Brignoli 1998). A fourth study reported a significant association between smoking and ulcers

only among *H. pylori*-positive persons (Martin et al. 1989). The remaining two studies (Schubert et al. 1993; Schlemper et al. 1996) reported little or no association, but the classification of smoking status in these studies is potentially unreliable.

Cigarette smoking has a number of effects on gastroduodenal physiology that could lead to the development of peptic ulceration, and evidence suggests that some of these effects may be potentiated in *H. pylori*-positive persons. Taken together, these data strongly suggest a causal relationship between smoking and the development of peptic ulcers, at least in *H. pylori*-positive persons. There is insufficient evidence to evaluate the relation between smoking and peptic ulcers in those who are *H. pylori* negative. Conflicting and inadequate data link smoking to ulcer occurrence in NSAID users and it is not possible to evaluate an independent effect for smoking in the development of NSAID-induced peptic ulcers.

There is evidence to suggest that after adjusting for NSAID use, smoking may be associated with an increased risk of peptic ulcer complications, including perforation and bleeding. Data from the most recent study (Weil et al. 2000), however, suggest that this effect may be restricted to nonusers of NSAIDs.

The effects of smoking cessation on ulcer risk have not been evaluated in the context of *H. pylori* infection. However, the transient nature of many of the physiologic effects of smoking suggests that an excess risk may be restricted to current smokers.

Ulcer Healing and Recurrence

Healing and recurring *H. pylori*-positive ulcers are closely associated with eradication and recurrence of the infection. The evidence strongly suggests that if *H. pylori* is eradicated, smoking has no effect on either the healing or recurrence of ulcers. There is, however, evidence to suggest that *H. pylori* eradication therapy is somewhat less successful for current smokers. There are no good data to evaluate the effects of smoking on the recurrence of ulcers associated with *H. pylori* infection when long-term *H. pylori* eradication fails, or on the treatment and recurrence of ulcers in persons negative for *H. pylori* infection.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

3. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of nonsteroidal anti-inflammatory drugs.

4. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

Implications

The prevalence of *H. pylori* has declined in developed countries (Banatvala et al. 1993; Kosunen et al. 1997) and, as a result, the proportion of patients with *H. pylori*-negative ulcers will increase, making them an important group to study. Also, an increasing number of *H. pylori*-negative ulcers may not be attributable to NSAID use or other established causes of ulcers (Jyotheeswaran et al. 1998). The rarity of ulcer recurrence when *H. pylori* is eradicated, regardless of smoking status, suggests that smoking is not an important factor in the initial development or recurrence of ulcers among persons who are *H. pylori* negative. However, this topic has not been well investigated, largely because of the paucity of such ulcers, and is likely to be an important area for future research.

Because the main effects of smoking on gastrointestinal physiology appear to be short-lived, it is likely that smoking cessation will both reduce ulcer occurrence in those persons who are *H. pylori* positive and improve the chances of eradication in patients (with or without ulcers) treated for *H. pylori* infection. Even if eradication is successful, it seems unlikely that a continuation of smoking will influence the course of peptic ulcer disease.

Table 6.33   Studies on *Helicobacter pylori* (*H. pylori*) eradication rates among smokers and nonsmokers

Study/location	Population	Therapy
Cutler and Schubert 1993 United States	96 patients with gastric ulcers, duodenal ulcers, or nonulcer dyspepsia	Bismuth, tetracycline, and metronidazole
Labenz et al. 1994 Germany	405 patients with *H. pylori*-related diseases of the gastroduodenum (231 with duodenal ulcer disease, 138 with gastric ulcer disease, 14 with gastroduodenal double ulcers, and 22 with *H. pylori* gastritis-associated dyspepsia)	Omeprazole and amoxicillin
O'Connor et al. 1995 Ireland	85 patients with gastric or duodenal ulcers and confirmed *H. pylori* infection	Bismuth, metronidazole, tetracycline
Goddard and Spiller 1996 United Kingdom	200 patients with endoscopically proven *H. pylori*	Bismuth, tetracycline, and metronidazole (BTT); omeprazole, clarithromycin, and metronidazole (OCM); omeprazole, clarithromycin, and tinidazole (OCT); omeprazole, clarithromycin, metronidazole, and tinidazole (OCN)
Bardhan et al. 1997 Canada, Ireland, United Kingdom, United States	284 duodenal ulcer patients with *H. pylori* infection	Clarithromycin, omeprazole
Breuer et al. 1997a Korea	72 patients with *H. pylori* infection and endoscopically confirmed gastric or duodenal ulcers	Amoxicillin, clarithromycin, and nizatidine
Breuer et al. 1997b Korea	79 patients with *H. pylori* infection and endoscopically confirmed gastric or duodenal ulcers	Metronidazole, amoxicillin, omeprazole
Kadayifçi and Simsek 1997 Turkey	232 patients with endoscopically verified *H. pylori*-positive active duodenal ulcer disease	Amoxicillin, clarithromycin, metranidazole, roxitromycin, and nitrimidazine (alone or in different combinations)

*NR = Data were not reported.
†NS = Not significant.

Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	**Nonsmokers**	
NR*	73.7	89.7	16.0 (p = 0.040)
NR	65	83	18 (p <0.001)
NR	82.6	94.4	11.8 (NS†)
NR	BTT: 76.3 OCM: 85.7 OCT: 68.7 OCN: 79.5	84.2 88.8 87.5 88.2	7.9 (NS) 3.1 (NS) 18.8 (NS) 8.7 (p <0.05)
NR	71	77	6 (NS)
NR	93.7	100	6.3 (p = 0.55)
5 cigarettes/day	65	88	23 (p = 0.035)
Eradication rates were stratified by cigarettes/day categories, but it is unclear how the analysis defined "nonsmokers"	5–20 cigarettes/day: 66 >20 cigarettes/day: 59	68	2 (NS) 9 (NS)

Table 6.33   Continued

Study/location	Population	Therapy
Moayyedi et al. 1997 United Kingdom	273 *H. pylori*-positive patients, diagnosed by ^{13}C-UBT (127 with normal endoscopy, 68 with duodenitis, 28 with duodenal ulcers, 8 with gastric ulcers, 18 with esophagitis, and 24 miscellaneous)	Omeprazole, clarithromycin, and tinidazole
Kamada et al. 1999 Japan	137 *H. pylori*-positive patients (60 with duodenal ulcers, 19 with gastric ulcers, and 58 with nonulcer dyspepsia)	Omeprazole, amoxicillin, clarithromycin

Definition of smoking	Eradication rate (%)		Absolute percent difference (%)
	Smokers	**Nonsmokers**	
NR	87	95	8
NR	57.7	80.0	22.3 (p <0.01)

Conclusions

Diminished Health Status

1. The evidence is sufficient to infer a causal relationship between smoking and diminished health status that may manifest as increased absenteeism from work and increased use of medical care services.

2. The evidence is sufficient to infer a causal relationship between smoking and increased risks for adverse surgical outcomes related to wound healing and respiratory complications.

Loss of Bone Mass and the Risk of Fractures

3. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and reduced bone density before menopause in women and in younger men.

4. In postmenopausal women, the evidence is sufficient to infer a causal relationship between smoking and low bone density.

5. In older men, the evidence is suggestive but not sufficient to infer a causal relationship between smoking and low bone density.

6. The evidence is sufficient to infer a causal relationship between smoking and hip fractures.

7. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and fractures at sites other than the hip.

Dental Diseases

8. The evidence is sufficient to infer a causal relationship between smoking and periodontitis.

9. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and coronal dental caries.

10. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and root-surface caries.

Erectile Dysfunction

11. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and erectile dysfunction.

Eye Diseases

12. The evidence is sufficient to infer a causal relationship between smoking and nuclear cataract.

13. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of nuclear opacity.

14. The evidence is suggestive but not sufficient to infer a causal relationship between current and past smoking, especially heavy smoking, with risk of exudative (neovascular) age-related macular degeneration.

15. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and atrophic age-related macular degeneration.

16. The evidence is suggestive of no causal relationship between smoking and the onset or progression of retinopathy in persons with diabetes.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and glaucoma.

18. The evidence is suggestive but not sufficient to infer a causal relationship between ophthalmopathy associated with Graves' disease and smoking.

Peptic Ulcer Disease

19. The evidence is sufficient to infer a causal relationship between smoking and peptic ulcer disease in persons who are *Helicobacter pylori* positive.

20. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and peptic ulcer disease in nonsteroidal anti-inflammatory drug users or in those who are *Helicobacter pylori* negative.

21. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and risk of peptic ulcer complications, although this effect might be restricted to nonusers of non-steroidal anti-inflammatory drugs.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between smoking and the treatment and recurrence of *Helicobacter pylori*-negative ulcers.

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Chapter 7
The Impact of Smoking on Disease and the Benefits of Smoking Reduction

Overview

The preceding chapters have reviewed the extensive scientific evidence regarding the diverse illnesses caused by tobacco use. The causation of multiple diseases by smoking and the related loss of life expectancy have long motivated policy actions to control tobacco use. To support policy actions and decision making based on the health evidence, quantitative estimates of the burden of disease associated with smoking in the population are made. These numbers complement the epidemiologic studies that estimate the risks to individuals associated with various smoking patterns.

This chapter reviews methods used to estimate the burden of disease attributable to smoking and provides updated estimates of this burden. The chapter is limited to consideration of risks from cigarette smoking and does not include those attributable to smokeless tobacco use, cigar smoking, or other forms of tobacco use. It considers methodologies and data sets used to estimate disease burden, summarizes past reports and critiques of smoking attributable disease estimates, presents current estimates of smoking attributable mortality for the nation and for individual states, and reviews estimates of the economic costs of illness attributable to smoking. Data are also presented on the reduction of mortality achievable nationwide by meeting the *Healthy People 2010* prevalence objectives for reducing smoking (U.S. Department of Health and Human Services [USDHHS] 2000).

Introduction

For diseases attributable to a causal risk factor, such as smoking, the "disease burden" associated with that risk factor can be estimated for a particular population using epidemiologic methods. Different types of estimates can be made, such as mortality, morbidity, disability-adjusted life years (DALYs) lost, changes in disability-adjusted life expectancy (DALE), quality-adjusted life years (QALYs) lost, years of potential life lost (YPLL), economic costs of illness, and population attributable risk (PAR) (Table 7.1). In 1996, the World Health Organization (WHO) published the landmark document *The Global Burden of Disease* (Murray and Lopez 1996), which used mortality and DALYs to describe the burden of disease associated with major risk factors for each country in 1990. Updated estimates were published in 2002 (Ezzati et al. 2002). A key goal of these efforts is to clearly link these burden-of-disease measurements to health policy decision making. The 1996 WHO report included the following rationales for estimating disease burden:

1. Assessing the performance of a health care system with respect to actual health outcomes.

2. Generating a forum for an informed debate of values and priorities.

3. Identifying national disease-control priorities.

4. Allocating training for clinical and public health practitioners according to priority illnesses.

5. Allocating research and development resources to address major disease burdens.

6. Allocating resources across health interventions in order to shift resources to the most cost-effective approaches for prevention.

This chapter focuses on the main measure of disease burden used to assess the impact of smoking in the United States, the PAR. The calculation of the PAR for a particular risk factor represents a form of quantitative risk assessment (National Research Council 1983), a systematic approach that translates research

Table 7.1   Disease burden measures used to evaluate the impact of population risk factors

Measure	Data elements	Use
Mortality	Information provided by death certificates on specific causes of death	Describes disease (death) according to age, gender, race, and other demographic factors for specific diagnoses and certain antecedent conditions
Morbidity	Information on hospitalizations, outpatient treatments, prescription drugs, nursing home admissions, other medical care	Describes the disability, costs, and medical care utilization related to specific diagnoses
Disability-adjusted life years (DALYs)*	Standard life table data, disability-adjusted ages at death, discounted contribution of years of life lost	Estimates a single measure of disease burden for comparisons across populations
Quality-adjusted life years (QALYs)	Arithmetic product of the life expectancy and the quality of the remaining years; quality of additional life was assessed by questionnaires or preference studies	Estimates the extra quantity and quality of life provided by an intervention combined within a single measure
Disability-adjusted life expectancy (DALE)†	Standard life table data, survey data on physical and cognitive disabilities and general health status	Determines the maximum level of health expected within the surveyed health care system
Years of potential life lost (YPLL)‡	Mortality data and life expectancy at the time (age) of death	Estimates the burden of premature death in a given population
Economic costs of illness	Costs of specific medical services, data on utilization of services by specific population groups, rates of utilization according to risk factors	Estimates the costs of illness attributable to a specific risk factor for a given population group
Population attributable risk (PAR)	Mortality data, life expectancy at death, relative risk of death according to risk factor prevalence	Estimates the proportion of deaths attributable to a specific risk factor in a given population
Smoking attributable fractions (SAFs)	Smoking prevalence data by smoking status, age, and gender; and relative risk of death for smoking-related diseases by age and gender	Estimates the proportion of an outcome that could be avoided if smoking were eliminated

*Includes life years lost to premature mortality and years lived with disability. For a comprehensive discussion of DALYs, see Murray and Lopez 1996, *The Global Burden of Disease*.
†Life expectancy was adjusted to account for disability and is simply premature mortality. For a comprehensive discussion of DALE, see Murray and Lopez 1996, *The Global Burden of Disease*.
‡YPLL is usually calculated from age at death to age 65 years, 85 years, or life expectancy.

Table 7.1   Continued

Measure	Data elements	Use
Smoking attributable mortality (SAM)	Mortality data for smoking-related diseases by age and gender; smoking prevalence data by smoking status, age, and gender; relative risk of death for smoking-related diseases by age and gender	Estimates the number of deaths that could be avoided if smoking were eliminated

Source: Murray and Lopez 1996.

findings for the purpose of guiding the implementation and evaluation of policies (Samet and Burke 1998). The elements of a risk assessment include hazard identification (e.g., does smoking cause disease[s]?), exposure assessment (e.g., what is the population pattern of smoking?), dose-response assessment (e.g., how does risk vary with duration and amount of smoking?), and risk characterization (e.g., what is the disease burden caused by smoking?). The PAR is estimated for a particular disease based on the conclusion that smoking causes the disease, an assumption equivalent to the hazard identification component of risk assessment. The PAR calculation incorporates the prevalence of smoking, analogous to exposure assessment, and the relative risk (RR) associated with various amounts of smoking, analogous to dose-response assessment. The PAR itself characterizes risk, and uncertainties associated with the PAR estimates can be described.

In applying this approach to smoking, researchers first evaluate epidemiologic and other evidence for causality for a particular disease or effect, as described in Chapter 1 of this report. Large cohort studies, such as the Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II) of the American Cancer Society (ACS) (Stellman and Garfinkel 1986), the U.S. Veterans Study (Kahn 1966), and the British Doctors Study (Doll and Peto 1976; Doll et al. 1994), provide robust RR estimates for current smokers and former smokers, compared with lifetime nonsmokers, for major causes of death. Population exposures to smoking are measured using survey data, biologic markers, or proxy information from relatives of decedents. For the United States, large population-based surveys of tobacco use provide uniform and consistent assessments of the prevalence of current and former smoking. Finally, the RRs and the smoking prevalence data are then combined to estimate the PAR, the proportion of deaths attributable to the exposure.

In addition, public health decision makers consider estimates of the population disease burden in terms of the number of deaths caused by exposure to smoking and the burden of premature deaths, which can be expressed as YPLL. YPLL can be calculated from the age at death up to specific ages or to full life expectancy. By making the calculation to specific ages, YPLL can be estimated at younger, middle, and older ages.

Measuring changes in smoking attributable mortality (SAM) over time provides a periodic ongoing indication of the burden of disease caused by tobacco use. This information can be used to guide national and state comprehensive tobacco control programs, facilitating decisions on resource allocation and needs by comparing the impact of tobacco use with other risk factor disease burdens (McGinnis and Foege 1993).

An appendix to this chapter reviews the methods used to estimate the burden of smoking along with previous SAM estimates in the United States. The appendix also describes the databases used for these calculations. The chapter includes new annual SAM and YPLL estimates for 1995–1999; state-specific, age-adjusted SAM; total SAM for 1964 (the year of the first Surgeon General's report on the health consequences of smoking and health) through 1999; and estimates of SAM that could be avoided by meeting the *Healthy People 2010* objectives for the nation (USDHHS 2000).

To summarize, the overall approach to estimating SAM includes the following:

- Identifying those diseases caused by (cigarette) smoking.

- Developing RR estimates for these diseases for current and former smokers, compared with lifetime nonsmokers; the currently used estimates are for CPS-II follow-up from 1982–1986.

- Developing estimates of smoking prevalence for the nation and the states using National Health Interview Survey (NHIS) data for the years of interest.

- Estimating the disease- and gender-specific PARs.

- Applying the PARs to the disease-specific mortality counts to estimate the SAM.

This listing makes the critical assumptions clear and acknowledges the cross-sectional nature of the SAM estimates, which are not for particular birth cohorts but for particular time points. They are representations of the SAM for a population with the smoking prevalence profile of a particular year, on the assumption that the population would experience the selected RR estimates across its full life span. The calculations thus refer to theoretical, nonexistent populations, albeit based in actual data, but the same methodology is applied uniformly over time, yielding estimates that are informative about relative changes in SAM over time. The estimates are useful for indicating the general scope of the public health burden from smoking.

Current Impact of Smoking

Smoking Attributable Mortality and Years of Potential Life Lost

For this report, the annual SAM and YPLL calculations for 1995–1999 have been updated from the most recent Centers for Disease Control and Prevention (CDC) report (CDC 2002a) by using the additional diseases now causally attributed to smoking (stomach cancer and acute myeloid leukemia), using new estimates for perinatal RRs, and excluding hypertension, which was previously included as a cause of smoking-related deaths on the assumption that smoking attributable heart disease deaths were included in this category. These estimates include adult and perinatal deaths for 19 disease categories among adults and 4 adverse infant health outcomes (also listed in the tenth revision of the *International Classification of Diseases* [ICD-10] [CDC 2002b,d]) that are caused by smoking (see Appendix 7-1). Deaths attributable to residential fires caused by smoking (589 males and 377 females [Hall 2001]) and deaths from secondhand smoke exposure for adults are also included (nationally, 3,000 for lung cancer and 35,000 to 62,000 for heart disease [National Cancer Institute (NCI) 1999; CDC 2002d; International Agency for Research on Cancer (IARC) 2002]).

Relative risks for smoking-related diseases and smoking prevalence estimates for current and former smokers 35 years of age and older and for maternal smokers were used to calculate smoking attributable fractions (SAFs) and SAMs as in the previous CDC report (2002a). Age-adjusted RR data were obtained from CPS-II (1982–1988, see Appendix 7-1), and gender-specific smoking prevalence data for adults aged 35 years and older were obtained from NHIS (Table 7.2). Relative risk estimates of the deaths of infants whose mothers smoked during pregnancy were obtained from McIntosh (1984) and Gavin and colleagues (2001). Maternal smoking prevalence data from most states for 1995–1999 were obtained from birth certificates (see http://www.cdc.gov/nchs/births.htm). Age- and gender-specific mortality data were obtained from National Center for Health Statistics (NCHS) reports (Hoyert et al. 2001). YPLL for persons aged 35 years and older were calculated using remaining life expectancy (life expectancy at any given age of death minus age at death and for infants, from birth). SAM and YPLL include nationally reported deaths from cigarette-caused residential fires; SAM includes lung cancer and heart disease deaths from secondhand smoke exposures (15,500 men and 22,500 women [NCI 1999]).

Smoking caused an estimated total of 263,600 deaths in males and 176,500 deaths in females (total 440,100) in the United States each year from 1995–1999 (Table 7.3). For men aged 35 years and older, annual smoking attributable deaths were 105,700 for cancers, 87,600 for cardiovascular diseases (CVDs), and 53,700 for respiratory diseases. For women aged 35 years and older, the annual SAM was 53,900 for cancers, 55,000 for CVDs, and 44,300 for respiratory diseases. Among adults, the most smoking attributable deaths were from lung cancer (124,800), ischemic heart disease (IHD) (82,000), and chronic airways obstruction (64,700).

Table 7.2 **Annual prevalence of current smoking and former smoking among adults aged 35 years and older, selected years, National Health Interview Survey, United States, 1965–1999**

	Men						Women					
	35–44 years		45–64 years		≥65 years		35–44 years		45–64 years		≥65 years	
Year	CS*	FS†	CS	FS	CS	FS	CS	FS	CS	FS	CS	FS
1965	54.3	22.8	54.3	22.8	36.4	21.5	36.5	9.0	36.5	9.0	9.6	4.5
1970	49.8	27.0	44.7	32.2	23.4	39.2	39.2	14.1	32.5	12.2	10.9	7.3
1974	51.4	26.9	42.7	36.5	24.7	41.6	39.7	14.4	33.4	14.8	12.1	10.8
1977	48.5	25.5	40.5	35.2	23.3	43.5	38.6	15.1	34.4	15.3	13.5	12.3
1980	42.6	27.8	40.6	37.2	17.8	47.8	34.9	18.9	30.6	17.2	17.1	14.4
1983	40.4	28.0	35.4	40.4	21.4	48.4	33.8	17.1	30.6	18.7	13.0	18.6
1985	39.0	30.6	34.4	41.5	19.9	51.8	33.4	19.2	31.4	21.3	14.2	20.3
1987	37.4	27.4	34.8	39.0	18.8	52.0	30.8	18.5	29.8	20.9	13.6	19.3
1988	37.2	26.0	33.4	40.7	18.8	52.9	29.0	18.7	29.0	24.3	13.4	20.7
1990	35.2	26.1	31.2	41.0	14.6	55.2	26.5	19.7	26.1	24.4	11.5	23.2
1992	32.9	26.2	30.6	40.5	16.2	54.0	28.5	18.3	26.8	23.8	12.4	24.0
1994	30.6	34.4	30.6	34.4	13.3	58.3	24.6	23.5	24.6	23.5	11.1	26.9
1995	29.1	31.4	29.1	31.4	14.9	52.9	25.4	21.9	25.4	21.9	11.5	26.8
1996	29.4	30.5	29.4	30.5	13.5	55.1	24.5	22.1	24.5	22.1	11.5	26.1
1997	29.6	30.1	29.6	30.1	12.8	56.2	24.0	22.1	24.0	22.1	11.5	25.8
1998	28.8	29.9	28.8	29.9	10.4	58.5	24.2	21.2	24.2	21.2	11.2	27.0
1999	27.6	29.5	27.6	29.5	10.5	57.9	23.3	21.7	23.3	21.7	10.7	27.8

*CS = Current smokers, defined as having smoked at least 100 cigarettes and currently smoked every day or some days (the some days condition was added in 1992).

†FS = Former smokers, defined as having smoked at least 100 cigarettes but not currently smoking.

Sources: National Center for Health Statistics, public use data tapes, 1965, 1970, 1974, 1977, 1980, 1983, 1985, 1987, 1988, 1990, 1992, 1994, 1995, 1996, 1997, 1998, 1999.

Smoking during pregnancy was estimated to result in 560 deaths in infant boys and 410 deaths in infant girls annually. Excluding adult deaths from second-hand smoke, the estimated SAM was responsible for a total annual YPLL of 3,319,000 for males and 2,152,600 for females.

The annual SAM will likely remain fairly stable if trends in smoking prevalence among adults do not decrease substantially. Adult smoking prevalence rates have decreased over the past few years (Table 7.2) (CDC 1999a, 2001a), but the prevalence of smoking among adolescents increased from 1992 until 1997. However, youth smoking has also decreased more recently (CDC 2002f). Yet, the burden of disease attributable to smoking is driven by those with long-term previous exposures, so unless smoking cessation among current smokers increases quite rapidly, SAM is not expected to decline substantially for many years. Estimates of various SAM projections under several scenarios of prevalence rate reductions are presented later in this chapter.

Total Smoking Attributable Mortality, 1965–1999

The total SAM estimates for 1965–1999 were derived from annual PAR estimates for the time since the publication of the first Surgeon General's report on the health consequences of smoking in 1964 (Table 7.4). The PARs for each of 19 smoking-related disease categories were calculated using smoking prevalence and the RR estimates for mortality for current and former smokers aged 35 years and older. The PARs for each of four adverse health outcomes were calculated using maternal smoking prevalence and RR estimates for smoking-related infant deaths. The mortality RR estimates for adults were obtained from both CPS-I and CPS-II data (see Appendix 7-1). CPS-I data (1959–1965) were used in conjunction with NHIS smoking prevalence data from 1965–1971, CPS-II data (1982–1988) were applied to NHIS prevalence data from 1982–1999, and the midpoint RRs between CPS-I and

Table 7.3   Annual deaths, smoking attributable mortality (SAM), and years of potential life lost (YPLL), stratified by cause of death and gender, United States, 1995–1999

Disease category (ICD-9 code)*	Males			Females		
	Total deaths	SAM	YPLL	Total deaths	SAM	YPLL
Neoplasms†						
Lip, oral cavity, pharynx (140–149)	5,200	3,900	64,000	2,600	1,300	20,600
Esophagus (150)	8,600	6,300	94,400	2,800	1,600	24,300
Stomach (151)	7,600	2,200	30,000	5,300	600	9,200
Pancreas (157)	13,400	3,100	46,100	14,300	3,400	49,800
Larynx (161)	3,000	2,500	37,800	800	600	10,300
Trachea, bronchus, lung (162)	91,300	80,600	1,106,100	61,600	44,200	719,900
Cervix uteri (180)	NA‡	NA	NA	4,100	500	13,400
Urinary bladder (188)	7,800	3,700	40,200	3,800	1,100	12,500
Kidney, other urinary (189)	7,100	2,800	41,900	4,500	200	4,000
Acute myeloid leukemia (205.0)	3,200	800	11,000	2,700	300	4,600
Total	**147,200**	**105,700**	**1,471,400**	**102,700**	**53,900**	**868,700**
Cardiovascular diseases†						
Ischemic heart disease (410–414)						
Aged 35–64 years	53,000	22,100	514,900	19,400	7,100	185,600
Aged 65 years	191,200	29,300	252,400	218,000	23,500	207,200
Other heart disease (390–398, 415–417, 420–429)	98,100	18,800	243,300	117,600	10,500	122,900
Cerebrovascular disease (430–438)						
Aged 35–64 years	9,700	3,900	93,900	8,100	3,600	101,500
Aged 65 years	51,400	4,700	37,800	88,500	5,300	45,000
Atherosclerosis (440)	9,000	1,600	14,900	10,100	900	7,700
Aortic aneurysm (441)	10,000	6,500	76,600	6,200	3,100	37,200
Other arterial disease (442–448)	4,700	700	8,500	6,200	900	11,800
Total	**424,000**	**87,600**	**1,242,300**	**474,000**	**55,000**	**718,900**
Respiratory diseases†						
Pneumonia, influenza (480–487)	38,300	8,800	84,900	47,400	6,800	69,100
Bronchitis, emphysema (490–492)	10,900	9,900	109,000	9,600	7,800	99,800
Chronic airways obstruction (496)	42,800	34,900	353,100	39,700	29,800	353,300
Total	**92,000**	**53,700**	**547,000**	**96,700**	**44,300**	**522,200**
Perinatal conditions†						
Short gestation/low birth weight (765)	2,200	220	15,970	1,770	180	13,870
Respiratory distress syndrome (769)	930	40	2,600	640	20	1,930
Other respiratory conditions in newborns (770)	910	50	3,460	650	30	2,650
Sudden infant death syndrome (798.0)	1,770	260	18,940	1,200	180	13,870
Total	**5,810**	**560**	**40,960**	**4,250**	**410**	**32,310**

Note: **All figures are rounded and hence do not add up.**
International Classification of Diseases, 9th Revision.
†Among persons aged 35 years.
‡NA = Not applicable.
¶NR = Data were not reported.

Table 7.3   Continued

Disease category (ICD-9 code)	Males			Females		
	Total deaths	**SAM**	**YPLL**	**Total deaths**	**SAM**	**YPLL**
Burn deaths	NA	590	17,300	NA	380	10,500
Secondhand smoke deaths						
Lung cancer	NR[¶]	1,100	NR	NR	1,900	NR
Ischemic heart disease	NR	14,400	NR	NR	20,600	NR
Total		**15,500**			**22,500**	
Overall total	**669,100**	**263,600**	**3,319,000**	**677,600**	**176,500**	**2,152,600**

Grand total	**Males and females**
SAM	440,100
YPLL	5,466,600

Sources: McIntosh 1984; U.S. Department of Health and Human Services 1989b; National Center for Health Statistics, public use data tapes, 1995–1999; Thun et al. 1997b; National Cancer Institute 1999; Gavin et al. 2001; Hall 2001; Hoyert et al. 2001; Mathews 2001; Centers for Disease Control and Prevention 2002a,b,d; International Agency for Research on Cancer 2002; American Cancer Society, unpublished data.

CPS-II were used with NHIS prevalence data for 1972–1981, applied to each year's mortality data during that period. Current and former smoking prevalence data, by gender and for ages 35 through 44 years, 45 through 64 years, and 65 years and older, were obtained from NHIS (Table 7.2). Linear extrapolation was used to estimate prevalence in the years that surveys were not conducted. Data on maternal smoking status for earlier years were extrapolated using the ratio of maternal smoking prevalence to current smoking prevalence among women aged 18 through 24 years from 1995–1999. These data produced more conservative prevalence estimates than smoking rates among women of childbearing age (18 through 44 years).

SAM estimates were calculated by multiplying each cause-specific SAF by the total number of annual deaths for each smoking-related disease. To compare mortality data across differing ICD code systems, data for 1965–1967 (ICD-7), 1968–1978 (ICD-8), and 1999 (ICD-10) were translated into ICD-9 codes using comparability ratios[1] obtained from NCHS (Klebba 1975; Anderson et al. 2001) (also see Appendix 7-1).

From 1965–1999, smoking has caused an estimated 4.1 million cancer deaths, 5.5 million CVD deaths, 2.1 million respiratory disease deaths, 94,000 infant deaths, and 11.9 million deaths total (Table 7.4). Excluding deaths from fires and exposures to secondhand smoke, approximately 350,000 persons in the United States have died each year from 1965–1999 because of smoking. Since 1995, annual deaths in the United States that were caused by smoking increased to more than 440,000 (Table 7.3).

Despite the methodologic variability in estimation techniques over the years, cigarette smoking remains the leading cause of preventable mortality in the United States, resulting in nearly 16 million deaths since the first Surgeon General's report on smoking and health in 1964. These calculations do not reflect all determinants of the disease impact of smoking. First, as previously discussed, the reported SAM rates were derived from smoking rates in the current year, whereas actual smoking attributable deaths in the current year were the result of higher smoking rates in previous decades. The lower RRs for former

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[1]Comparability ratios measure the effect of changes in classification and coding rules between versions of the ICD. These ratios are derived by coding the same deaths by both ICD-10 and ICD-9 (for example) criteria separately, and then dividing the number of classified ICD-10 deaths by classified ICD-9 deaths.

Table 7.4   Smoking attributable mortality in the United States, 1965–1999, stratified by gender*

Disease category (ICD-9 code)[†]	Males	Females	Total
Neoplasms[‡]			
Lip, oral cavity, pharynx (140–149)	145,100	36,200	181,300
Esophagus (150)	151,000	38,500	189,500
Stomach (151)	97,000	14,400	111,300
Pancreas (157)	116,500	77,100	193,500
Larynx (161)	85,000	14,600	99,600
Trachea, bronchus, lung (162)	2,286,800	812,200	3,099,000
Cervix uteri (180)	NA[§]	18,000	18,000
Urinary bladder (188)	113,900	29,700	143,600
Kidney, other urinary (189)	74,700	8,200	82,900
Acute myeloid leukemia (205.0)	21,800	4,800	26,600
Total	**3,091,600**	**1,053,700**	**4,145,400**
Cardiovascular diseases[‡]			
Ischemic heart disease (410–414)			
Aged 35–64 years	1,302,400	335,700	1,638,100
Aged 65 years	1,214,800	646,100	1,860,900
Other heart disease (390–398, 415–417, 420–429)	608,300	253,800	862,100
Cerebrovascular disease (430–438)			
Aged 35–64 years	170,400	156,100	327,200
Aged 65 years	175,200	134,200	309,400
Atherosclerosis (440)	145,800	61,800	207,500
Aortic aneurysm (441)	203,300	75,100	278,500
Other arterial disease (442–448)	33,000	22,300	55,300
Total	**3,853,200**	**1,685,800**	**5,539,000**
Respiratory diseases[‡]			
Pneumonia, influenza (480–487)	287,300	127,100	414,400
Bronchitis, emphysema (490–492)	459,000	169,800	628,800
Chronic airways obstruction (496)	694,400	419,000	1,113,400
Total	**1,440,700**	**715,800**	**2,156,500**
Perinatal conditions			
Short gestation/low birth weight (765)	16,700	13,300	29,900
Respiratory distress syndrome (769)	10,800	6,700	17,500
Other respiratory conditions in newborns (770)	20,600	15,400	36,000
Sudden infant death syndrome (798.0)	6,140	4,800	10,900
Total	**54,200**	**40,200**	**94,400**
All conditions	**8,439,700**	**3,495,500**	**11,935,200**

Note: All figures are rounded and hence do not add up.

*Estimates exclude deaths from residential fires caused by smoking and deaths from secondhand smoke exposure.

[†]*International Classification of Diseases, 9th Revision.*

[‡]Among persons aged 35 years.

[§]NA = Not applicable.

Sources: National Center for Health Statistics, public use data tapes, 1965–1999; Klebba 1975; Klebba and Scott 1980; McIntosh 1984; U.S. Department of Health and Human Services 1989b; Thun et al. 1997b; Gavin et al. 2001; American Cancer Society, unpublished data.

smokers may not fully capture their risks from past smoking behaviors because they may have quit very recently and thus have RRs similar to long-term current smokers (CDC 1993). Second, the RR estimates were restricted to adults aged 35 years and older based on available CPS-I and CPS-II data, and thus may exclude risks for death in earlier ages. Third, the RRs were adjusted for the effects of age but not for other potential confounders. As described in Appendix 7-1, there was little additional impact on the SAM estimates for lung cancer, chronic airways obstruction, IHD, and cerebrovascular disease when the effects of education, alcohol, and other confounders were included (Malarcher et al. 2000; Thun et al. 2000). Fourth, deaths from cigar smoking, pipe smoking, and smokeless tobacco use were not included, nor were deaths from fires and secondhand smoke.

1999 State Smoking Attributable Mortality Estimates

Four sets of data are necessary to calculate SAM and SAM rates per 100,000 population for each state (Nelson et al. 1994): (1) state-specific smoking prevalence, (2) mortality (number of deaths), (3) demographic data that are available for all states and for some large municipalities, and (4) national RR estimates—those from CPS-II (CDC 2002d). State-specific smoking prevalence data are available for states that conducted the telephone-based Behavioral Risk Factor Surveillance System (BRFSS) survey supported by CDC. By 1995, all 50 states conducted the BRFSS (CDC 1996b). Mortality data were obtained from vital statistics registries (Hoyert et al. 2001).

Total SAM was approximately 398,000 (ranging from 460 in Alaska to 38,050 in California) (Table 7.5). The 50-state SAM total (397,640) differs somewhat from the average annual national total reported in the previous section (440,200) for several reasons. First, state-specific prevalence estimates from BRFSS data that were used in the PAR calculation are somewhat lower than those from the NHIS data used in national estimates (CDC 2001c, 2002c). Second, cigarette-caused fire deaths, secondhand smoke deaths, and deaths attributable to stomach cancer and myeloid leukemia are not included in each state SAM estimate. Third, California, with the largest state population, has the second-to-lowest smoking prevalence and associated lower mortality rates for many smoking-related diseases of those found in most other states; thus, California weighs down the national SAM total.

The average age-adjusted SAM rate per 100,000 persons was 289.5 (ranging from 156.6 per 100,000 in Utah to 398.8 per 100,000 in Nevada) (Table 7.6). These rates reflect, in part, differences in smoking prevalence and in population and mortality distributions among states. In general, lower SAM rates are found in states with lower rates of smoking.

Smoking Attributable Economic Costs

Economic Cost-of-Illness Measures

Measuring the economic costs of smoking gives policymakers and the public an additional dimension for understanding the burden of disease caused by smoking. Until the early 1990s, only a few estimates of the cost of smoking had been made in the United States (Warner et al. 1999). Estimates of the costs of smoking received increased attention in the 1990s when the states were estimating damages for purposes of lawsuits. For instance, states then engaged in negotiations that led to the 1998 Master Settlement Agreement among 46 states, the District of Columbia, and five commonwealths and territories with the tobacco industry. Published studies on the medical costs of smoking have used a number of approaches to estimate costs, including PAR calculations (Shultz et al. 1991), model-based approaches (CDC 1994; Miller et al. 1998, 1999; Adams et al. 2002), incidence-based measures of present and future costs attributable to smoking (Hodgson 1992), indirect costs of human capital lost from disability and premature deaths, and net social costs (Manning et al. 1989; Herdman et al. 1993; Barendregt et al. 1997; Warner et al. 1999). These studies have produced a wide range of estimates, depending on methodologies, assumptions incorporated into models, data sets used, and other methodologic issues. One key issue is the comparison of the net versus the gross costs of smoking to society. Net costs would include consideration of the economic benefits of taxes, agricultural revenue, ancillary economic activity, and the "costs" of longer lives among nonsmokers that might offset the medical care costs of smokers or their lost productivity while they are alive (Warner 1987; Viscusi 1994; Barendregt et al. 1997; U.S. Department of the Treasury 1998). A thorough discussion of the various methodologies and results is beyond the scope of this chapter, but Warner and colleagues (1999), Chaloupka and Warner (2000), Lightwood and colleagues (2000), and Max (2001) have provided extensive reviews of these issues. The discussion that

Table 7.5 **State annual smoking attributable mortality (SAM) estimates, selected causes of death, United States, 1999**

State	Lung cancer*	Ischemic heart disease*	Cerebro- vascular diseases*	Chronic obstructive pulmonary disease*	Total SAM
Alabama	2,360	1,410	390	1,680	7,540
Alaska	150	90	20	110	460
Arizona	2,010	1,390	300	1,880	6,870
Arkansas	1,620	990	260	1,040	4,900
California	10,900	8,830	1,620	9,920	38,050
Colorado	1,090	750	170	1,410	4,300
Connecticut	1,440	1,030	190	1,080	4,810
Delaware	440	250	40	250	1,210
District of Columbia	230	150	40	110	690
Florida	9,260	6,340	1,020	7,000	28,610
Georgia	3,260	2,050	570	2,350	10,650
Hawaii	340	220	70	190	1,100
Idaho	400	300	70	430	1,510
Illinois	5,500	4,260	870	3,890	18,360
Indiana	3,230	2,140	470	2,350	10,260
Iowa	1,330	1,010	170	1,220	4,620
Kansas	1,160	690	160	1,010	3,920
Kentucky	2,480	1,590	330	1,830	7,780
Louisiana	2,170	1,360	310	1,200	6,350
Maine	660	400	80	580	2,140
Maryland	2,280	1,440	270	1,450	6,750
Massachusetts	2,870	1,620	300	2,150	9,020
Michigan	4,390	3,510	620	3,280	14,700
Minnesota	1,740	930	240	1,450	5,620
Mississippi	1,560	1,080	260	960	4,900
Missouri	2,990	2,370	450	2,370	10,220
Montana	420	220	50	440	1,440
Nebraska	720	400	100	690	2,450
Nevada	980	670	160	830	3,290
New Hampshire	530	340	60	460	1,690
New Jersey	3,560	2,350	380	2,270	10,760
New Mexico	510	440	90	650	2,120
New York	7,450	6,520	760	5,050	24,450
North Carolina	3,760	2,380	560	2,640	11,500
North Dakota	230	200	40	200	860
Ohio	5,840	4,160	750	4,470	18,860
Oklahoma	1,780	1,360	260	1,290	5,780
Oregon	1,520	850	250	1,330	4,970
Pennsylvania	6,200	4,240	730	4,540	19,770
Rhode Island	570	410	60	380	1,720

Note: **All figures are rounded and hence do not add up.**

International Classification of Diseases, 9th Revision **(ICD-9), codes 162, 410–414, 430–438, 490–492, and 496.**

Table 7.5   Continued

State	Lung cancer	Ischemic heart disease	Cerebro-vascular diseases	Chronic obstructive pulmonary disease	Total SAM
South Carolina	1,880	1,220	360	1,290	5,950
South Dakota	320	230	50	250	1,080
Tennessee	3,120	2,150	460	2,110	9,570
Texas	7,390	5,440	1,070	5,650	24,080
Utah	300	210	50	380	1,230
Vermont	270	150	30	220	820
Virginia	3,060	1,710	420	2,010	9,120
Washington	2,450	1,450	340	2,060	7,770
West Virginia	1,260	830	130	950	4,230
Wisconsin	2,190	1,670	400	1,760	7,830
Wyoming	190	120	30	260	740
Total					**397,640**

Sources: Thun et al. 1997b; Behavioral Risk Factor Surveillance System: Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health, public use data tape, 1999; Gavin et al. 2001; Hoyert et al. 2001; CDC 2002a,d,e; American Cancer Society, unpublished data.

follows includes a brief review of recently published findings.

In the United States, direct medical costs for the detection, treatment, and rehabilitation of persons with smoking attributable clinical diseases have been the primary outcome variable in the cost models. These smoking attributable costs have been consistently estimated at 6 to 8 percent of the total annual expenditures for health care, with an estimated upper bound as high as 14 percent (Warner et al. 1999). Indirect morbidity and mortality costs are defined as the costs for excess sickness and disability days for smoking-linked illnesses, as well as lost productivity due to premature death from the effect of smoking on longevity (Rice et al. 1985).

The earliest attempts to estimate national health care expenses date from around 1950, and the cost-of-illness methodology was formalized and upgraded by Rice and colleagues through multiple iterations during the last three decades (Cooper and Rice 1976; Hodgson and Kopstein 1984; Rice et al. 1985). In 1986, Rice and colleagues (1986) estimated costs for direct health care, including physician care, hospital care, pharmaceuticals, home health care, and nursing home care for broad disease categories including CVD, respiratory diseases, and cancers. Using ratios of hospital days and physician visits for ever smokers compared with lifetime nonsmokers, these investigators estimated $14.4 billion in 1984 direct medical care costs attributable to smoking from neoplastic, circulatory, and respiratory diseases only.

Rice and colleagues (1986) applied NHIS data for work-loss days, disability days, and the percentage of the population unable to work due to disabling illnesses or premature death in a similar fashion to the direct-cost method used to estimate smoking attributable indirect morbidity and mortality costs. Relative rates of disability and work-loss for ever smokers and lifetime nonsmokers were used to estimate the SAF of morbidity costs at $7.4 billion in 1984. Indirect mortality costs, defined as the economic value of forfeited future earnings for persons who die prematurely from smoking-related causes (Herdman et al. 1993), were valued at $16.8 billion in 1984. Thus, the total estimate of smoking attributable costs for 1984 was $38.6 billion in 1980 dollars. Indirect costs are substantial and account for one-half to three-quarters of total costs, with mortality alone accounting for 40 to 66 percent of total costs (Max 2001).

The Office of Technology Assessment (OTA 1985) calculated smoking attributable costs using the same method as Doll and Peto (1981), applying attributable mortality to CPS-I data from the 1960s and 1970s. OTA staff consulted with an expert committee of health

Table 7.6   State age-adjusted smoking attributable mortality (SAM) rates per 100,000 persons, selected causes of death, United States, 1999

State	Lung cancer*	Ischemic heart disease*	Cerebro-vascular diseases*	Chronic obstructive pulmonary disease*	Total SAM
Alabama	104.3	63.1	17.3	75.5	336.5
Alaska	84.7	46.0	16.1	83.9	288.2
Arizona	81.3	61.4	12.4	74.7	286.1
Arkansas	113.2	70.3	18.4	72.3	342.1
California	73.3	60.0	10.9	67.6	257.0
Colorado	61.5	41.1	9.1	84.6	247.0
Connecticut	78.6	54.8	9.8	55.5	255.3
Delaware	113.0	67.8	10.9	66.6	317.1
District of Columbia	82.4	52.1	12.7	39.2	245.5
Florida	91.9	64.2	10.8	65.6	278.4
Georgia	101.4	63.5	17.5	77.6	335.0
Hawaii	51.9	33.7	10.4	28.7	167.8
Idaho	66.4	48.5	11.5	71.6	247.7
Illinois	91.5	69.9	14.2	63.9	302.1
Indiana	107.9	71.4	15.6	78.6	342.6
Iowa	79.8	57.8	9.8	68.9	266.0
Kansas	83.4	48.0	11.2	69.6	271.6
Kentucky	122.4	79.1	16.7	92.4	388.8
Louisiana	105.6	66.4	15.1	60.3	312.2
Maine	95.5	56.6	10.7	82.4	305.5
Maryland	93.6	60.0	11.3	61.4	280.3
Massachusetts	86.0	47.6	8.5	61.3	263.8
Michigan	88.8	71.3	12.6	66.7	297.4
Minnesota	73.5	37.6	9.7	58.8	229.6
Mississippi	117.5	81.7	19.3	72.7	368.9
Missouri	102.0	80.1	15.1	79.3	344.6
Montana	84.6	43.6	10.9	88.9	290.5
Nebraska	80.6	43.0	10.2	72.3	263.0
Nevada	110.8	81.3	19.9	106.4	398.8
New Hampshire	92.0	58.1	9.6	78.9	290.6
New Jersey	81.1	53.7	8.7	51.0	244.3
New Mexico	61.3	54.4	11.0	80.5	259.4
New York	77.0	67.0	7.8	51.6	251.5
North Carolina	96.3	63.4	14.9	70.9	305.0
North Dakota	62.6	51.8	10.1	49.6	225.0
Ohio	98.2	70.8	12.7	74.7	317.2
Oklahoma	98.6	75.5	14.6	71.4	319.9
Oregon	84.7	46.2	13.8	73.4	273.6
Pennsylvania	86.0	59.6	10.3	60.1	272.2
Rhode Island	98.7	69.9	9.7	61.0	288.6

International Classification of Diseases, 9th Revision (ICD-9), **codes 162, 410–414, 430–438, 490–492, and 496.**

Table 7.6   Continued

State	Lung cancer	Ischemic heart disease	Cerebro-vascular diseases	Chronic obstructive pulmonary disease	Total SAM
South Carolina	97.7	65.0	19.0	70.3	316.6
South Dakota	78.3	53.5	11.5	55.1	250.6
Tennessee	112.0	78.2	16.5	77.9	347.6
Texas	87.1	64.0	12.5	69.8	287.3
Utah	37.6	26.2	6.9	48.8	156.6
Vermont	90.2	49.4	7.8	75.6	272.3
Virginia	95.5	54.3	13.3	66.0	291.2
Washington	89.1	51.4	10.0	75.4	279.4
West Virginia	116.3	77.4	11.7	87.4	392.8
Wisconsin	79.2	58.5	13.9	61.4	275.9
Wyoming	80.5	48.8	11.0	113.0	315.1
Average age-adjusted SAM rate					**289.5**

Sources: Thun et al. 1997b; Behavioral Risk Factor Surveillance System: Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health, public use data tape, 1999; Gavin et al. 2001; Hoyert et al. 2001; CDC 2002a,d,e; American Cancer Society, unpublished data.

economists and epidemiologists to develop a consensus methodology for performing these computations. In 1985 dollars, the median estimate for direct health care costs was $22 billion, indirect lost productivity costs were $43 billion, and total costs were $65 billion. The confidence interval (CI) around this estimate was large, ranging from $38 billion to $95 billion. National direct costs were equivalent to $0.72 per pack sold in 1985 dollars, and indirect costs were equal to $1.45 per pack, for a total of $2.17 per pack (OTA 1985).

An incidence-based method reported by Hodgson (1992) estimates costs of illness over the lifetimes of smokers and former smokers, separating the survivors and decedents. This approach models expected expenditures during different age intervals given survival, death, the probability of survival, and the probability of dying during these age intervals.

Expected per person expenditures during age interval t are

$$E(st) = E(st)P(st) + E(dt)P(dt),$$

where $E(st)$ = expenditures during age interval t for survivors s,

$E(dt)$ = expenditures during age interval t if the individual dies in t,

$P(st)$ = probability of surviving through age interval t, and

$P(dt)$ = probability of dying during age interval t.

Expenditures are discounted to obtain the present value of the stream of dollars that occurs over time. This method accounts for uneven medical care expenditures for different age groups, especially at the end of life. Higher medical care use among smokers may be partially offset by the higher mortality of smokers, which reduces lifetime expenditures. Hodgson (1992) estimated that the current population of smokers would increase the cost of health care by about $500 billion over their remaining lifetimes.

CDC (1994) used a two-stage econometric model from Duan and colleagues (1983) and estimated that smoking attributable costs were $50 billion annually in 1993 dollars. Researchers developed a model for smoking attributable risks using data from the 1987 National Medical Expenditures Survey (NMES-2) and from the Health Care Financing Administration (now called the Centers for Medicare & Medicaid Services) to provide estimates for direct medical care expenditures for adults resulting from smoking attributable illnesses for five cost categories (Table 7.7) (CDC 1994;

Table 7.7 National medical expenditures and percentage of total health care expenditures attributable to cigarette smoking for adults, United States, 1993

Expense category	Smoking attributable fraction (%)	Expense ($ in billions)
Hospitals	7.5	26.9
Ambulatory care	7.7	15.5
Nursing home care	6.6	4.9
Prescription drugs	2.6	1.8
Home health care	7.0	0.9
Total	**7.1**	**$50.0**

Source: Centers for Disease Control and Prevention 1994.

Miller et al. 1998). NMES-2 data were first used to estimate the effect of smoking history on the presence of smoking-related medical conditions (i.e., heart disease, emphysema, arteriosclerosis, stroke, and cancer). They were also used to estimate the probability of having any expenditures, and the level of expenditures, for those with positive expenditures related to prescription drugs, hospitalizations, ambulatory care, home health care, and nursing home care as a function of smoking, medical conditions, and health status. This method controlled for age, race, ethnicity, poverty status, marital status, education level, medical insurance status, region of residence, and other variables associated with health status. The model estimated smoking-related expenditures for the U.S. population during the 1988 NMES-2 study period (Figure 7.1).

Using the national model described above with data on populations likely to be receiving publicly funded medical care and data from various state-specific behavioral risk factor surveys, Miller and colleagues (1998) calculated the SAFs for Medicaid costs for each state (national average, 14.4 percent; range, 8.6 percent in Washington, D.C., to 19.2 percent in Nevada). The total Medicaid cost to the states attributable to smoking in 1993 was $12.9 billion. This

Figure 7.1 Schematic representation of the national model to estimate smoking-related expenditures for 1988
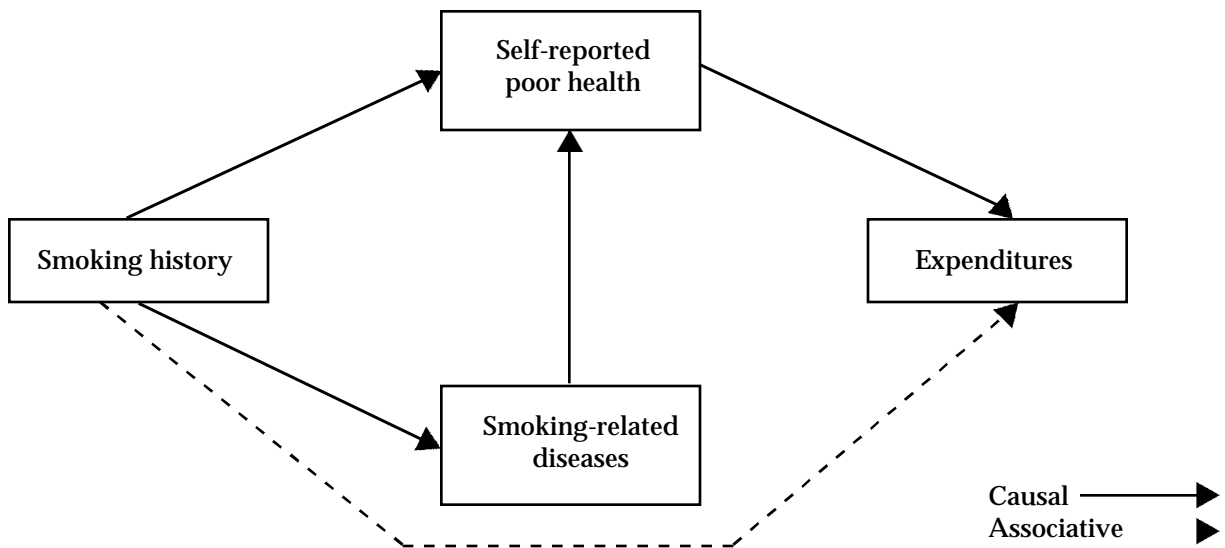
Note: Data elements shown in each box were collected on the National Medical Expenditure Survey in 1988–1989.
Source: Miller et al. 1998.

estimate (as well as the national estimate of $50 billion noted earlier) may be low because it does not include neonatal costs or costs for illnesses among children exposed to smoking in the home (estimated at $1.97 billion in 1993 [Aligne and Stoddard 1997]), costs of burn injuries from cigarette-caused fires, costs of medical care for persons terminally ill or institutionalized (including military and veterans hospitals), and costs of secondhand smoke-caused illnesses among adults (Novotny 1998). The estimates are also limited by not having direct information on the risk of nursing home utilization for smokers compared with nonsmokers. The calculations for direct nursing home care costs used the SAF for hospitalization costs for persons aged 65 years and older because data from institutionalized persons were not collected in NMES-2. A later study (Miller et al. 1999) attempted to model the SAF for nursing home expenditures using a separate NMES survey on nursing home admissions. This model estimated the probability of admission to a nursing home, given a smoking history. Large potential costs were indicated by the model. However, multiple admissions and length of stay were not considered, and these elements may increase the SAF for nursing home costs substantially.

CDC (2002a) used the methodology of Miller and colleagues (1999) to estimate annual total and per smoker indirect morbidity costs and smoking attributable medical expenditures for 1995–1999 (Table 7.8). Total annual costs (including all sources of payment) were approximately $75.5 billion using this methodology. Approximate losses of $82 billion are attributed to lost productivity resulting from smoking attributable diseases. Costs for neonatal health care attributable to smoking were estimated for one year, 1996, and equaled $366 million. Total direct SAF costs were in the 6 percent range reported in previous studies (Warner et al. 1999; Max 2001). Total annual direct and indirect costs for 1995–1999 were $157.7 billion.

These estimates vary with the methodology used to estimate costs (Chaloupka and Warner 2000). The studies described earlier emphasized current smoking history, using cross-sectional prevalence data and current year mortality data to estimate costs. The cost-of-smoking estimates were an important part of the damage claims used during negotiations of the 1998 Master Settlement Agreement between the states' Attorneys General and the tobacco industry (American Legacy Foundation 2002). These state-specific estimates (Miller et al. 1998) addressed losses to state budgets through Medicaid and other state health program expenditures that would not "benefit" from premature deaths and reduced pensions or long-term

Table 7.8   Annual smoking attributable economic costs for adults and infants, United States, 1995–1999

Cost component	Total ($ in millions)
Lost productivity	
Men	55,389
Women	26,483
Total	**81,872**
Direct medical care (adults)	
Ambulatory care	27,182
Hospital care	17,140
Prescription drugs	6,364
Nursing home	19,383
Other care	5,419
Total	**75,488**
Neonatal care*	366
Total costs	**$157,726**

*1996 only
Source: Centers for Disease Control and Prevention 2002a.

care costs borne by the Medicare program. This agreement reimbursed the states for medical care provided by taxpayers for smoking-related diseases, resulting in annual payments through 2025 totaling $246 billion.

In 2001, the American Legacy Foundation (2002) estimated that states had spent $12 billion on smoking attributable diseases and that $1.1 billion annually could be saved if the prevalence of adult smoking were 50 percent less in 2001. The cost-of-illness approach offers one perspective on the disease burden from tobacco. The cost estimates should be useful for policymakers with fiduciary responsibility to taxpayers to reduce current preventable disease burdens and the subsequent economic costs of these burdens. As economic burdens for health care increase both for governments and private individuals, such analyses might provide a stimulus to fund tobacco prevention and control programs at higher levels (American Legacy Foundation 2002).

Cost Offsets: Extended Life Expectancy for Nonsmokers and Former Smokers

The U.S. health system is based on an ethical construct that values increased life expectancy and quality of life (USDHHS 2000). However, economists have used econometric models to estimate the net effects of

prolonged life on health and social support systems, considering not only the costs of smoking but of potential economic gains from smoking.

For example, Barendregt and colleagues (1997) concluded that successful smoking cessation and health promotion activities would produce positive economic outcomes (referred to as gross outcomes) in the short run. Barendregt and colleagues (1997), however, did not consider the higher contribution made by longer living nonsmokers to pension and tax systems in making their calculations (Max 2001).

Manning and colleagues (1989) estimated the lifetime, discounted costs that smokers impose on others. Instead of total economic costs, the study focused on only those financial costs that are external to the smokers and their family members; that is, costs paid by insurance companies, the state, or public agencies in caring for smokers and borne by nonsmokers because these are the costs relevant to tax policy. Results indicate that nonsmokers subsidize smokers' medical care and group life insurance while smokers subsidize non-smokers' pension and nursing home payments because of their shorter life expectancy. The net external financial costs that smokers impose on nonsmokers are positive at a 5 percent discount rate ($0.15 per pack), but the excise tax revenue from cigarettes at the time of the analysis exceeded those external costs. The costs of lung cancer deaths caused by involuntary smoking and deaths caused by smoking-related fires were not included in this estimate because they were considered internal costs (costs to the individual or to his/her family unit). Costs related to maternal smoking were also omitted. With all lives lost to involuntary smoking and to smoking-related fires defined as external costs, the total external cost per pack was estimated at $0.38 in 1986 dollars. This may be an uncertain estimate of net external costs due to imperfect data sources and unquantifiable confounding factors. In addition, there was no consideration of annoyance, pain and suffering, or other noneconomic costs (Gravelle and Zimmerman 1994). This same study found that the range of costs produced by various authors varied between net external savings of $0.17 per pack to costs of $2.36 per pack. These estimates depended on discount rates used in calculations, costs assigned to involuntary smoking, and various other differences, and therefore Gravelle and Zimmerman (1994) asserted that the net cost estimates produced by Manning and colleagues (1989) provided a satisfactory midpoint estimate.

In an extensive review by the World Bank (Lightwood et al. 2000), the gross health care costs of smoking for high-income countries ranged from 0.10 to 1.1 percent of the gross domestic product, and most of the net-versus-gross cost studies showed net costs for smoking.

The value of longevity and quality of life may be difficult to economically quantify. However, at least one study has discussed the issue of compression of morbidity when smoking is reduced. Using a cross-sectional study of Dutch nationals, Nusselder and colleagues (2000) found that a nonsmoking population spends fewer years with disability than a reference population of smokers and nonsmokers. The nonsmokers had lower mortality risks, but they also had a lower incidence of disability and a higher level of recovery from disability. This status resulted in reduced average time lived with disability (-0.9 years for men aged 30 years and -1.1 years for women) and increased average time lived without disability (2.5 years for men and 1.9 years for women) (Nusselder et al. 2000). Thus, with a nonsmoking population the length of life as well as the length of a disability-free life will be extended. This extension will then compress the disability for nonsmokers into a shorter period toward death; smokers, with lengthier periods of disability, will suffer earlier mortality, but they will also have more disability and certainly more medical care expenditures while disabled when compared with nonsmokers. Although the disability suffered by former smokers will be less than that of current smokers, mortality and disability risks will still be higher among former smokers than among lifetime nonsmokers.

It is clear that methodologic variability and different approaches to gross-versus-net cost estimates can lead to a wide variety of results. However, these should all be considered in the context of the public health premise that prolonging disability-free life is the goal of the health care system (Murray et al. 1994; USDHHS 2000), and thus any negative economic impacts from gains in longevity with smoking reduction should not be emphasized in public health decisions.

Other Costs

Other considerations in the net-versus-gross cost debate are presented in the following section. Previously described studies do not describe all dimensions of the impact of smoking and smoking attributable disease. For example, the pain and suffering, decreased

quality of life, and related psychosocial aspects of physical illness are not measured (Hodgson and Meiners 1982). Prevalence-based, cost-of-illness calculations do not account for economic factors such as Social Security disbursements, pension claims, changes in the demand for health specialties related to the treatment of smoking-related illnesses, and the employment by or monetary dividends from the tobacco industry (Warner 1987). Smoking can cause costs without impacting mortality or even morbidity among smokers. For example, the health or mortality of a smoking spouse may have an effect on nursing home admission rates for the nonsmoking spouse; in addition, lost income to family members who must care for smokers with prolonged disabilities is not usually measured (Max 2001). These are actually direct costs rather than indirect or human capital losses. Costs to employers for absenteeism, lost productivity, higher insurance premiums for smokers (Weis 1981; Kristein 1983), and liability incurred for exposing nonsmokers to passive smoke may also be included as an economic cost of smoking.

Several studies (Warner et al. 1999; Chaloupka and Warner 2000; Lightwood et al. 2000; Max 2001)

have reviewed these economic issues and ongoing controversies that primarily involve the net-versus-gross cost of tobacco on society. This controversy, however, ignores the main burden—that of health—when it dwells on the "benefits" of smoking that result from premature death. Generally, however, it appears that direct costs attributable to smoking comprise 6 to 9 percent of the total national health care budget. Cost estimates have tended to increase over time, reflecting improvements in methodology, increases in medical expenditures for smoking-related diseases because of inflation and/or technology, and expansion of the list of diseases caused by smoking.

Further research on the economic costs of nursing home care is needed as the impact of smoking on admissions to and utilization of nursing homes is not well described. There are also insufficient data on the costs from passive smoking-related illnesses (Max 2001). Indirect costs need more research at the national level, and costs to employers resulting from smoking by their employees should also be the subject of additional research (Max 2001).

Health Benefits of Reducing Cigarette Smoking

Premature Deaths Prevented If the *Healthy People 2010* Prevalence Objectives Are Achieved

To reduce the health consequences of smoking, the Public Health Service targeted substantial reductions in youth and adult smoking rates in the *Healthy People 2010* objectives (USDHHS 2000). The purpose of the *Healthy People 2010* goals is to reduce current smoking from 35 percent (in 1999) to 16 percent among high school youth aged 14 through 17 years, and to reduce current smoking from 24 percent (in 1998) to 12 percent among adults aged 18 years and older. Current smoking among young people was defined as having smoked on 1 or more days in the past 30 days, as reported in the Youth Risk Behavior Survey (CDC 2001e). Current smoking among adults was defined

as ever having smoked 100 cigarettes or more and currently smoking every day or some days, as reported in the NHIS (NCHS 2002).

Whether or not the necessary changes in smoking initiation and cessation are achievable has been the source of some debate. Mendez and Warner (2000) suggested that the *Healthy People 2010* objective to halve U.S. adult smoking prevalence by 2010 was unattainable, and proposed that a more realistic scenario involving a 50 percent reduction in youth initiation rates and the doubling of adult cessation rates could bring the smoking prevalence among adults to 16.7 percent by 2010. A scenario involving a gradual one-third decline in youth initiation and a 50 percent increase in adult cessation rates by 2010 would achieve an estimated youth prevalence rate of 22 percent and an estimated adult prevalence rate of 18 percent.

CDC (unpublished data) has estimated the SAM that could be averted if the *Healthy People 2010* goals for tobacco use were achieved or if the more modest prevalence reductions projected by Mendez and Warner (2000) were made. CDC used a three-step process to estimate the burden of SAM that could be prevented by reducing smoking prevalence. In step one, the number of future smokers in 2010 (by age) was projected based on current smoking prevalence estimates derived from each of three scenarios (Table 7.9): (1) youth initiation and cessation rates as well as adult cessation rates remain unchanged (status quo prevalence), (2) youth initiation declines by one-third and adult cessation increases by 50 percent by 2010 (modest reductions in prevalence), and (3) youth smoking prevalence declines from 35 to 16 percent and adult prevalence is halved for all age groups (i.e., the *Healthy People 2010* objectives are met). For each prevalence reduction scenario, smoking prevalence rates and the number of smokers in 2010 were estimated for persons aged (in years) 10 through 17, 18 through 24, 25 through 44, 45 through 64, and 65 and older. These calculations projected overall that the number of current smokers in 2010 would be approximately 56.2 million for the status quo prevalence scenario, 49.1 million for the modest prevalence scenario, and 32.3 million for the *Healthy People 2010* prevalence reductions.

For the second step, the investigators estimated the proportion of preventable premature SAM by age through the reductions in smoking (Table 7.10). For each age, the proportion of lifelong smokers

Table 7.9 Smoking prevalence and the number of smokers in 2010 for alternative smoking reduction scenarios, stratified by age, United States

Age	Status quo prevalence*	Modest reductions[†]	*Healthy People 2010* reductions[‡]
	Current smoking prevalence (%)		
10–17 years	36.0	24.4	16.0
Adults	19.5	18.1	12.0
18–24 years	26.9	22.6	14.0
25–44 years	24.1	23.8	13.8
45–64 years	17.4	15.8	12.5
65 years	9.3	7.9	5.5
	Number of smokers[§]		
10–17 years	11,714,200	7,948,200	5,210,400
18–24 years	8,104,100	6,803,600	4,207,700
25–44 years	18,896,800	18,640,400	10,765,400
45–64 years	13,821,400	12,599,000	9,948,600
65 years	3,682,400	3,132,500	2,164,500
Total	**56,218,900**	**49,123,600**	**32,296,600**

Note: Figures for the number of smokers are rounded and hence do not add up.

*Assumes constant youth smoking prevalence of 35% (1998 data) and adult cessation rates of 0.21%, 2.15%, and 5.96% for ages 18–30, 31–50, and   51 years, respectively. Smoking prevalence estimates for adults are from the 1998 National Health Interview Survey. Data from the 1999 Youth Risk Behavior Survey were used to project the percentage of 10–17-year-olds expected to become smokers (Centers for Disease Control and Prevention [CDC] 2001b).

[†]Assumes constant annual changes: by 2010, youth initiation rates will decline by one-third and adult cessation rates will increase by 50%.

[‡]Assumes *Healthy People 2010* goals are met: reducing youth smoking prevalence among persons aged <18 years to 16% and prevalence among persons aged   18 years and for each age group by 50% overall (U.S. Department of Health and Human Services 2000).

[§]Based on U.S. Census Bureau population projections (U.S. Census Bureau 2002).

Source: CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Table 7.10 Low-, middle-, and high-range estimates of proportions of smoking-related disease (SRD) deaths and preventable deaths among current smokers, stratified by age, United States

Age	Low	Middle	High
A. Percentage of lifelong smokers expected to die from a SRD* (%)			
10–17 years	24	32	50
18–24 years	24	32	50
25–44 years	32	32	50
45–64 years	32	50	50
65 years	50	50	50
B. Expected preventable[†] SRD deaths of lifelong smokers (%)			
10–17 years	100	100	100
18–24 years	100	100	100
25–44 years	75	100	100
45–64 years	26	53	80
65 years	9	24	64
C. Percentage of future SRD deaths preventable with cessation (A x B) (%)			
10–17 years	24.0	32.0	50.0
18–24 years	24.0	32.0	50.0
25–44 years	24.0	32.0	50.0
45–64 years	8.3	26.5	40.0
65 years	4.5	12.2	32.0

*Centers for Disease Control and Prevention (CDC) 1996b; *Federal Register* 1996; Peto et al. 2000.

[†]Assumes that 100% of future SRD deaths are preventable if smokers quit before 45 years of age; the low estimate for smokers aged 25–44 years assumes that only 75% are preventable (100% for 25–34-year-olds and 50% for 35–44-year-olds). For smokers aged 45–64 years, 10% (low), 23.5% (middle), and 37% (high) of deaths among quitters are not considered preventable. For persons aged 65 years, the preventable proportion was reduced by the same percentage as the decline in the preventable proportion between the 25–44-year-old and the 45–64-year-old age groups.

Source: CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

anticipated to die from a smoking-related disease was multiplied by the percentage of future deaths that are likely preventable through cessation or by preventing initiation. Between 24 and 50 percent of lifelong smokers, depending on age, are expected to die of a smoking-related disease (*Federal Register* 1996; Thun et al. 1997a; Peto et al. 2000). Depending on the age at which smokers quit, all or some of the expected future excess premature deaths are preventable. The percentages of preventable future premature deaths are listed in Table 7.10, Section B. The investigators assumed that 100 percent of future premature deaths from smoking are preventable for persons 10 through 44 years of age if they quit or if they do not initiate smoking (CDC, unpublished data), except for persons aged 25 through 44 years in the low-range column for whom

they assumed that 75 percent of future SAM was preventable (i.e., 100 percent preventable for persons aged 25 through 34 years and 50 percent preventable for persons aged 35 through 44 years).

For former smokers aged 45 years and older, the percentage of preventable future deaths was calculated using published estimates of the proportions of risk among quitters that were not preventable through cessation (i.e., the remaining risks of future deaths). An estimated 10 to 37 percent of former smokers will die of a smoking-related disease even after quitting smoking (CDC, unpublished data). This finding suggests that the percentage of deaths that are preventable ranges from as much as 80 percent (1 minus [0.1 divided by 0.5]) to as little as 26 percent (1 minus [0.37 divided by 0.5]) for former smokers aged 45 through

64 years. For the middle-range estimate, the assumption is that 23.5 percent (the midpoint of 10 to 37 percent) of former smokers aged 45 through 64 years will still die of a smoking-caused disease. Thus, 53 percent (1 minus [0.235 divided by 0.5]) of expected SAM is preventable. For smokers aged 65 years and older, the same percentage decrease in preventable SAM was assumed to occur between the ages of 45 through 64 years and 65 years and older, plus the decreases estimated for ages 25 through 44 and 45 through 64 years. For each age group and risk-of-death range, the proportion of lifelong smokers expected to die from a smoking-related death was multiplied by the percentage of preventable deaths. The results are age-specific estimates of the proportions of future SAM that would be preventable if lifelong smokers were to quit.

For the final step, the investigators calculated the number of smoking-related deaths that would be prevented as a result of a reduction in smoking prevalence in 2010 by multiplying the differences in the number of current smokers for each of the two prevalence reduction goals by the actual proportions of preventable SAM in Section C of Table 7.10. This approach produced low-, middle-, and high-range projections of the number of premature deaths avoided for each of the two levels of reduction in current smoking prevalence. The investigators then calculated how many premature deaths would be avoided by achieving the *Healthy People 2010* goals compared with meeting the modest reductions in prevalence.

The results indicate that under the middle-range preventable proportion assumptions, achieving the modest prevalence reductions by 2010 will prevent approximately 2.5 million expected premature deaths from smoking, compared with the number of projected premature deaths for the status quo youth and adult prevalence rates in 2010 (Table 7.11). The range of projected averted premature deaths is 1.7 to 4 million for the modest prevalence reductions, depending on assumptions about the proportions of future premature deaths that are preventable through quitting (Table 7.11). Compared with the status quo prevalence, achieving the *Healthy People 2010* smoking prevalence objectives will prevent approximately 7.1 million expected premature deaths from smoking, with a range of 4.8 to 11 million. Assuming that recent tobacco control efforts are able to achieve the modest reductions in smoking prevalence, meeting the *Healthy People 2010* goals will prevent an additional 5 million deaths under the middle-range preventable proportion assumptions, with a range of 3.4 to 8 million.

These results demonstrate that reducing smoking prevalence can prevent millions of the future premature deaths expected if youth smoking and initiation rates as well as adult cessation rates stay at 1998 levels. Modest reductions in youth and adult smoking prevalence by 2010 could prevent about 2.5 million deaths, compared with the status quo prevalence estimates.

Existing interventions have led to reductions in tobacco use prevalence and per capita consumption (CDC 2001b). A comprehensive review of programs in California, Massachusetts, Oregon, Arizona, and Florida by Siegel (2002) covers both the positive effects of such programs on smoking prevalence and the negative effects that follow reduced support from the states. In general, comprehensive programs have substantially reduced adult smoking prevalence and per capita consumption following their implementation in the late 1980s and early 1990s. Secular trends in California and Massachusetts before program implementation may have also contributed to reduced disease burdens attributable to smoking over time.

Nevertheless, substantial declines in the per capita use of cigarettes and in adult smoking prevalence in California through the 1990s were associated with a comprehensive program implemented in 1988 (Siegel et al. 2000). During the first years of the program (1989–1993), adult prevalence declined 1.1 percentage points per year in California, compared with 0.6 percentage points per year in the rest of the United States. Adult smoking prevalence is now 17.2 percent in California, compared with the median of 23.3 percent for all states (CDC 2002c). Moreover, there is now evidence to suggest that this reduction has contributed to a decline in the tobacco-related disease burden over time. During 1988–1997, age-adjusted incidence rates for lung cancer declined 14 percent in California, compared with only 2.7 percent in non-California cancer surveillance regions (CDC 2000). In an analysis of trends in mortality from heart disease between 1989 and 1997, there were 33,300 fewer deaths from heart disease than expected in California compared with the rest of the United States (Fichtenberg and Glantz 2000). However, lung cancer mortality will change slowly in response to population smoking prevalence changes, and thus the secular changes present in California before the start of the program contributed to the decline in lung cancer mortality. Cardiovascular mortality changes will be much more rapid, and these changes appear to be closely associated with program activity level.

Table 7.11   Estimated number of preventable smoking-related disease (SRD) deaths and *Healthy People 2010** prevalence reduction goals, stratified by age, United States

Age	Preventable number of smoking-related deaths		
	Low	**Middle**	**High**
A. *Healthy People 2010* vs. status quo prevalence†			
10–17 years	1,570,000	2,100,000	3,250,000
18–24 years	935,000	1,250,000	1,950,000
25–44 years	1,950,000	2,600,000	4,070,000
45–64 years	322,000	1,020,000	1,550,000
65 years	68,500	161,000	486,000
Total	**4,800,000**	**7,100,000**	**11,000,000**
B. Modest‡ reductions vs. status quo prevalence			
10–17 years	904,000	1,200,000	1,880,000
18–24 years	448,000	599,000	934,000
25–44 years	164,000	219,000	342,000
45–64 years	124,000	395,000	596,000
65 years	28,000	75,000	197,000
Total	**1,700,000**	**2,500,000**	**4,000,000**
C. *Healthy People 2010* vs. modest reductions in prevalence			
10–17 years	657,000	876,000	1,370,000
18–24 years	623,000	831,000	1,300,000
25–44 years	1,890,000	2,500,000	3,940,000
45–64 years	220,000	702,000	1,060,000
65 years	44,000	118,000	310,000
Total	**3,400,000**	**5,000,000**	**8,000,000**

Note: All figures are rounded and hence do not add up.

**Healthy People 2010* goals are to reduce smoking among persons aged <18 years to 16% and among persons aged   18 years by 50% overall and for each age group (U.S. Department of Health and Human Services [USDHHS] 2000).

†The status quo prevalence assumes that smoking initiation and cessation rates will remain constant between 1998 and 2010.

‡The modest reductions in prevalence assume constant annual changes: by 2010, youth initiation rates will decline by one-third and adult cessation rates will increase by 50%.

Sources: USDHHS 2000; Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

In Massachusetts, a comprehensive tobacco control program implemented in 1992 was associated with a decline of 0.43 percentage points per year in adult smoking prevalence between 1992 and 1999 (Biener et al. 2000). In Arizona, state-specific surveys following implementation of a comprehensive program in 1994 indicate that adult prevalence declined from an estimated 23 percent to approximately 20 percent between 1996 and 1999 (CDC 2001d). In Oregon, adult smoking prevalence declined from 23.4 percent in 1996 to 21.4 percent in 1999 after implementation of the 1996 tobacco control program (CDC 1999b). These changes, although modest, compare favorably with the 0.03 annual percentage point increase in adult prevalence in comparison states during approximately the same period (Siegel 2002).

Information regarding the population burden of the health effects of smoking helps to quantify the potential health and economic impacts of reduced smoking prevalence. What studies are needed to

assess the actual versus the imputed potential consequences for health of reducing smoking? PAR projections have been used to assess the impact of population-based health programs, such as in the Framingham study on CVD (Sturmans et al. 1977). In this study, a 37.3 percent attributable risk reduction in CVD mortality might have been achievable through the elimination of smoking, but because of the complex mix of strengths of association for different parts of the population, the baseline risks of the population, the proportion of the population affected by the intervention, and the degree of risk factor reduction achieved, only a few percentage point changes attributable to smoking reductions by a specific program per se were achieved. Keying interventions to specific risk groups may improve health results for these groups without necessarily reducing the population burden of mortality (Rothenberg et al. 1991). Thus, the PAR approach sets the stage for additional analyses and helps drive policies to address the population effects as well as the individual effects of smoking.

Summary

Regardless of the methodologic issues around the estimation methods, cigarette smoking remains the leading single cause of preventable mortality in the United States. This chapter reviewed various methods for assessing the disease burden of smoking-related illnesses, including epidemiologic calculations, indirect estimates, and model-based approaches for assessing smoking attributable mortality. The PAR calculation, with appropriate controls for age and gender, offers useful estimates of the mortality burden of disease attributable to tobacco use in the U.S. population. These estimates are not biased strongly by confounding factors, even though smokers, compared with nonsmokers, tend to have different profiles for a number of lifestyle-related risk factors for disease and may have different costs for even the same condition. Economic disease burden estimates have been used to provide a more compelling argument as to the costs of smoking to governments and society in general, thus adding information that can be used to support comprehensive tobacco use prevention and control programs.

Conclusions

1. There have been more than 12 million premature deaths attributable to smoking since the first published Surgeon General's report on smoking and health in 1964. Smoking remains the leading preventable cause of premature death in the United States.

2. The burden of smoking attributable mortality will remain at current levels for several decades. Comprehensive programs that reflect the best available science on tobacco use prevention and smoking cessation have the potential to reduce the adverse impact of smoking on population health.

3. Meeting the *Healthy People 2010* goals for current smoking prevalence reductions to 12 percent among persons aged 18 years and older and to 16 percent among youth aged 14 through 17 years will prevent an additional 7.1 million premature deaths after 2010. Without substantially stronger national and state efforts, it is unlikely that this health goal can be achieved. However, even with more modest reductions in tobacco use, significant additional reductions in premature death can be expected.

4. During 1995–1999, estimated annual smoking attributable economic costs in the United States were $157.7 billion, including $75.5 billion for direct medical care (adults), $81.9 billion for lost productivity, and $366 million in 1996 for neonatal care. In 2001, states alone spent an estimated $12 billion treating smoking attributable diseases.

Implications

Population attributable risk estimates that indicate how much of the disease burden attributable to smoking can be avoided through tobacco control interventions are an important starting point for policy development. In addition, economic cost-of-illness studies on tobacco-related diseases can help inform policymakers about the benefits of supporting comprehensive tobacco use prevention and control programs, especially at the state level. Comprehensive interventions at state and federal levels, including educational, clinical, regulatory, and economic actions, have been shown to reduce smoking rates and to subsequently reduce the population disease burden caused by tobacco.

There is a need for additional research on the costs of illnesses related to tobacco use, the economic impact of tobacco control programs, how to quantify specific program effects on reductions in tobacco use, subsequent disease impact, and the cost and effectiveness of alternative approaches.

Appendix 7-1: Estimating the Disease Impact of Smoking in the United States

Methodology

Six approaches to calculating smoking attributable mortality (SAM) in the United States are reviewed in this section. The first approach, the population attributable risk (PAR) calculation, is the most commonly used and was the earliest method used to estimate SAM (Levin 1953). Levin originally used this approach, sometimes referred to as "Levin's attributable risk," to describe the burden of preventable lung cancer associated with smoking. The PAR and variants also have been referred to as the assigned share, excess risk, etiologic fraction, attributable proportion, attributable risk, and incidence density fraction (IDF) (Levin 1953; Walter 1976; Rothman 1986; Greenland and Robins 1988; U.S. Department of Health and Human Services [USDHHS] 1989a; Greenland 1999). These measures are basically all estimates of the total disease burden (usually mortality) or of the specific disease burden attributable to smoking. When multiplied by the reported number of deaths in these disease categories, numbers of deaths for a given time period attributable to tobacco use can then be estimated. The IDF further incorporates the concept of timing of the excess disease; that is, the onset of exposure-caused disease occurs earlier among the exposed than among the unexposed (Greenland 1999). Unless a population is in a steady state with regard to exposure and disease, estimates of attributable risk may not reflect the cumulative burden of disease for exposed cohorts (Greenland and Robins 1988). Based on this first application of the attributable risk calculation to available case-control data, Levin reported that from 62 to 92 percent of all cases of lung cancer in the study populations were caused by smoking. PAR is derived as follows:

If the excess rate (or risk) of disease (D_x) from a given exposure is the rate of death in the exposed group (D_e) minus the rate of death in the unexposed group (D_u), then

$$D_x = D_e - D_u$$

The excess proportion of the disease attributable (AP) to the exposure is

$$AP = \frac{D_x}{D_e}$$

The relative risk (RR) (or relative rate) of deaths caused by the exposure is

$$RR = \frac{D_e}{D_u}$$

and therefore the AP can be rewritten as

$$AP = \frac{RR-1}{RR}$$

The fraction (F) of all cases of the disease that occurs among exposed persons in the participant population depends on the prevalence rate (P) of the risk factor. Thus,

$$F = \frac{P(RR)}{P(RR-1) + 1}$$

If the fraction (F) of all cases occurs among exposed persons, and if the proportion of all cases attributable to the exposure is AP, then the attributable risk for all cases in the entire population (PAR) (exposed and unexposed) is

$$PAR = AP \times F$$

Thus, PAR depends on the RR of deaths or disease due to the specific risk factor (exposure) prevalence (P) in the entire population, and the formula for PAR can then be written as

$$PAR = \frac{P(RR - 1)}{P(RR - 1) + 1}$$

The PAR calculation underlies the Centers for Disease Control and Prevention's (CDC) Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) methodology. This tool was developed to assist states and other jurisdictions to estimate the burden of disease caused by tobacco in their jurisdictions (Shultz et al. 1991; CDC 2002d). SAMMEC applies the PAR calculation to men and women separately and to broad age groups (35 to 64 years and 65 years and older) to account for variability in risk and exposure according to age and gender. However, SAMMEC does not adjust the PAR estimates for other risk factors for the various smoking-related diseases.

In a second approach, Doll and Peto (1981) used the risk difference to estimate cancer deaths attributable to smoking in the United States in 1978. Excess cancer deaths attributable to smoking were computed by subtracting from the observed number of deaths (D_{obs}) for a specific diagnosis (x) the number of deaths expected (D_{ns}) if the population at risk had the same mortality rate as nonsmokers for the disease.

$$SAM_x = D_{obs} - D_{ns}.$$

Cancer Prevention Study I (CPS-I), conducted during 1959–1972, provided mortality rates for cancers and other leading causes of death in lifetime nonsmokers, and these rates were then used to calculate overall expected deaths of smokers (Garfinkel 1985). This method also inherently assumes that the comparison of smokers and lifetime nonsmokers is not affected by confounding.

One methodologic concern raised with regard to PAR estimates is the potential effect from confounding by differences in other risk factors across smoking groups (Sterling et al. 1993). The third approach, a model-based approach for estimating PAR, was used by Malarcher and colleagues (2000) to develop cause-specific, age- and confounder-adjusted attributable fractions (AF_A) (as a weighted sum of the age-specific estimates from CPS-II data) and 95 percent confidence limits around these estimates. They expanded the basic formula for PAR to include adjustment for potential confounding factors, including education, alcohol consumption, hypertension, and diabetes.

$$AF_C = 1 - \sum_j \frac{j}{\tilde{}},$$

where $_j$ is the proportion of deaths in the jth cell in a matrix defined by exposure and confounder status

(e.g., smoking and age), and RR_j is the RR for smokers compared with lifetime nonsmokers adjusted for confounders C (e.g., age). This calculation provides an estimate of SAM that is adjusted for the selected, potential confounding factors. The estimates obtained with this model were very similar to the national SAM estimates that adjusted risks only for age and gender, as in the SAMMEC software.

In the fourth method, Thun and colleagues (2000) also used a model-based approach to evaluate SAM estimates based on the CPS-II data both with and without adjustment for possible confounders, including race, education, marital status, "blue collar" occupation, dietary factors, body mass index, and physical activity. The Cox proportional hazard model was used by the investigators to estimate the hazard ratio (HR) for various diseases for current and former smokers compared with lifetime nonsmokers, adjusting for sociodemographic factors, diet, alcohol consumption, aspirin use, physical activity, body mass index, and asbestos exposure. The authors compared the SAM estimates obtained using this adjusted HR to estimates made for current and former smokers, among men and women separately, with adjustment for age only. The HR corresponds to the RR in the PAR calculation. Only small differences were found in the SAM estimates using the confounder-adjusted risk model compared with the calculation with risks and exposures adjusted only for gender and broad age groups.

Another method for estimating disease impact among state populations uses smoking status data collected from death certificates, first implemented in 1989 by the state of Oregon (McAnulty et al. 1994). In Oregon, the physician completing the death certificate lists the primary causes of death followed by secondary conditions that may have contributed to the death. The question "Did tobacco use contribute to the death?" has four possible responses: yes, probably, no, or unknown. Comparisons of estimates based on this direct method with estimates based on the PAR approach show close similarities. Of 212,448 deaths in Oregon during 1989–1996, the PAR estimate attributed 20.1 percent (42,778 deaths) to cigarette smoking. Based on the physician assignment that attributed 27 causes of death to smoking, the corresponding estimate was 20.2 percent (42,839 deaths). Nine jurisdictions (Colorado, Louisiana, Maryland, Nebraska, North Dakota, Oregon, Texas, Utah, and New York City) now ask physicians to indicate on death certificates whether tobacco use contributed to the death (Thomas et al. 2001).

Peto and colleagues (1992) developed an approach for broad, international applications that uses the absolute rate of lung cancer mortality in a particular country as the anchoring point. The lung cancer rate is used to estimate the proportions of smokers and nonsmokers in the population and then the RR estimates from CPS-II are scaled proportionately, with a 50 percent reduction in the estimated excess risk to produce "conservative" estimates.

Key Data Sets Used to Estimate Smoking Attributable Mortality and Years of Potential Life Lost

Numerous cohort studies provide RR estimates for smoking-related diseases and mortality (Pearl 1938; Hammond and Horn 1954; Kahn 1966; Doll and Peto 1976; Garfinkel 1980a,b; Rice et al. 1986; Lew and Garfinkel 1988; USDHHS 1989a; Doll et al. 1994; Thun et al. 1997a). These studies are extensively described in several publications, including Monograph 8 of the Smoking and Tobacco Control Monograph Series published by the National Cancer Institute (NCI 1997). The RR estimates from CPS-II have been incorporated by CDC into SAMMEC for the purpose of estimating state-specific SAM, smoking attributable years of potential life lost (YPLL), and economic costs (SAMMEC, version III) (CDC 2002d).

The CPS-II data set currently used to estimate the burden of disease comes from a six-year follow-up of participants recruited by American Cancer Society (ACS) volunteers from all states and some territories in 1982. On recruitment, smoking status (current, former, or never) and other lifestyle factors (medical history, current health status, age, gender, and race) were ascertained (Stellman and Garfinkel 1986; Thun et al. 1997a). Volunteers reported the vital status of participants each year, and for participants who died, the underlying cause of death was obtained from death certificates. Information from death certificates was obtained for 94.1 percent of the deaths. The selected sample differed from the U.S. population in that participants tended to be white (93 percent), and had more education and a higher socioeconomic status than the national population (Malarcher et al. 2000). Although follow-up continues to the present, RRs from these subsequent years have not been used in SAMMEC software because smoking status (current and former) was assessed for all cohort members only on

enrollment, leading to an increased potential for misclassification of smoking status over time. National smoking prevalence data from the National Health Interview Survey (NHIS) and from various state-specific surveys (CDC 1996b) were used, along with RR estimates from CPS-II, to estimate PAR and SAM either for the nation or for individual states (CDC 1997, 2001b, 2002d).

The first ACS study (CPS-I) of one million persons in the United States provides an appropriate comparison data set for evaluating changes in RR estimates associated with smoking between the mid-1960s and the mid-1980s (Table 7-1.1) (Hammond 1966; USDHHS 1989a; Shopland et al. 1991; Thun et al. 1997a). The RRs for current smokers versus lifetime nonsmokers for lung cancer across the time periods when CPS-I and CPS-II were conducted increased substantially for both men (from 11.4 to 23.3) and women (from 2.7 to 12.7) (Thun et al. 1997a). The RRs for most of the cardiovascular diseases (CVDs) showed increases between the studies, and the RRs for all-cause mortality in smokers increased from 1.7 to 2.3 in men and from 1.2 to 1.9 in women across the interval.

Mortality rates for several smoking-related diseases have changed in recent years. Age-standardized lung cancer death rates decreased among men, and rates have begun to plateau among women (Ries et al. 2000). Cardiovascular disease and stroke mortality rates declined between CPS-I and CPS-II, regardless of smoking status, which is consistent with trends for the various CVDs in general (National Center for Health Statistics 1996). Although there was a documented decline in smoking in the United States between CPS-I and CPS-II, mortality rates reflect the effects of many factors that may change over time. For smoking, prevalence may vary and the strength of the association between smoking and particular diseases may change. There also may be changes in other risk factors for the diseases caused by smoking, and in their treatment and survival rates. Estimates of SAM at any particular point in time reflect the earlier birth cohort patterns in smoking initiation and cumulative exposures to lifetime smoking, as well as more recent patterns in cessation.

The codes from the *International Classification of Diseases, 9th Revision* (ICD-9) (USDHHS 1989b) have been changed in Web SAMMEC to reflect the newer 10th revision classifications (ICD-10) (CDC 2002b). The codes from both revisions are listed in Table 7-1.2.

Table 7-1.1 Age-adjusted relative risks of death from smoking-related diseases from the Cancer Prevention Study (CPS) I and CPS-II, stratified by gender

Disease category (ICD-9 code)*	CPS-I (1959–1965)				CPS-II (1982–1988)			
	Males		Females		Males		Females	
	CS†	FS‡	CS	FS	CS	FS	CS	FS
Neoplasms§								
Lip, oral cavity, pharynx (140–149)	6.3	2.7	2.0	1.9	10.9	3.4	5.1	2.3
Esophagus (150)	3.6	1.3	1.9	2.2	6.8	4.5	7.8	2.8
Stomach (151)	1.8	1.7	1	1	2	1.5	1.4	1.3
Pancreas (157)	2.3	1.3	1.4	1.4	2.3	1.2	2.3	1.6
Larynx (161)	10	8.6	3.8	3.1	14.6	6.3	13	5.2
Trachea, bronchus, lung (162)	11.4	5	2.7	2.6	23.3	8.7	12.7	4.5
Cervix uteri (180)			1.1	1.3			1.6	1.1
Urinary bladder (188)	2.9	1.8	2.9	2.3	3.3	2.1	2.2	1.9
Kidney, other urinary (189)	1.8	1.8	1.4	1.5	2.7	1.7	1.3	1.1
Acute myeloid leukemia (204–208)	1.6	1.6	1	1	1.9	1.3	1.1	1.4
Cardiovascular diseases§								
Ischemic heart disease (410–414)								
Aged 35–64 years	2.3	1.6	1.8	1.7	2.8	1.6	3.1	1.3
Aged ≥65 years	1.4	1.3	1.2	1.3	1.5	1.2	1.6	1.2
Other heart disease (390–398, 415–417, 420–429)	1.4	1.1	1.1	1.4	1.8	1.2	1.5	1.1
Cerebrovascular disease (430–438)								
Aged 35–64 years	1.8	1	1.9	1.8	3.3	1	4	1.3
Aged ≥65 years	1.2	1	1	1.1	1.6	1	1.5	1
Atherosclerosis (440)	3.1	2	1.9	1.5	2.4	1.3	1.8	1
Aortic aneurysm (441)	4.1	2.4	4.6	3.7	6.2	3.1	7.1	2.1
Other arterial disease (442–448)	3.1	2	1.9	1.5	2.1	1	2.2	1.1
Respiratory diseases§								
Pneumonia, influenza (480–487)	1.8	1.6	1	1	1.8	1.4	2.2	1.1
Bronchitis, emphysema (490–492)	8.8	10.2	5.9	5.9	17.1	15.6	12	11.8
Chronic airways obstruction (496)	5.5	9.6	5.1	5.3	10.6	6.8	13.1	6.8
Perinatal conditions								
Short gestation/low birth weight (765)			1.8				1.8	
Respiratory distress syndrome (769)			1.8				1.3	
Other respiratory conditions in newborns (770)			1.8				1.4	
Sudden infant death syndrome (798.0)			1.5				2.3	

International Classification of Diseases, 9th Revision.
†CS = Current smokers.
‡FS = Former smokers.
§Among persons aged ≥35 years.
‖Perinatal relative risks for 1959–1965 are from McIntosh 1984; 1982–1988 data are from Gavin et al. 2001 and Malloy et al. 1992; see also ftp://ftp.cdc.gov/pub/health_statistics/nchs/publications/icd-9/.
Sources: McIntosh 1984; U.S. Department of Health and Human Services 1989b; National Center for Health Statistics, public use data tapes, 1995–1999; Thun et al. 1997b; National Cancer Institute 1999; Gavin et al. 2001; Hall 2001; Hoyert et al. 2001; Mathews 2001; Centers for Disease Control and Prevention 2002a,b,d; International Agency for Research on Cancer 2002; American Cancer Society, unpublished data.

Limitations of Smoking Attributable Mortality and Years of Potential Life Lost Calculations

The PAR calculation and the extension to estimate SAM and YPLL involve assumptions associated with uncertainties. These assumptions and other methodologic issues have been debated in the literature in recent years. This section addresses limitations of SAM and YPLL estimates and concerns that have been raised about these estimates.

SAM and YPLL derived from the PAR calculation may be underestimates in several respects. First, the SAM and YPLL estimates from SAMMEC are based on the prevalence of current and former smokers in the current year; however, the deaths that occur during a given year are primarily among persons who began smoking 30 to 50 years earlier, many of whom had quit smoking (Schulman et al. 1997). The prevalence of smoking among these persons 30 to 50 years ago was almost double that of similarly aged adults today, and many of the participants in CPS-II were former smokers at entry into the study. The current RRs for former smokers are lower than those of current smokers, but do not reflect the risk that was sustained up to the present age. The likelihood of dying from a smoking-related disease for those who began smoking 30 to 50 years ago and quit only recently is far higher than that for former smokers who began smoking at the same age but quit smoking earlier. Thus, the cross-sectional PAR and SAM estimates do not accurately estimate the risks of past cohorts of smokers.

The use of survey data to estimate exposure may contribute to some uncertainty in the PAR calculation. Although population-based surveys provide reasonably accurate estimates of adult prevalence, there may be some underestimation of true exposure (Caraballo et al. 2001). The degree of underestimation has likely increased in recent years.

The SAM estimates also do not include mortality caused by cigar smoking, pipe smoking, or smokeless tobacco use. Approximately 1,000 deaths in the United States were attributable to pipe smoking in 1991 (Nelson et al. 1996). Finally, diseases have now been causally associated with smoking in this report of the Surgeon General that were not included in previous estimates of SAM. Additional ICD-10 codes have now been included for RRs (Table 7-1.2) as part of the PAR calculations presented earlier in this chapter.

Previous SAM calculations have been criticized, however, for overestimating the disease burden of smoking. Estimates using PARs based on RRs that were not adjusted for potential confounding factors have been criticized as being too high (Sterling et al. 1993; Levy and Marimont 1999). As an alternative, Weinkam and colleagues (1992) and Sterling and colleagues (1993) developed RR estimates using data from the NHIS, a cross-sectional household survey of health status with self-reported smoking status, and from the 1986 National Mortality Followback Survey (NMFS), a representative sample of all decedents aged 25 years or older in the United States. The method produced somewhat lower PARs than those incorporated into SAMMEC, and RR estimates were below 1.0 for some diseases, including some for which there is a causal association with smoking, such as cancers of the lip, oral cavity, and pharynx. Relative risk estimates must be internally valid (Greenland and Robins 1988), and strong biologic relationships between smoking and disease have been demonstrated for the diseases discussed in previous chapters of this report. Siegel and colleagues (1994) pointed out that the approach used by Weinkam and colleagues (1992) can be criticized for lacking internal validity. For example, the analysis of Weinkam and colleagues (1992) produced a RR for laryngeal cancer that was higher for men who formerly smoked than for current smokers, and a risk for lung cancer that was similar among women who were current and former smokers. These findings are not consistent with the strong evidence documented in previous reports of the Surgeon General that quitting smoking reduces the population risk for these diseases (USDHHS 1990). These surprising findings from the NMFS analyses might result from the small number of deaths from some diseases in the data Weinkam and colleagues (1992) used in their sampling process.

Two studies evaluated the methodology Sterling and colleagues (1993) used and the effects of adjusting for potential confounding factors within the CPS-II data set (Malarcher et al. 2000; Thun et al. 2000). Both analyses found that adjustment for potential confounders and consideration of effect modifiers did not appreciably alter the partially adjusted overall PAR and SAM estimates reported by CDC using the SAMMEC methodology. Thun and colleagues (2000) found that adjusting for multiple potential confounders slightly decreased the RR and PAR for current smokers among both men and women while they increased slightly for women who were former smokers. Overall, the estimated SAM for 1990 decreased by approximately 1 percent, from 401,000 to 397,000 deaths with fully adjusted rather than only age-adjusted RR estimates from CPS-II. Malarcher and colleagues (2000) found that for four of the main classes of disease (lung cancer, chronic airways obstruction,

Table 7-1.2 *International Classification of Diseases* (ICD) codes and comparability ratios* (CR) for smoking-related diseases, 1965–1999

Disease category	ICD-10[†] code (1999)	CR	ICD-9[‡] code (1979–1988)	CR	ICD-8[§] code (1968–1978)	CR	ICD-7[△] code (1965–1967)
Neoplasms[¶]							
Lip, oral cavity, pharynx	C00–14	0.960	140–149	1.012	140–149	1.060	140–148
Esophagus	C15	0.997	150	1.033	150	0.991	150
Stomach	C16	1.006	151	NR**	NR	NR	NR
Pancreas	C25	0.998	157	1.033	157	1.002	157
Larynx	C32	1.005	161	1.001	161	1.032	161
Trachea, bronchus, lung	C33–34	0.984	162	1.001	162	1.032	162–163
Cervix uteri	C53	0.987	180	1.011	180	1.003	171
Urinary bladder	C67	0.997	188	0.992	188	1.017	181
Kidney, other urinary	C64–66, C68	1.000	189	0.992	189	1.017	180
Acute myeloid leukemia	C91–95	1.012	204–208	NR	NR	NR	NR
Cardiovascular diseases[¶]							
Rheumatic heart disease	I00–09	0.821	390–398	0.665	390–398	1.152	400–402, 410–416
Ischemic heart disease	I20–25	0.999	410–414	0.878	410–413	1.146	420
Pulmonary heart disease	I26–28	0.972	415–417	2.504	426, 450	0.810	434, 465
Other heart disease	I29–51	0.972	420–429	2.504	420–425, 427–429	0.239	421–422, 430–433
Cerebrovascular disease	I60–69	1.059	430–438	1.005	430–438	0.991	330–334
Atherosclerosis	I70	0.964	440	1.065	440	0.896	450
Aortic aneurysm	I71	1.001	441	0.741	441	1.082	451
Other arterial disease	I72–78	0.850	442–448	0.741	442–444, 446–447	NR	452–454, 456, 4671–72
Respiratory diseases[¶]							
Pneumonia, influenza	J10–18	0.698	480–487	0.926	470–474, 480–486	1.044	480–483, 490–493
Bronchitis, emphysema	J40–43	0.894	490–492	0.969	490–492	1.056	501, 502, 5271
Chronic airways obstruction	J44	1.097	496	1.005	519.3	NR	5272
Perinatal conditions							
Short gestation/low birth weight	P07	1.106	765	0.963	777	NR	774, 776
Other respiratory conditions in newborns	P23–28	0.846	770	NR	776.0, 776.9	NR	762, 763
Respiratory distress syndrome	P22	1.026	769	NR	776.1, 776.2	NR	NR
Sudden infant death syndrome	R95	1.036	798.0	0.910	795.0	NR	NR

*Comparability ratios may not exactly match the included disease codes for each condition. Complete descriptions of the comparability ratios are available from the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC).

[†]ICD, 10th revision.

[‡]ICD, 9th revision.

[§]ICD, 8th revision.

 ICD, 7th revision.

[¶]Among persons aged   35 years.

**NR = Data were not reported.

Sources: World Health Organization 1955, 1965; U.S. Department of Health and Human Services 1989b; Anderson et al. 2001; CDC 2002b.

CVD, and cerebrovascular disease), the CPS-II-based SAM was 19 percent larger than the estimates based on the NMFS/NHIS combined data set. The authors set any of the RR estimates that were less than 1.0 in the Sterling and colleagues (1993) study to 1.0 because RRs less than 1.0 were not plausible for diseases such as oropharyngeal cancer and CVD, for which there is sufficient evidence of causality. Fully adjusting the RRs for potential confounders in this study, including alcohol consumption, resulted in only a 2.5 percent difference in the SAM in comparison with that of Sterling and colleagues (1993). However, adjusting for alcohol consumption in the case of oral cancer is inappropriate because it is not only a potential confounding factor but also an effect modifier, acting synergistically with smoking to increase risk for oral cancer. Effect modification refers to a change in the magnitude of risk for smoking according to the presence or level of another variable (alcohol).

A second major criticism of SAMMEC involves the use of RR estimates from CPS-II because CPS-II participants were not representative of the entire U.S. population—being a cohort recruited primarily from friends and families of ACS volunteers. Differences in study populations, in the model-based versus stratified analyses, and in possible bias from the use of proxy respondents in NMFS may also contribute to the differences in SAM rates calculated by Sterling and colleagues (1993) and Malarcher and colleagues (2000). Studies have found that proxy respondents (used in NMFS) misclassify smoking by decedents more than self-reports do, thereby tending to reduce the RR of diseases associated with smoking (Lerchen and Samet 1986; Boyle and Brann 1992). A key assumption of SAMMEC is that the CPS-II RR estimates have external validity; they can be extended to the entire U.S. population. The extent of their external validity, or generalizability, is a matter of judgment based on characteristics of the CPS-II population that may modify the effects of smoking, and is based on the biologic understanding of the mechanisms underlying the causal effects of smoking on disease. Sufficient variability must also exist in both the exposure and the outcome of interest in cohort studies such as the CPS-II to assure generalizability. Szklo (1998) asserted that a cohort study need not be a representative sample of the population to develop useful *relative* measures of association, but it should be representative in order to estimate an *absolute* measure of disease frequency that can be generalized with confidence. Thus, CPS-II provides sufficient population representation for the establishment of valid RRs for the entire

population as these are *relative* and not *absolute* measures of disease occurrence.

One other major issue concerning the SAM calculation is that the results produced using any of the cited methodologies are approximations, useful for describing the magnitude of the disease burden. The input data have limitations, and there is uncertainty associated with the estimates that is only partially represented by a confidence interval (CI). For example, deaths in any given year are due to incident cases of disease in prior years, and these cases depend on a complex history of smoking exposure, including age at onset, duration, number of cigarettes smoked per day, types of cigarettes smoked, secondhand smoke exposure, age at quitting, and other risk factors for the specific disease. Relative risks are calculated for populations for a fixed period of time (e.g., 1982–1988 in CPS-II), but changes in the population exposure are difficult to capture during this fixed time period. In addition, prevalence of smoking and the RR for different smoking-related diseases vary across age groups. This variance may lead to distortions in the PAR estimation because higher smoking prevalence among younger members of the population, which contributes to a higher incidence of disease at older ages in the population, is not matched to the higher mortality among the older population.

In addition, for some of the diseases linked to smoking, for example CVD and cerebrovascular diseases, other risk factors such as hypertension, diet, and heredity add greatly to the complexity of estimating the population disease burden attributable solely to tobacco use. Varying the combinations of these contributing risk factors will alter the mortality rate and thus the preventable fraction of death from such diseases more than simply reducing the smoking prevalence (Rothenberg et al. 1991). For diseases such as lung cancer and chronic obstructive pulmonary disease (COPD), there are virtually no other risk factors, and thus the variability in these disease burdens while accounting for other risk factors would be extremely limited.

Review of Previous Estimates

Since 1964, several Surgeon General's reports have commented on the burden of smoking attributable deaths and diseases. In 1964, the Advisory Committee to the Surgeon General reviewed seven prospective cohort studies on smoking and mortality and found that the ratio of the death rate among current

smokers to the death rate of nonsmokers was 1.68 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). In 1979, the Surgeon General labeled cigarette smoking the single most important preventable environmental factor contributing to illness, disability, and death in the United States (USDHEW 1979). In 1989, the Surgeon General reported that data from CPS-II indicated a substantial increase in RRs for smoking along with an increase in the disease burden of smoking (SAM) since 1964 (USDHHS 1989a). These changes were attributed in part to birth cohort changes in smoking patterns. Several previous reports of the Surgeon General, as well as other reports, have used CPS-I, CPS-II, and other cohort study results to produce estimates of total smoking attributable deaths (CDC 1987, 1991, 1993, 1997) from cancers caused by smoking (Garfinkel 1980a; USDHHS 1982), CVD (Garfinkel 1980b; USDHHS 1983), chronic airways obstruction (or chronic obstructive pulmonary disease) (USDHHS 1984; Davis and Novotny 1989), adverse perinatal effects (Gavin et al. 2001), and other adverse effects.

Several national SAM estimates have been reported, including 270,000 deaths for 1980 (Rice et al. 1986), 314,000 deaths for 1982 (Office of Technology Assessment 1985), 320,000 deaths for 1984 (CDC 1987), 390,000 deaths for 1985 (USDHHS 1989a), 434,000 deaths for 1988 (CDC 1991), 418,690 deaths for 1990 (CDC 1993), an annual average of 430,700 deaths for 1990–1994 (CDC 1997), and an annual average of 442,398 deaths for 1995–1999 (CDC 2002a).

Rice and colleagues (1986) used the PAR calculation to estimate national SAM as well as morbidity and economic costs. Pooled RR estimates were derived from three cohort studies on smoking and health. The mathematical PAR formula was expanded to include current and former smoking separately, and CDC incorporated this stratification into SAMMEC I software (Shultz et al. 1991). States and other jurisdictions used SAMMEC I and later SAMMEC versions (II and III) to estimate the mortality and economic disease burden attributable to smoking in their populations (Nelson et al. 1994; CDC 2001b). A set of RRs from CPS-II was incorporated into the program to develop a smoking attributable fraction (SAF), and users entered mortality, prevalence, and economic cost data into the program for the jurisdiction under study. Web SAMMEC is now used extensively by states and by CDC to provide periodic estimates of SAM and YPLL for adults aged 35 years and older and, separately, for perinatal conditions associated with maternal smoking (CDC 2002d).

In 1997, CDC used national mortality data for 1990–1994 with SAMMEC II, estimating that 2,153,600 deaths (1,393,200 men and 760,400 women) were attributable to smoking over the five years (19.5 percent of all deaths), an average of 430,700 deaths per year (CDC 1997). A total of 906,600 of these deaths were attributed to CVDs, 778,700 to neoplasms, 454,800 to nonmalignant respiratory diseases, 7,900 to diseases among infants, and 5,500 to smoking-related fires. Lung cancer (616,800 deaths), ischemic heart disease (490,000 deaths), and chronic airways obstruction (270,100 deaths) accounted for most of the deaths. During 1990–1994, cigarette smoking resulted in 5,732,900 YPLL before 65 years of age and a total YPLL to life expectancy of 28,606,000. On average, each smoker who dies from a smoking-related disease forfeits 12 to 15 years of life compared with his or her lifetime nonsmoking counterparts (Peto et al. 1992; CDC 1997).

CDC later calculated annual SAM and YPLL estimates for 1995–1999 for the United States (CDC 2002a). Calculated annual estimates of deaths attributed to smoking were 264,087 in men and 178,311 in women (total 442,398) in the United States each year during 1995–1999. Excluding deaths in adults from secondhand smoke, the estimated SAM was responsible for a total annual YPLL to life expectancy of 3,332,272 for men and 2,284,113 for women. Thus, adult male and female smokers dying from smoking lost estimated averages of 13.2 and 14.5 years of life, respectively, compared with nonsmokers. The findings in this study differ from previous SAM estimates (CDC 1993, 1997) and reflect (1) the inclusion of 35,100 heart disease deaths attributable to secondhand smoke; (2) the inclusion of 966 burn deaths from cigarette-caused fires; and (3) declines in current smoking prevalence among men, women, and pregnant women since the early 1990s (CDC 2002a).

In 1996, CDC evaluated a model based on Behavioral Risk Factor Surveillance System data for the projected prevalence of smoking among young adults, the NMFS for death estimates among smokers and former smokers, and projected future SAM based on data from CPS-II. Assuming that one-third of adult current smokers and 10 percent of adult former smokers die from smoking-related diseases, and that current smoking patterns continue without a marked increase in cessation, an estimated 25 million persons (adults and children) alive in 1995 will die prematurely from smoking-related illnesses (CDC 1996a); among persons who were 0–17 years of age in 1995, more than five million are expected to die from smoking attributable causes.

Peto and colleagues (1992) estimated mortality from tobacco use in developed countries using an indirect method that was conceptually similar to the excess mortality method described previously. Using the lifetime nonsmoker lung cancer mortality rates from CPS-II (Stellman and Garfinkel 1986), they calculated the absolute excess mortality rate for lung cancer in all developed countries, and used the observed lung cancer rate in those countries as an index of overall population exposure to smoking. Smoking is the predominant cause of lung cancer, and little else contributes to lung cancer incidence (Thun et al. 1997a). Using the lung cancer rate as the anchoring point, Peto and colleagues (1992) then estimated the relative impact of smoking for several diagnostic categories other than lung cancer by age and gender. A smoking impact ratio was established for these categories (upper aerodigestive cancers, other cancers, chronic airways obstruction, other respiratory diseases, and vascular diseases). The ratio estimated the excess mortality rate for the other disease categories based on the excess lung cancer ratio, but the authors halved the apparent excess for these other categories because it would then provide a reasonable degree of protection against overestimating the epidemic. The adjusted PAR was then calculated using the smoking impact ratio to obtain a SAM estimate for developed countries.

Using this approach, the SAM for developed countries in 1985 totaled 1.7 million (Table 7-1.3), and was projected at 2.1 million in 1995. This method has been criticized for comparing lung cancer mortality rates for the study populations in various countries with the American lifetime nonsmoker lung cancer mortality rates of participants in CPS-II (Sterling and Weinkam 1987; Lee 1996). In this analysis, the lifetime nonsmoker lung cancer rates were assumed to be similar throughout all populations.

In 2002, the World Health Organization (WHO) released *The World Health Report 2002: Reducing Risks, Promoting Healthy Life* that apportioned deaths worldwide to various risk factors including smoking (WHO 2002). This report estimated that 4.9 million deaths worldwide were attributable to tobacco (8.8 percent of all global deaths), and tobacco was also responsible for 59.1 million lost disability-adjusted life years (DALYs) (4.1 percent of the global total lost DALYs). Compared with 1990, WHO reported at least one million more tobacco-related deaths in 2000, with the highest increases in developing countries (WHO 2002).

Table 7-1.3 Smoking attributable mortality (deaths in thousands), all developed countries, 1985, stratified by age group, gender, and cause

Age/gender	Lung cancer	Upper aero-digestive cancer	Other cancers	Chronic obstructive pulmonary disease	Other respiratory diseases	Vascular diseases	Other medical conditions	All
35–69 years								
Men	203	47	64	71	14	297	78	774
Women	37	4	7	19	3	54	18	141
70 years								
Men	134	19	48	126	15	180	37	561
Women	29	4	6	42	6	72	16	175
All								
Men	338	66	112	197	30	477	115	1,335
Women	65	8	13	61	9	126	34	316

Source: Peto et al. 1992.

Infants and Children

Smoking during pregnancy has serious, adverse consequences that lead to increased risks for death in the perinatal period and to substantial YPLL. Since the early 1990s, a number of estimates have been made related to smoking during pregnancy using the parameter values from the original SAMMEC software, which were set based on the meta-analysis by McIntosh (1984). The four diagnoses and RRs used in the original SAMMEC software included the following:

ICD-9	Description	RR
765	Short gestation, low birth weight (LBW)	1.76
769	Respiratory distress syndrome (RDS)	1.76
770	Respiratory conditions in newborns	1.76
798.0	Sudden infant death syndrome (SIDS)	1.50

CDC commissioned a meta-analysis of literature published through 1999 on the risks of death to infants born to mothers who smoked during pregnancy (Gavin et al. 2001). Gavin and colleagues (2001) estimated pooled and adjusted pooled odds ratios (ORs) for infant/neonatal mortality related to smoking during pregnancy. (The RR for SAM estimates is interchangeable with the OR for rare diseases [Rothman 1986].) The pooled estimates showed a stronger effect of smoking on birth weight and intrauterine growth than on gestational age at birth: OR = 1.75 (95 percent CI, 1.39–2.19) for preterm, small for gestational age (SGA) infants; 1.84 (95 percent CI, 1.48–2.28) for LBW infants regardless of gestational age; and 1.95 (95 percent CI, 1.51–2.51) for SGA infants, including term and preterm infants. The single crude OR for mortality among short gestation, LBW infants found in the literature was in the same range (OR = 1.95 [95 percent CI, 1.29–2.95]). However, after adjustment for other factors, the 95 percent CI for this OR overlapped unity (OR = 1.52 [95 percent CI, 0.98–2.37]). The SAM estimate used the pooled OR (1.84) for LBW, regardless of gestational age, because evidence shows that smoking affects mortality at all birth weights (Wilcox 1993). Although Gavin and colleagues (2001) suggested that most neonatal mortality was captured by the excess

risk associated with LBW, excess mortality attributable to RDS and other respiratory diseases of the newborn is still evident after adjusting for gestational age, which is the major determinant of LBW. The excess risk for RDS deaths is not fully captured by the risk of death from LBW, so it is appropriate to include RDS and other respiratory diseases in assessments of neonatal mortality attributable to smoking. The most recent RRs for these conditions (1.30 for RDS and 1.41 for other respiratory diseases) are from Malloy and colleagues (1992). Although they used a predominantly white population to assess the RRs, these RRs were applied to all populations.

Compared with the quantitative review by Anderson and Cook (1997) on SIDS, the original RR of 1.50 that was used in SAMMEC appears low; a pooled adjusted OR of 2.29 (95 percent CI, 2.03–2.59) for SIDS reported by Gavin and colleagues (2001) was considered more appropriate and was used in the updated SAMMEC version. There is evidence of an increased risk of SIDS from smoking by parents and others during the postnatal period. The additional OR for maternal smoking in the postnatal period, after controlling for prenatal smoking, may be as high as 2.04 (95 percent CI, 1.56–2.68), and smoking by the father or by others in the household during the postnatal period may also increase risk. The data suggest a small independent effect from smoking by fathers or others only in addition to maternal smoking. However, the differences are not statistically significant, and they are not included in the current Web SAMMEC software. The revised RRs for perinatal mortality attributable to maternal cigarette smoking (including respiratory distress and respiratory diseases in newborns) are shown below and are included in Table 7-1.2, in addition to a comparison with ICD-9 categories. These RR values are used in the updated SAM calculations presented in this report.

ICD-10	Description	RR
P07	Short gestation, LBW	1.84
P22	RDS	1.30
P23–28	Other respiratory diseases in newborns	1.41
R95	SIDS	2.29

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Chapter 8
A Vision for the Future

Introduction

This report of the Surgeon General on the health effects of smoking returns to the topic of the first Surgeon General's report on active smoking and disease. This current report discusses many diseases associated with smoking including cancer, cardiovascular diseases, respiratory diseases, reproductive effects, and other adverse health consequences, and also updates prior estimates of the burden of diseases caused by smoking.

The courses of action highlighted below are potential next steps presented by the Surgeon General.

Given his role as the nation's spokesman on matters of public health, these recommendations represent a vision for the future built on information available today. They do not constitute formal policy statements, but are intended to inform and guide policymakers, public health professionals, professional and advocacy organizations, researchers, and most important, the American people, to ensure that efforts to prevent and control tobacco use are proportionate to the harmful effects it causes.

Tremendous Progress Since 1964

The publication of the first Surgeon General's report on smoking and health in January of 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964) was a landmark and pivotal event in the history of public health. By that time, there was a rapidly accumulating amount of evidence on the dangers of smoking, and it was inevitable that action would follow the publication of a comprehensive expert report with the powerful conclusion that smoking causes disease. Since 1964, there has been a broad societal shift in the acceptability of tobacco use and in the public's knowledge about the accompanying health risks. In 1963, per capita annual adult consumption in the United States peaked at 4,345 cigarettes, a figure that included both smokers and nonsmokers (Giovino et al. 1994). By 2002, per capita annual consumption in this country had declined to 1,979 cigarettes, the lowest level since before the start of World War II (U.S. Department of Agriculture 2003). In 1964, the majority of men smoked and an increasing number of women were becoming smokers. Today, there are more former smokers than current smokers, and each year over half of all daily smokers try to quit (Centers for

Disease Control and Prevention [CDC] 2003a). In 1964, smoking a cigarette was viewed as a "rite of passage" by almost all adolescents. Today, only about half of all high school seniors have ever smoked a cigarette and less than one in four is a current smoker, the lowest level since researchers started monitoring smoking rates among high school seniors in the mid-1970s (University of Michigan 2003).

In 1964, smoking was permitted almost everywhere, and even the U.S. Public Health Service had logo ashtrays on its conference tables. Today, secondhand tobacco smoke is widely accepted as a public health hazard and levels of exposure among nonsmokers have declined dramatically over the last decade. In fact, there is an unprecedented level of activity to achieve clean indoor air quality at both the local and state levels. More communities and states are considering and adopting laws that are even more comprehensive in the range of venues they cover. The 1964 Surgeon General's report on smoking and health started this country on an epic process of change toward a society free of tobacco-related disease and death. Yet many challenges remain.

The Need for a Sustained Effort

Smoking remains the leading preventable cause of disease and death in the United States, resulting in more than 440,000 premature deaths each year (CDC 2002; see also Chapter 7, "The Impact of Smoking on Disease and the Benefits of Smoking Reduction"). In 1964, the list of diseases known to be caused by smoking was short: chronic bronchitis and cancers of the lung and larynx (USDHEW 1964). Each subsequent Surgeon General's report has expanded the understanding of the magnitude of the health consequences of tobacco use. According to this 2004 report, the number of diseases caused by smoking has continued to increase. The list is now so long, this report concludes that smoking harms nearly every organ of the body and causes generally poorer health. For this reason, the burden of tobacco use on the physical and economic health of this country remains staggering. Since the release of the 1964 Surgeon General's report on smoking and health, more than 12 million Americans have died prematurely due to smoking. Currently, estimates of annual smoking attributable economic costs in the United States are over $157 billion (CDC 2002; see also Chapter 7, "The Impact of Smoking on Disease and the Benefits of Smoking Reduction").

Some may view the progress achieved in the country since 1964 as evidence that the problem has been solved. Unfortunately, the data indicate that future reductions in the morbidity, mortality, and economic costs of tobacco use will require a continuing and sustained effort. Since 1965, the overall proportion of adults in this country who are current smokers has been reduced by half; however, the rate of decline in adult smoking prevalence has slowed in recent years (CDC 2003a). Equally disturbing, the rates of smoking among some racial and ethnic minority populations and among less educated Americans remain high (CDC 2003a). Although the percentage of high school seniors who are current smokers has been reduced from 36.5 percent in 1997 to 24.4 percent in 2003, the trends in youth smoking over the last few years indicate that the rate of decline is slowing appreciably (CDC 2003d; University of Michigan 2003).

Although the level of secondhand tobacco smoke that nonsmokers are exposed to has declined significantly in the last decade, the decline has been greater among adults than among children, who are largely exposed at home. Currently, levels of exposure to this known human carcinogen are more than twice as high among nonsmoking children than among nonsmoking adults (CDC 2003c). Finally, while the knowledge that smoking can adversely affect health has become widespread among the general public, the grave health risks remain poorly understood.

In recognition of the need to enhance public understanding of these health consequences of smoking, this Surgeon General's report introduces a "Public Summary" that will serve as the foundation of a continuing effort to disseminate the findings of this report more widely and comprehensively at the national, community, and local levels (among individuals and families). In 1964, the conclusion that smoking causes lung cancer was major news; today, it is widely accepted. Unfortunately for many people, the multiple ways in which smoking damages almost every organ of the human body are not well understood.

To help educators, the media, and health professionals more fully understand the scientific basis for all of the conclusions in this Surgeon General's report, a companion database of the more than 1,600 articles cited in this report will be available for the first time on the Internet at <http://www.cdc.gov/tobacco>. This database will be easily accessed with readily available search criteria that can create detailed evidence tables related to each of the health topics reviewed in this report, such as cancer risks at individual organ sites, various types of cardiovascular and lung risks and diseases, reproductive health effects, and other health outcomes. This comprehensive database will be regularly updated as new studies are published and as the scientific knowledge about the health consequences of tobacco use continues to expand. Thus, it will be a living resource that health professionals and the general public can use to keep up with the latest findings.

The Need for a Comprehensive Approach

The 2000 Surgeon General's report, *Reducing Tobacco Use*, provided a detailed framework for comprehensive tobacco use prevention and control efforts: educational, clinical, regulatory, economic, and social approaches (U.S. Department of Health and Human Services [USDHHS] 2000). That report noted that "…our recent lack of progress in tobacco control is attributable more to the failure to implement proven strategies than it is to a lack of knowledge about what to do" (USDHHS 2000, p. 436). A comprehensive approach—one that optimizes synergy from a mix of educational, clinical, regulatory, economic, and social strategies—has emerged as the guiding principle for effective efforts to reduce tobacco use.

There is a very strong scientific base to guide these sustained efforts. In addition to recent Surgeon General's reports, the Community Preventive Services Task Force, the U.S. Public Health Service, and other professional bodies have reviewed the efficacy of specific strategies (Fiore et al. 2000; *American Journal of Preventive Medicine* 2001). Additionally, CDC's *Best Practices for Comprehensive Tobacco Control Programs* provides a broad framework for comprehensive statewide tobacco control programs (CDC 1999). Recent analyses of evidence from these state programs conclude that the magnitude and rate of change in smoking behaviors are significantly related to the level and continuity of investments in comprehensive program efforts (Farrelly et al. 2003; Stillman et al. 2003). The results from these programs indicate that reducing youth initiation rates, promoting smoking cessation,

and increasing protections for nonsmokers from secondhand tobacco smoke exposure necessitate changing many facets of the social and policy environments. Thus, *Best Practices* provides effective guidance for efforts at the state level, but a comprehensive national tobacco control effort requires strategies that go beyond guidance to the states. Based on the evidence reviewed in *Reducing Tobacco Use* (USDHHS 2000), a comprehensive national effort should involve a broad mix of strategies. That report also noted that some of the program and policy changes needed within these strategies can be most effectively addressed at the national level.

There is a need for a continuing and sustained national tobacco use prevention and control effort. Many factors encourage tobacco use in this country: the positive imagery of smoking in movies and in the popular culture, the billions of dollars spent by the tobacco industry to advertise and promote cigarettes (e.g., $11.2 billion in 2001 [Federal Trade Commission 2003]), acceptance of secondhand smoke in public places, and the perception by some that the problem has been solved. Additionally, funding levels for many effective state and national counter-advertising campaigns were recently reduced. We know enough to take action. As in many areas of public health, there is a need to improve the dissemination, adoption, and implementation of effective, evidence-based interventions, and to continue to investigate new methods to prevent and reduce tobacco use.

Continuing to Build the Scientific Foundation

Progress in tobacco control always has been built upon a foundation of conclusive scientific knowledge. Each of the previous 27 Surgeon General's reports on smoking and health has contributed to this ever-enlarging foundation not only about the health consequences of tobacco use, but also about effective strategies to prevent tobacco use among youth, to help current tobacco users quit, and to protect nonsmokers from exposure to secondhand tobacco smoke.

Progress in tobacco control always has been built upon a foundation of conclusive scientific knowledge. Each of the previous 27 Surgeon General's reports on smoking and health, as well as numerous other publications, have contributed to this ever-enlarging foundation of data. These reports include information about the health consequences of tobacco use, effective strategies to prevent tobacco use among young people and to help current tobacco users quit, and approaches to

protect nonsmokers from exposure to secondhand to-bacco smoke (Fiore et al. 1996, 2000; National Cancer Institute 1999, 2001). Nevertheless, there are scientific questions remaining to be addressed on the adverse health effects of tobacco use, methods for the efficient surveillance of thetobacco-related epidemic, strategies to eliminate tobacco-related disparities, and innova-tive approaches for the prevention of tobacco use and treatment of nicotine addiction.

One major topic in need of more research is to complete the understanding of the mechanisms by which tobacco-related diseases are caused. A greater understanding of these causal mechanisms should have implications for disease prevention that extend to agents other than smoking. This report reviews the association between smoking and cancer, cardiovascular diseases, respiratory diseases, repro-ductive effects, and other health consequences, and defines a variety of specific research questions and issues related to the biologic mechanisms by which the multiple toxic agents in tobacco products and tobacco smoke cause specific adverse health outcomes. For example, the lung remains the primary site for elevated tobacco-related cancer risk; however, during the past 40 years, the type of lung cancer caused by smoking has changed for reasons still unknown. Similarly, as the evidence that smoking damages the heart and cir-culatory system and is a primary preventable cause of heart disease and stroke continues to expand, impor-tant research questions remain about how smoking interacts with other cardiovascular risk factors and accelerates the atherosclerotic disease process. With respect to these and the other research questions, the public health message remains the same: smoking greatly increases the risk of many adverse health ef-fects. Therefore, never start smoking or quit as soon as possible.

For several organ sites, there is a need for more evidence regarding the possible causal role of smok-ing on cancer risk (see Chapter 2, "Cancer"). For pros-tate and colorectal cancers, the evidence is suggestive but not sufficient to determine a possible causal rela-tionship. For breast cancer, even though there is no evidence overall for a causal role of smoking, on a ge-netic basis some evidence suggests that some women may be at an increased risk if they smoke. For other sites such as the liver, confounding exposures to other risk factors have made the evaluation of the risk of smoking very complex, but this report finds the evi-dence to be suggestive of causation. There should be further research on those sites where the evidence is suggestive but not yet sufficient to warrant a causal conclusion. As this new evidence emerges it will be evaluated using the causal criteria and standardized language applied in the Surgeon General's reports to express the strength of the evidence bearing on cau-sality for all adverse health effects of smoking. As new evidence emerges with respect to the research ques-tions raised in this report, the individual chapter con-clusions in this report will be re-evaluated.

Chapter 6, "Other Effects," of this report con-cludes that, overall, smokers are less healthy than non-smokers. Most often the risks of smoking are discussed with respect to a specific cancer, to heart disease, or to respiratory disease risk. Unfortunately, because smok-ing is such a powerful cause of disease, most smokers suffer from adverse health effects in many parts of their bodies at once. Additionally, before a death from one of the diseases caused by smoking, which is often quite premature, many smokers live for years with a dimin-ished quality of life from the burden of chronic and disabling health effects (e.g., reduced breathing capac-ity, poor heart functioning, greater susceptibility to lung infections, visual loss due to cataracts, and oth-ers). More research emphasis needs to be placed on the broad health consequences of smoking—namely, how smoking has a negative impact on many aspects of the body at the same time, and how these multiple adverse health effects combine to produce an overall reduced quality of life and greater health care costs prior to causing premature death. Recently, prelimi-nary estimates indicated that for every premature death caused each year by smoking, there were at least 20 smokers living with a smoking-related disease (CDC 2003b).

This report highlights the diversity of the health effects caused by smoking, and how dramatically smoking affects the risk of the leading causes of death in this country (e.g., cancer, heart disease, respiratory disease). These findings emphasize that tobacco pre-vention and control should be key elements in a na-tional prevention strategy for all of these major causes of death. Additionally, there is great disparity in tobacco-related disease and death among populations and the need to address the research gaps that exist for many special populations. Research is needed not only on disease outcome but also on the development of more effective strategies to reach and involve high risk populations (e.g., race/ethnicity, low income, low education, the unemployed, blue-collar and service workers, and heavily addicted smokers).

Finally, more research is needed on how changing tobacco products, as well as pharmaceutical products, have affected and could continue to affect health. In this report, one major conclusion finds that cigarettes with lower machine-measured yields of tar and nicotine (i.e., low-tar/nicotine cigarettes) have not produced a lower risk of smoking-related diseases. Yet there are rapidly growing numbers of modified tobacco products characterized as Potentially Reduced Exposure Products (PREPs) (Institute of Medicine 2001). Research has demonstrated that with the expectation of reducing risk, many smokers switched to low machine-measured tar/nicotine cigarettes, and may thus have been deterred from quitting (National Cancer Institute 2001). Therefore, it is critically important that the health risks of the emerging PREPs be evaluated comprehensively and quickly to avoid a replication of that unfortunate low-tar/nicotine cigarette experience. Research on the biologic mechanisms by which the multiple toxic agents in tobacco products and tobacco smoke cause specific adverse health outcomes can help establish an important scientific foundation for evaluating the potential health effects of PREPs. Similarly, the public health and policy implications of changes in manufactured cigarettes, other tobacco-containing products, and pharmaceutical products will require the continued attention of public health researchers and policymakers.

Tobacco Control in the New Millennium

As the world enters this new millennium, it is faced with many new public health challenges even as many of the old risks to good health remain. During the last 40 years, people have become increasingly more aware of the adverse health consequences of tobacco use. Currently, tobacco use is the leading cause of preventable illness and death in this nation, in the majority of other high-income nations, and increasingly in low- and middle-income nations. Unfortunately, the high rates of tobacco-related illnesses and deaths will continue until tobacco prevention and control efforts worldwide are commensurate with the harm caused by tobacco use. At the start of the last century, lung cancer was a very rare disease. Now lung cancer is the leading cause of cancer deaths in both men and women in this country (see Chapter 2, "Cancer"; USDHHS 2001). Our success in reducing tobacco use during the last 40 years has led to a reversal in the epidemic of lung cancer among men; nationwide, rates of lung cancer deaths among men have declined since the early 1990s (Weir et al. 2003). In California, where there has been a comprehensive tobacco control program in place since 1989, reductions in rates of tobacco-related disease and deaths already have been observed (CDC 2000; Fichtenberg and Glantz 2000; Scott et al. 2003). If we apply what we know works, we can make lung cancer a rare disease again by the end of this century!

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Abbreviations

AAA	abdominal aortic aneurysm	**CPS-I**	Cancer Prevention Study I
AAI	ankle-arm index	**CPS-II**	Cancer Prevention Study II
AANL	adult acute nonlymphocytic leukemia	**CT**	computed tomography
ABI	ankle/brachial blood pressure index	**CVD**	cardiovascular disease
ACS	American Cancer Society	**DALE**	disability-adjusted life expectancy
ADT	aerodigestive tract	**DALYs**	disability-adjusted life years
AF	attributable fraction	**df**	degrees of freedom
AGL	acute granulocytic leukemia	**DFS**	decayed or filled surfaces
AHA	American Heart Association	**DFT**	decayed or filled teeth
AIDS	acquired immunodeficiency syndrome	**DMF**	decayed, missing, or filled teeth
ALL	acute lymphocytic leukemia	**DMFS**	decayed, missing, or filled surfaces
AMD	age-related macular degeneration	**DMFT**	decayed, missing, or filled teeth
AML	acute myelocytic leukemia	**DNA**	deoxyribonucleic acid
ANCOVA	analysis of covariance	**DR**	diabetic retinopathy
ANLL	acute nonlymphocytic leukemia	**DS**	decayed surfaces
ANOVA	analysis of variance	**EBCT**	electron beam computed tomography
AR	attributable risk	**ED**	erectile dysfunction
ARI	acute respiratory illness	**EF**	etiologic fraction
ARIC	Atherosclerosis Risk in Communities Study	**eNOS**	endothelial nitric oxide synthase
AZT	azidothymidine or zidovudine	**EPA**	Environmental Protection Agency
BMC	bone mineral content	**ER**	estrogen receptor
BMD	bone mineral density	**ERT**	estrogen replacement therapy
BMI	body mass index	**ETS**	environmental tobacco smoke
BRFSS	Behavioral Risk Factor Surveillance System	**FEF**	forced expiratory flow
BUA	broadband ultrasound attenuation	**FEV$_1$**	forced expiratory volume in one second
CABG	coronary artery bypass graft	**FL**	Flanders and Rothman model
CAL	clinical attachment level	**FS**	filled surfaces
CDC	Centers for Disease Control and Prevention	**FTC**	Federal Trade Commission
CEJ	cemento-enamel junction	**FVC**	forced vital capacity
CGL	chronic granulocytic leukemia	**g**	gram
CHD	coronary heart disease	*GSTM1*	glutathione transferase classes mu
CHF	congestive heart failure	***H. pylori***	*Helicobacter pylori*
CHS	Cardiovascular Health Study	**HBV**	hepatitis B virus
CI	confidence interval	**HCFA**	Health Care Financing Administration
CLL	chronic lymphocytic leukemia	**HDL**	high-density lipoprotein
cm	centimeter	**Hg**	mercury
CML	chronic myelogenous leukemia	**HI**	hemagglutination inhibition
COLD	chronic obstructive lung disease	**HIV**	human immunodeficiency virus
COPD	chronic obstructive pulmonary disease	**HMO**	health maintenance organization
CPITN	Community Periodontal Index of Treatment Needs	**HPV**	human papilloma virus

HR	hazard ratio		**NNK**	nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
HRT	hormone replacement therapy		**NPT**	nocturnal penile tumescence
IARC	International Agency for Research on Cancer		**NR**	data were not reported
ICD	*International Classification of Diseases*		**NRC**	National Research Council
IDF	incidence density fraction		**NS**	not significant
Ig	immunoglobulin		**NSAID**	nonsteroidal anti-inflammatory drug
IHD	ischemic heart disease		**O/E**	observed/expected
IL	interleukin		**OR**	odds ratio
IMT	intimal-medial thickness		**OTA**	Office of Technology Assessment
IOM	Institute of Medicine		**p**	probability
IPF	idiopathic pulmonary fibrosis		**PAH**	polyaromatic hydrocarbon
IUGR	intrauterine growth retardation		**PAR**	population attributable risk
IVF	in vitro fertilization		**PBI**	penile-brachial index
kg	kilogram		**PDAY**	Pathobiological Determinants of Atherosclerosis in Youth Study
LBW	low birth weight		**PDR**	proliferative diabetic retinopathy
LDL	low-density lipoprotein		**PMN**	polymorphonuclear neutrophilic leukocyte
LL	log-linear model		**POR**	prevalence odds ratio
LOH	loss of heterozygosity		**PPD**	probing pocket depth
LPA	loss of periodontal attachment		**PR**	progesterone receptor
LRI	lower respiratory illness		**PROM**	premature rupture of membranes
MD	myelodysplasia		**PSA**	prostate-specific antigen
MeSH	Medical Subject Heading		**QALYs**	quality-adjusted life years
mg	milligram		**R²**	prediction values
MI	myocardial infarction		**RDFS**	root decayed or filled surfaces
mL	milliliter		**RDS**	respiratory distress syndrome
mm	millimeter		**RDS**	root decayed surfaces
MRFIT	Multiple Risk Factor Intervention Trial		**REM**	rapid eye movement
MRI	magnetic resonance imaging		**RH**	relative hazard
MS	missing surfaces		**RR**	relative risk
N	total population size		**RSV**	respiratory syncytial virus
n	total sample size		**SAF**	smoking attributable fraction
NA	not applicable		**SAM**	smoking attributable mortality
NAEC	National Advisory Eye Council		**SAMMEC**	Smoking-Attributable Mortality, Morbidity, and Economic Costs
NAT2	*N*-acetyltransferase 2		**SD**	standard deviation
NCHS	National Center for Health Statistics		**SE**	standard error
NCI	National Cancer Institute		**SEER**	Surveillance, Epidemiology, and End Results Program
NEI	National Eye Institute		**SES**	socioeconomic status
ng	nanogram		**SGA**	small for gestational age
NHANES	National Health and Nutrition Examination Survey		**SIDS**	sudden infant death syndrome
NHIS	National Health Interview Survey		**SMR**	standardized mortality ratio
NHLBI	National Heart, Lung, and Blood Institute		**SRD**	smoking-related disease
NIH	National Institutes of Health		**SWI**	surgical wound infections
NMES	National Medical Expenditures Survey			
NMFS	National Mortality Followback Survey			

TBARS	thiobarbituric acid reactive substances		**USDHHS**	U.S. Department of Health and Human Services
TGF-α	transforming growth factor alpha		**VEGF**	vascular endothelial growth factor
Th	T-helper		**VLBW**	very low birth weight
TNF	tumor necrosis factor		**VLDL**	very low-density lipoprotein
TPA	tissue plasminogen activator		**V$_{max}$FRC**	maximal flow at functional residual capacity
tPTEF/tE	the ratio of time to peak tidal expiratory flow to expiratory time		**vWF**	von Willebrand factor
UC	ulcerative colitis		**WHO**	World Health Organization
URI	upper respiratory illness		**YPLL**	years of potential life lost
USDHEW	U.S. Department of Health, Education, and Welfare		**YRBS**	Youth Risk Behavior Survey

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Appendix

Publication lags, even short ones, prevent an up-to-the-minute inclusion of all recently published articles and data. Therefore, by the time the public reads this report, there may be additional published studies or data. To provide published information as current as possible, this Appendix lists more recent studies that represent major additions to the literature.

Chapter 1
Introduction and Approach to Causal Inference

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