

# Chapter 1

## Introduction and Approach to Causal Inference

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## Introduction

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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
<b>Cancer</b>		
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."
<b>Cardiovascular diseases</b>		
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."
<b>Respiratory diseases</b>		
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**

<b>Disease</b>	<b>Highest level conclusion from previous Surgeon General's reports (year)</b>	<b>Conclusion from the 2004 Surgeon General's report</b>
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)	<p>"The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence."</p> <p>"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. "</p> <p>"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."</p> <p>"The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence."</p>
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)	<p>"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."</p> <p>"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."</p>

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)	<p>"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."</p> <p>"The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control."</p>
<b>Reproductive effects</b>		
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)	<p>"The evidence is sufficient to infer a casual relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption."</p> <p>"The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation."</p>

**Table 1.1 Continued**

Disease	Highest level conclusion from previous Surgeon General's reports (year)	Conclusion from the 2004 Surgeon General's report
<b>Other effects</b>		
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	<p>"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)</p> <p>"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)</p>	<p>"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."</p> <p>"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."</p>
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 <i>Helicobacter pylori</i> 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

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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
<b>Atherosclerosis/peripheral vascular disease</b>	
"Autopsy studies suggest that cigarette smoking is <b>associated with a significant increase</b> in atherosclerosis of the aorta and coronary arteries." (p. 4)	1969
"Data from a number of retrospective studies have indicated that cigarette smoking is <b>a likely risk factor</b> in the development of peripheral vascular disease. Cigarette smoking also appears to be a <b>factor</b> in the aggravation of peripheral vascular disease." (p. 9)	1971
"Data from several epidemiological and experimental studies suggest that cigarette smoking is a <b>major risk factor</b> in the development of peripheral vascular disease." (p. 23)	1973
"Epidemiologic data reveal <b>strong associations</b> between cigarette smoking and development of peripheral vascular disease." (p. 19)	1974
"Smoking cigarettes is a <b>major risk factor</b> for arteriosclerotic peripheral vascular disease and is <b>strongly associated</b> 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 <b>major, independent risk factor</b> for the development of arteriosclerotic peripheral vascular disease in women." (p. 7)	1980
"Cigarette smoking is <b>the most powerful risk factor</b> predisposing to atherosclerotic peripheral vascular disease." (p. 8)	1983
". . . cigarette smoking is a <b>cause of and the most powerful risk factor</b> for atherosclerotic peripheral vascular disease." (p. 63)	1989
<b>Bladder cancer</b>	
"Epidemiological studies have demonstrated a <b>significant association</b> between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the <b>risk</b> of developing bladder cancer <b>increases</b> with inhalation and the number of cigarettes smoked." (p. 75)	1972
"Epidemiological studies have demonstrated a <b>significant association</b> 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 <b>increase the risk</b> 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 <b>dose-response relationship</b> 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 <b>cause</b> of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking." (p. 178)	1990
<b>Cerebrovascular disease</b>	
"Additional evidence strengthens the <b>association</b> between cigarette smoking and cerebrovascular disease, and suggests that some of the pathogenetic [ <i>sic</i> ] 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 <b>contribute</b> to the development of cardiovascular disease and particularly to death from coronary heart disease." (p. 3)	1968
"Women cigarette smokers experience an <b>increased risk</b> for subarachnoid hemorrhage. . . ." (p. 7)	1980
"Cigarette smoking is a <b>major cause</b> of cerebrovascular disease (stroke), the third leading cause of death in the United States." (p. 12)	1989
<b>Chronic obstructive pulmonary disease<sup>†</sup> (COPD)</b>	
"Cigarette smoking is <b>the most important of the causes</b> of chronic bronchitis in the United States, and <b>increases the risk of dying</b> from chronic bronchitis." (p. 302)	1964
"Cigarette smoking is <b>the most important of the causes</b> of chronic non-neoplastic bronchopulmonary diseases in the United States. It <b>greatly increases the risk of dying</b> not only from both chronic bronchitis but also from pulmonary emphysema." (p. 31)	1967
"Epidemiological and laboratory evidence supports [ <i>sic</i> ] the view that cigarette smoking can <b>contribute</b> to the development of pulmonary emphysema in man." (p. 5)	1969
"Cigarette smoking is <b>the most important cause</b> of chronic obstructive bronchopulmonary disease in the United States. Cigarette <b>smoking increases the risk of dying</b> from pulmonary emphysema and chronic bronchitis." (p. 9)	1971
"Recent autopsy studies confirm that pulmonary emphysema is <b>much more frequent and severe in cigarette smokers</b> than nonsmokers." (p. 55)	1973

<sup>†</sup>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
<b>Coronary heart disease</b>	
“It is also more prudent to assume that the <b>established association</b> 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 <b>caused by</b> 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 <b>can cause death</b> 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 <b>contribute</b> 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 <b>causally related</b> to coronary heart disease for both men and women in the United States.” (p. 1-15)	1979
<b>Esophageal cancer</b>	
“Epidemiological studies have demonstrated that cigarette smoking is <b>associated</b> 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 <b>risk increases</b> with the amount smoked.” (p. 1-17)	1979
“Cigarette smoking is <b>causally associated</b> with cancer of the lung, larynx, oral cavity, and esophagus in women as well as in men. . . .” (p. 126)	1980
“Cigarette smoking is a <b>major cause</b> of esophageal cancer in the United States.” (p. 7)	1982
<b>Kidney cancer</b>	
“Cigarette smoking is a <b>contributory factor</b> in the development of kidney cancer in the United States. The term ‘contributory factor’ <b>by no means excludes</b> the possibility of a <b>causal role</b> for smoking in cancers of this site.” (p. 7)	1982
<b>Laryngeal cancer</b>	
“Evaluation of the evidence leads to the judgment that cigarette smoking is a <b>significant factor</b> in the causation of laryngeal cancer in the male.” (p. 37)	1964
“Cigarette smoking is <b>causally associated</b> 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
<b>Lung cancer</b>	
“Cigarette smoking is <b>causally related</b> to lung cancer in men; the magnitude of the effect of cigarette smoking <b>far outweighs all other factors</b> . 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 <b>causal relationship</b> of smoking to lung cancer in women.” (p. 36)	1967
“Cigarette smoking is <b>causally related</b> to lung cancer in women. . . .” (p. 4)	1968
“Cigarette smoking is <b>causally associated</b> with cancer of the lung. . .in women as well as in men. . . .” (p. 126)	1980
<b>Oral cancer</b>	
“Smoking is a <b>significant factor</b> . . .in the development of cancer of the oral cavity.” (p. 4)	1968
“Recent epidemiologic data strongly indicate that cigarette smoking plays an <b>independent role</b> in the development of oral cancer.” (p. 59)	1974
“Epidemiological studies indicate that smoking is a <b>significant causal factor</b> in the development of oral cancer.” (p. 1-17)	1979
“Cigarette smoking is <b>causally associated</b> with cancer of the. . .oral cavity. . .in women as well as in men. . . .” (p. 126)	1980
“Cigarette smoking is a <b>major cause</b> of cancers of the oral cavity in the United States.” (p. 6)	1982
<b>Pancreatic cancer</b>	
“Epidemiological evidence demonstrates a <b>significant association</b> between cigarette smoking and cancer of the pancreas.” (p. 75)	1972
“Recent epidemiologic data <b>confirm the association</b> between smoking and pancreatic cancer.” (p. 59)	1974
“Cigarette smoking is <b>related</b> to cancer of the pancreas, and several epidemiological studies have demonstrated a <b>dose-response relationship</b> .” (p. 1-17)	1979
“Cigarette smoking is a <b>contributory factor</b> in the development of pancreatic cancer in the United States. The term ‘contributory factor’ <b>by no means excludes</b> the possibility of a <b>causal role</b> for smoking in cancers of this site.” (p. 7)	1982

Table 1.2 Continued

Disease and statement	Surgeon General's report
<b>Peptic ulcer disease</b>	
“Epidemiological studies indicate an <b>association</b> between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer.” (p. 340)	1964
“The <b>relationship</b> between cigarette smoking and death rates from peptic ulcer, especially gastric ulcer, <b>is confirmed</b> . 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 <b>significant dose-related excess mortality</b> 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, <b>confirms and extends the association</b> between cigarette smoking and gastric ulcer mortality.” (p. 162)	1973
“Epidemiological studies have found that cigarette smoking is <b>significantly associated</b> with the incidence of peptic ulcer disease and <b>increases the risk</b> of dying from peptic ulcer disease.” (p. 1-23)	1979
“Female smokers show a <b>prevalence</b> of peptic ulcer <b>higher</b> 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 <b>significant</b> enough to suggest a <b>causal relationship</b> .” (p. 76)	1989
“The 1979 Report stated that the evidence of an association between cigarette smoking and peptic ulcer was <b>strong</b> enough to suggest a <b>causal relationship</b> .” (p. 429)	1990
<b>Diminished health status/respiratory morbidity</b>	
“Cough, sputum production, or the two combined are <b>consistently more frequent</b> among cigarette smokers than among non-smokers.” (p. 302)	1964
“Even relatively young cigarette smokers frequently have <b>demonstrable respiratory symptoms</b> and reduction [ <i>sic</i> ] in ventilatory function.” (p. 31)	1967
“Cigarette smokers have <b>higher rates of disability</b> 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 <b>increased prevalence</b> 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 <b>more prevalent and severe</b> 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 <b>more common</b> in smokers than nonsmokers." (p. 48)	1972
"Cigarette smokers have also been shown to have a <b>significantly longer duration</b> of respiratory symptoms following mild viral illness than nonsmokers." (p. 78)	1975
"In addition to an increased risk of COPD, cigarette smokers are more <b>frequently subject to and require longer convalescence from</b> other respiratory infections than nonsmokers. Also, if they require surgery, they are <b>more likely to develop</b> 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 <b>wide variety of alterations</b> in the immune system have been observed due to cigarette smoking." (p. 1-18)	1979
" <b>Cessation of smoking definitely improves</b> pulmonary function and <b>decreases the prevalence of</b> respiratory symptoms." (p. 1-18)	1979
"Cigarette smokers have an <b>increased frequency</b> of respiratory symptoms, and at least two of them, cough and sputum production, are <b>dose-related</b> ." (p. 1-18)	1979
"The relationship between smoking and an <b>increased prevalence</b> of respiratory symptoms in the adult has been <b>well established</b> 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 <b>higher frequency</b> 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 <b>strong and consistent</b> ; they have been amply documented and are judged to be <b>causal</b> ." (p. 47)	1984
"Consideration of evidence from many different studies has led to the conclusion that cigarette smoking is <b>the overwhelmingly most important cause</b> 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

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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

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### 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 hyperresponsiveness.
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 neurocognitive 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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