Chapter 2
Cancer

Introduction

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

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

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

Previous Surgeon General's reports have concluded that smoking causes cancer in several organ sites. The list of cancers caused by smoking has included cancers of the urinary bladder, esophagus, kidney, larynx, lung, oral cavity, and pancreas. The past conclusions are detailed in the text that follows and are summarized in Table 2.1. The International Agency for Research on Cancer (IARC) has also reviewed the evidence on tobacco and cancer on two occasions, in 1986 and again in 2002 (IARC 1986, 2002). The system used by IARC differs from that applied in the Surgeon General's reports, but conclusions have generally been similar.

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

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

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

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

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

Table 2.1 Continued

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

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

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

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

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

Lung Cancer

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

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

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

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

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

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

Conclusions of Previous Surgeon General's Reports

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

Biologic Basis

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

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

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

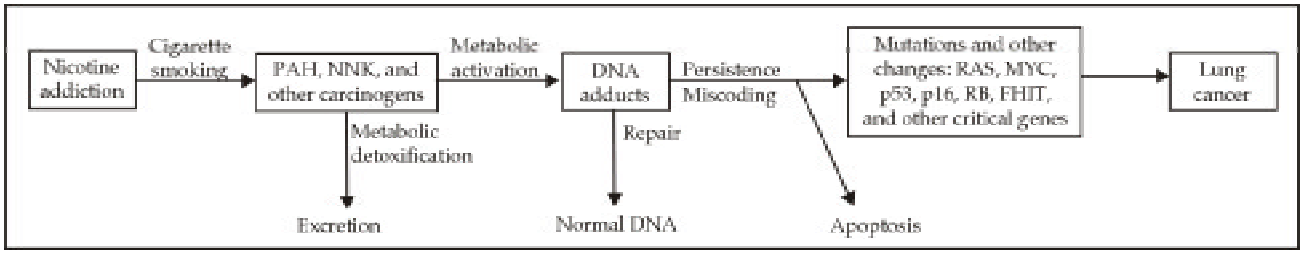
The epidemiologic evidence is limited and mixed as to whether age at onset of smoking may be an independent risk factor for lung cancer, beyond the inherently longer duration of smoking by those starting to smoke at younger ages (Hegmann et al. 1993; Benhamou and Benhamou 1994). Some recent molecular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

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

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

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

Figure 2.1 Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens and their induction of multiple mutations in critical genes



Note: PAHs = polycyclic aromatic hydrocarbons; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
Source: Hecht 1999, p. 1195. Reprinted with permission.

relationships have been shown (Wiencke et al. 1995a). Hence, current smokers have significantly elevated PAH-DNA adducts in their lungs. As smokers quit, it is believed that the amount of adducts declines rapidly. This notion is based on cross-sectional studies in former smokers that have shown significant differences in the adduct burdens of current compared with former smokers (Wiencke et al. 1995a, 1999).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Epidemiologic Evidence

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

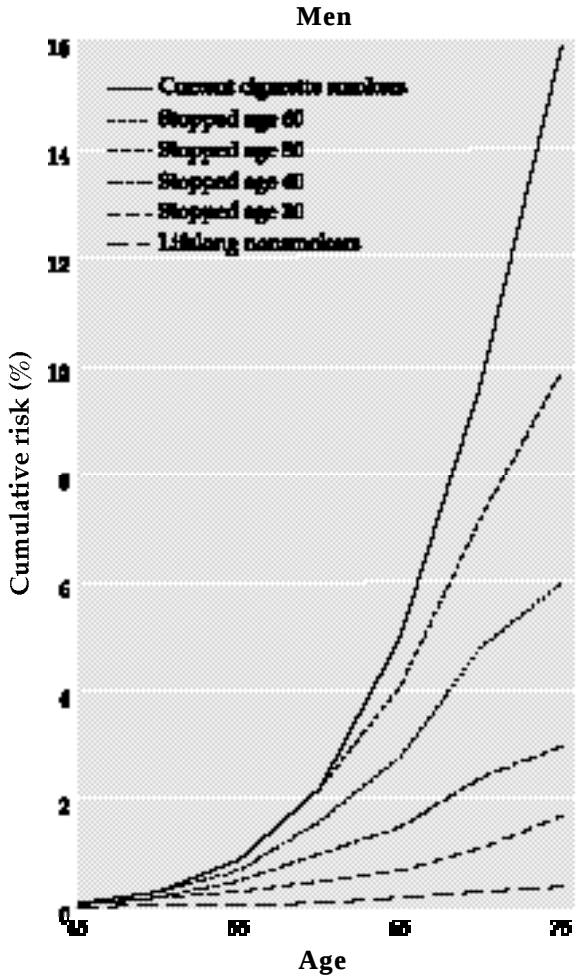
Among the principal issues addressed have been

- the characterization of the dose-response relationship for lung cancer risk with smoking;
- the consequences of changing the characteristics of cigarettes, including the addition of filters and the reduction of machine-measured tar and nicotine yields;
- changes in lung cancer occurrence following smoking cessation; and
- factors influencing the shift in lung cancer histopathology in recent decades.

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

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

Figure 2.2 Effects of smoking cessation at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in United Kingdom in 1990



Note: Nonsmoker risks are taken from a U.S. prospective study of mortality.
Source: Peto et al. 2000, p. 326. Reprinted with permission.

Changes in Relative Risks Following Smoking Cessation

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

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

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

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

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

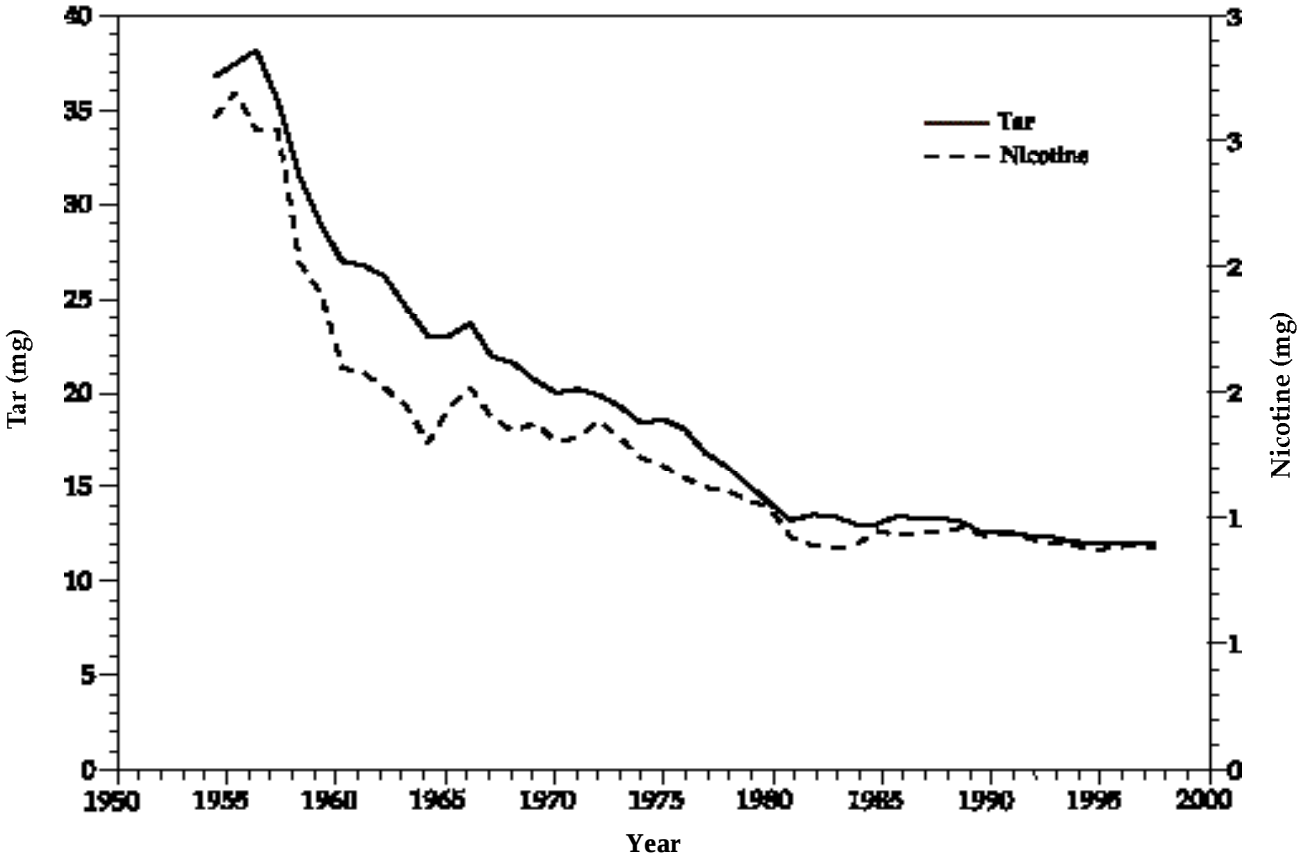
Changing Characteristics of Cigarettes

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

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

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

Figure 2.3 Sales-weighted tar and nicotine values for U.S. cigarettes as measured by machine using the Federal Trade Commission (FTC) method, 1954–1998*



*Values before 1968 are estimated from available data.
Source: Hoffmann and Hoffmann 2001, p. 167.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2.2 Continued

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

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

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

Table 2.2 Continued

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

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

The relevant cohort data come from the ACS CPS-I and CPS-II studies and the British physicians cohort. In a 1976 publication, Hammond and colleagues (1976) used tar yields of products smoked by CPS-I participants to compare mortality risks from lung cancer and other diseases. The 12-year follow-up interval spanned 1960–1972. Smokers were placed into three categories of products smoked: low yield (<17.6 mg/cigarette), high yield (25.8–35.7 mg/cigarette), and medium yield (intermediate). The standardized mortality rate for lung cancer in smokers of low-yield cigarettes was approximately 80 percent of the rate found in high-yield smokers. A further analysis of tar yields using the same data set confirmed that risks for lung cancer deaths increased with tar yield (Stellman and Garfinkel 1989).

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

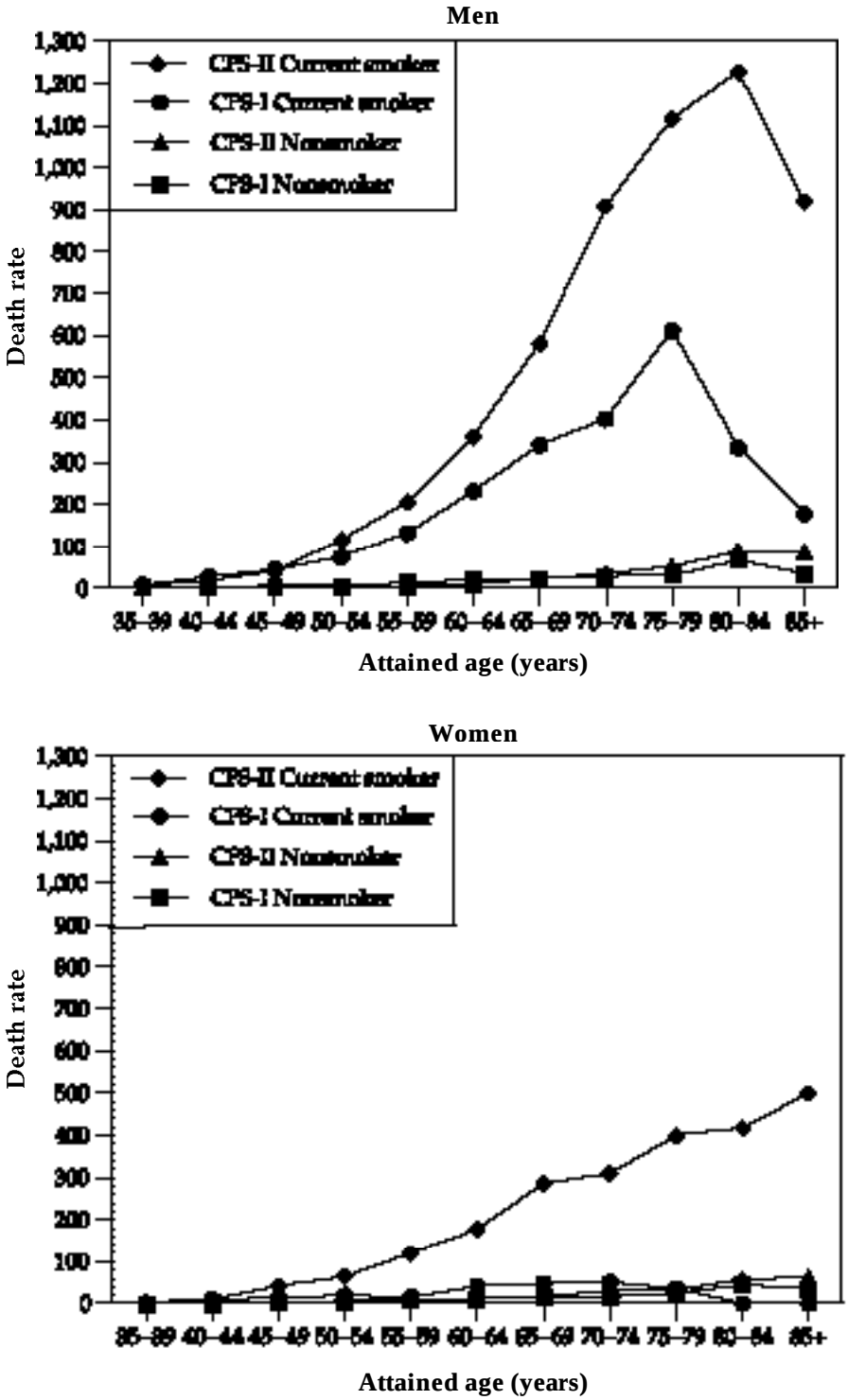
Outcome	Results
Lung cancer incidence	• Tar yield of current cigarette brand was not associated with lung cancer incidence (RR = 1.02 / 1 mg tar yield in men and 0.99 / 1 mg tar yield in women)
Lung cancer	• Increased RR for smokers of both plain and filter-tipped cigarettes (RR = 1.6 [95% CI, 0.9–2.7])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

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

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

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

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



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

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

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

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

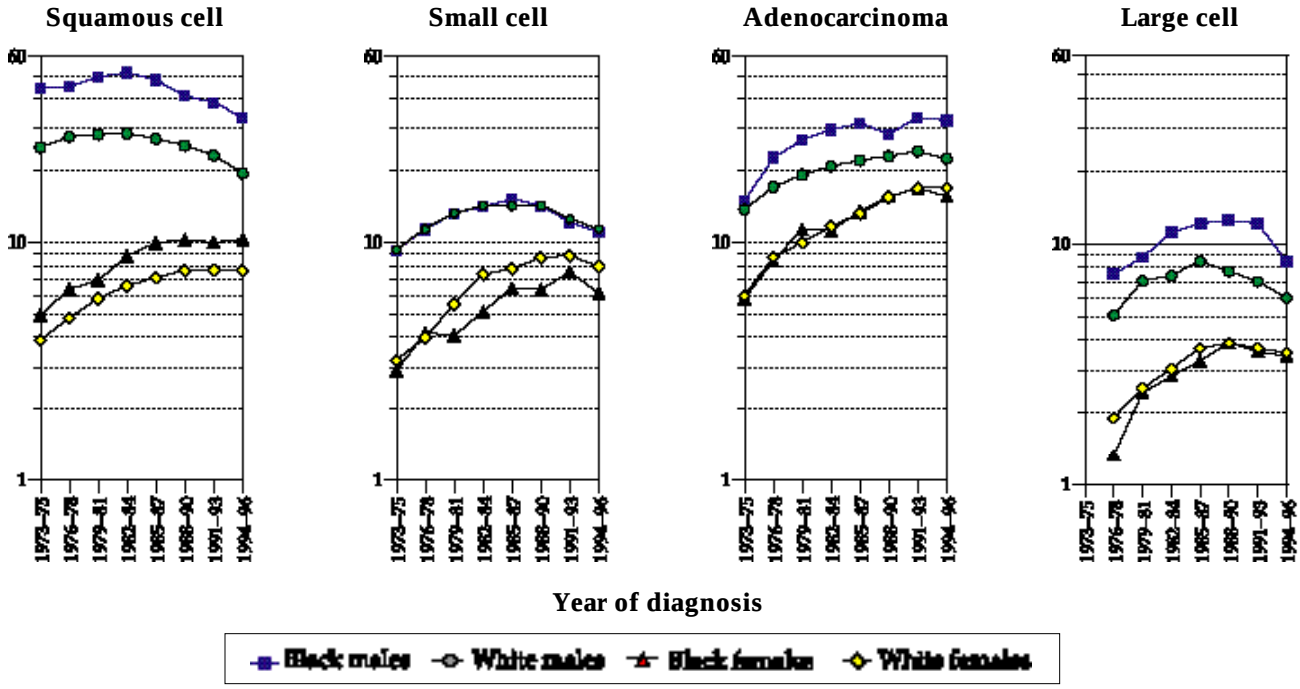
Lung Cancer Histopathology

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

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

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

Figure 2.5 Cancer of the lung and bronchus: Surveillance, Epidemiology, and End Results (SEER) incidence rates by histologic type, gender, race, and ethnicity, all ages, 1973–1996



Note: Rates are per 100,000 (log scale) and are age-adjusted to 1970 U.S. standard million population.
Source: Wingo et al. 1999, p. 681. Reprinted with permission.

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

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

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

Evidence Synthesis

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

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

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

Conclusions

The scope of the evidence on cigarette smoking and lung cancer is extraordinary. Epidemiologists continue to refine the characterization of the risks from smoking, rapidly gaining new insights concerning respiratory carcinogenesis from the application of increasingly informative modern cellular and molecular biology techniques. This chapter has not covered the full sweep of this extensive evidence. Even the selected review presented here, however, is sufficient to support additional conclusions about smoking and lung cancer, particularly in relation to key issues that have emerged since prior reviews. These conclusions are as follows:

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

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

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

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

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

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

Implications

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

Laryngeal Cancer

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

Conclusions of Previous Surgeon General's Reports

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

Biologic Basis

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

Epidemiologic Evidence

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

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

Evidence Synthesis

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

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

Conclusions

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

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

Implications

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

Oral Cavity and Pharyngeal Cancers

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

Conclusions of Previous Surgeon General's Reports

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

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

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

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

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

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

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

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

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

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

Biologic Basis

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

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

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

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

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

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

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

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

Epidemiologic Evidence

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

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

Table 2.5 shows the results of two cohorts, the United States veterans study (McLaughlin et al. 1995a) and CPS-II (ACS, unpublished data), and four case-control studies (Franceschi et al. 1992; Muscat et al. 1996; Levi et al. 1998; La Vecchia et al. 1999) that met the above criteria for inclusion and provided results by smoking status. The RR estimates among male current smokers compared with lifetime nonsmokers ranged from 3.6 to 11.8 (Franceschi et al. 1992) for cancers within the oral cavity, and up to 14.1 (McLaughlin et al. 1995a) for cancers of the pharynx. Risk was higher among current than former smokers in all studies. The RR of death from any cancer of the oral cavity or pharynx in CPS-II was 9.3 (95 percent confidence interval [CI], 6.4–13.5) among male current smokers and 4.9 (95 percent CI, 3.5–6.8) among female current smokers who were followed from 1982–1996 (ACS, unpublished data). These numbers are likely to be underestimates of the true risk of continuing to smoke, because many persons classified as current smokers at enrollment into the study will have quit during the 14-year follow-up period.

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

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

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

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

Evidence Synthesis

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

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

Conclusion

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

Implications

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

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

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

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

Findings	Risk estimates (95% CI)*	Comments
• There was a significant positive association with bidi smoking and a positive association with cigarette smoking and snuff inhalation	Pan chewing Never smoked OR† = 1.0 (referent) <5 times / day OR = 0.69 (0.38–1.24) 5–9 times / day OR = 0.67 (0.39–1.15) ≥10 times / day OR = 0.73 (0.36–1.46) Bidi smoking Never smoked OR = 1.0 (referent) ≤10 / day OR = 1.79 (1.09–2.92) 11–20 / day OR = 2.13 (1.29–3.51) ≥21 / day OR = 5.09 (2.69–9.63) Cigarette smoking No OR = 1.0 (referent) Yes OR = 1.37 (0.77–2.42) Bidi and cigarette smoking Never smoked OR = 1.0 (referent) ≤10 / day OR = 0.33 (0.09–1.10) 11–20 / day OR = 2.94 (1.54–5.58) ≥21 / day OR = 4.29 (2.50–7.34) Snuff inhalation No OR = 1.0 (referent) Yes OR = 1.24 (0.31–4.88)	ORs were calculated using unconditional logistic regression; risk estimates were adjusted for age and religion

Table 2.3 Continued

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

‡RR = Relative risk.

Findings	Risk estimates (95% CI)	Comments
• Risk decreased with years of cessation, p <0.01 for linear trend	Never smoked OR = 1.0 (referent) Current smoking OR = 3.8 (0.96–14.66) 1–5 years of cessation OR = 2.4 (0.45–12.90) 6–15 years of cessation OR = 1.4 (0.28–7.43) ≥16 years of cessation OR = 0.9 (0.17–4.25)	ORs were calculated using unconditional logistic regression, and were adjusted for age
• Dose-response relationship, but no p value for trend was provided	Cigarettes / day 0–5 cigarettes / day RR = 1.0 (referent) 6–10 cigarettes / day RR = 8.4 (1.5–46.0) 11–15 cigarettes / day RR = 18.1 (3.9–83.2) 16–20 cigarettes / day RR = 29.9 (7.0–128) 21–30 cigarettes / day RR = 33.7 (7.6–150) >30 cigarettes / day RR = 59.7 (13.0–274) Age at smoking initiation <16 years RR = 1.28 (0.74–2.23) 16–22 years RR = 1.0 (referent) >22 years RR = 0.60 (0.30–1.19) Years since cessation Current smokers RR = 1.0 (referent) 5–10 years RR = 0.76 (0.32–1.80) >10 years RR = 0.60 (0.30–1.19)	RRs were calculated using unconditional logistic regression, and were adjusted for age, residence, and educational level
• Dose-response relationship with a 9-fold increase in risk in heavy smokers, but no p value for trend was provided	<5 tobacco-years RR = 1.0 (referent) 5–50 tobacco-years RR = 2.6 (1.63–3.99) >50 tobacco-years RR = 9.0 (5.21–15.53)	RRs were calculated using logistic regression models

Table 2.3 Continued

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

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

Findings	Risk estimates (95% CI)	Comments
• Significant dose-response relationship for duration of smoking ($p < 0.01$), cigarettes / day ($p < 0.01$), and pack-years ($p < 0.01$)	Duration of smoking <20 years OR = 1.4 (0.4–4.6) 20–29 years OR = 4.1 (1.6–11.1) 30–39 years OR = 12.0 (4.8–30.1) ≥40 years OR = 13.2 (5.6–31.2) Cigarettes / day <10 cigarettes / day OR = 1.6 (0.5–4.9) 10–19 cigarettes / day OR = 7.1 (3.1–16.6) 20 cigarettes / day OR = 12.4 (4.6–33.2) >20 cigarettes / day OR = 25.1 (9.9–63.2) Pack-years <10 pack-years OR = 1.4 (0.4–4.5) 10–19 pack-years OR = 2.9 (1.1–7.9) 20–29 pack-years OR = 3.1 (1.1–8.6) 30–39 pack-years OR = 15.4 (6.0–39.6) ≥40 pack-years OR = 25.1 (10.3–61.2)	ORs were calculated using unconditional logistic regression, and were adjusted for age and education
• Significant dose-response relationship ($p < 0.0001$)	Men Never smoked RR = 1.0 (referent) Moderate smokers RR = 3.5 (2.1–6.0) Heavy smokers RR = 10.4 (6.2–17.5)	RRs were calculated using multivariate unconditional logistic regression, and were adjusted for center, age, and education

Table 2.3 Continued

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

Findings	Risk estimates (95% CI)	Comments
• Significant dose-response relationship for cigarettes / day ($p < 0.001$), duration of smoking ($p < 0.001$), and pack-years ($p < 0.001$)	Cigarettes / day 1–10 cigarettes / day RR = 1.1 (0.6–1.9) 11–20 cigarettes / day RR = 4.8 (3.1–7.4) ≥21 cigarettes / day RR = 4.1 (2.8–6.0) Duration of smoking 1–10 years RR = 1.1 (0.6–1.9) 11–20 years RR = 4.8 (3.1–7.4) ≥21 years RR = 4.1 (2.8–6.0) Pack-years 1–10 pack-years RR = 1.9 (1.3–3.0) 11–20 pack-years RR = 4.4 (2.9–6.7) ≥21 pack-years RR = 6.0 (3.8–9.5)	ORs were calculated using Gart's Method, and were adjusted for age and alcohol use
• Dose-response relationship, but no p value for trend was provided • 9.5-fold increase in risk in heavy smokers (more than 100 tobacco-years)	<5 tobacco-years RR = 1.0 (referent) 5–19 tobacco-years RR = 4.0 (1.7–9.2) 50–74 tobacco-years RR = 6.3 (3.0–13.3) 75–99 tobacco-years RR = 7.8 (3.6–16.7) ≥100 tobacco-years RR = 9.5 (4.6–19.6)	RRs were calculated using logistic regression, and were adjusted for alcohol consumption; risk estimates were not provided for 20–49 tobacco-years

Table 2.3 Continued

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

[Δ]ADT = Aerodigestive tract.

Findings	Risk estimates (95% CI)	Comments
• After 15 years of cessation, RRs for former smokers decreased to near baseline levels	Years since smoking cessation (all tobacco types) Never smoked RR = 1.0 (referent) Current smokers RR = 11.7 (4.4–31.5) ≤1 year RR = 10.5 (3.0–36.6) 2–5 years RR = 7.7 (2.4–25.2) 6–10 years RR = 2.7 (0.8–9.6) 11–15 years RR = 5.9 (1.4–24.2) 16–20 years RR = 1.5 (0.3–8.6) >20 years RR = 3.1 (1.0–9.4) Type of tobacco Never smoked RR = 1.0 (referent) Filter-tipped cigarettes RR = 8.4 (3.1–22.8) Unfiltered cigarettes RR = 12.2 (4.1–35.9) Commercial cigarettes 1–20 pack-years RR = 8.2 (3.0–22.6) 21–40 pack-years RR = 9.4 (3.0–22.6) >40 pack-years RR = 16.3 (5.3–49.87) Black tobacco 1–20 pack-years RR = 7.3 (2.4–22.4) 21–40 pack-years RR = 8.9 (2.9–27.2) >40 pack-years RR = 8.5 (3.0–23.9) Pipes 1–20 pack-years RR = 7.7 (1.4–42.8) >20 pack-years RR = 2.4 (0.4–13.1)	RRs were calculated using conditional logistic regression (matching variables: age, gender, location, and admission period); RRs associated with smoking cessation were adjusted for alcohol and tobacco use; RRs associated with tobacco habits were adjusted for cumulative alcohol and tobacco use, race, beverage temperature, religion, wood stove use, and consumption of spicy foods

Table 2.3 Continued

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

[Δ]ADT = Aerodigestive tract.

Findings	Risk estimates (95% CI)	Comments
• No statistical evidence of effect modification (p = 0.945) • Effect of alcohol was most marked only at the highest consumption level among light smokers • Significant dose-response relationships for both tobacco (p <0.0001) and alcohol (p = 0.0004)	0–10 kg ethanol 0–5 pack-years OR = 1.0 (referent) 6–42 pack-years OR = 13.5 (2.7–66.8) >42 pack-years OR = 11.4 (2.1–62.0) 11–530 kg ethanol 0–5 pack-years OR = 1.2 (0.1–14.4) 6–42 pack-years OR = 16.1 (3.4–76.2) >42 pack-years OR = 22.0 (4.5–107) >530 kg ethanol 0–5 pack-years OR = 5.5 (0.4–71.5) 6–42 pack-years OR = 36.9 (0.7–1,800) >42 pack-years OR = 43.1 (9.1–206)	ORs were calculated using multivariate conditional logistic regression, and were adjusted for race, beverage temperature, religion, wood stove use, and consumption of spicy foods; interaction assessments were based on a multiplicative model; risk estimates only were provided as stratified

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

Study	Population	Alcohol exposure	Tobacco exposure
Wynder et al. 1976	258 male and 56 female cases with histologic evidence of laryngeal cancer 516 male and 168 female hospital controls matched for gender, year of interview, hospital status, and age at diagnosis New York City, Houston, Los Angeles, Birmingham, Miami, New Orleans 1970–1973	• Nondrinkers / occasional drinkers • 1–6 units / day • ≥7 units / day 1 unit = 1 ounce (oz.) hard liquor = 4 oz. wine = 6 oz. beer	Cigarette equivalents: 0 / day 1–15 / day 16–34 / day ≥35 / day 1 cigar = 5 cigarettes 1 pipe = 2.5 cigarettes
Burch et al. 1981	204 incident cases 204 community controls matched for neighborhood, gender, and age Ontario, Canada 1977–1979	Lifetime consumption (oz.) of ethanol (in thousands): 0 <10 10–25 ≥26	Lifetime cigarette habit (in thousands): 0 <150 150–299 ≥300

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

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

Table 2.4 Continued

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

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

Table 2.4 Continued

Study	Population	Alcohol exposure	Tobacco exposure
Herity et al. 1982	59 male cases 152 male hospital controls Dublin, Ireland	• Nondrinkers and light drinkers • Heavy drinkers	• Nonsmokers and light smokers • Heavy smokers
Walter and Iwane 1983	87 male cases with laryngeal cancer 956 male controls with cancers of other sites (excluding oral cavity, pharynx, esophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder, and kidney cancers) 7 cities and 2 states (not named) 1969–1971	Lifetime alcohol consumption: 0–49 units 50–349 units 350–699 units ≥700 units 1 unit = 1.5 oz. liquor = 6 oz. wine = 12 oz. beer	Lifetime tobacco habit: 1–49 units 50–549 units 550–899 units ≥900 units

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

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

Table 2.4 Continued

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

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

Table 2.4 Continued

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

**df = Degrees of freedom.

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

Table 2.4 Continued

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

**df = Degrees of freedom.

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

Table 2.4 Continued

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

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

Table 2.4 Continued

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

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

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

Table 2.4 Continued

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

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

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

Cohort studies

Study Location/population	Cancer site	Smoking status (number of deaths)
McLaughlin 1995a United States, 26-year follow-up of 248,046 U.S. veterans Outcome = total cancer mortality	Oral	Never smoked (see comments) Ever smoked Former smokers Current smokers
	Pharynx	Never smoked (see comments) Ever smoked Former smokers Current smokers
American Cancer Society, unpublished data United States, 1982–1996, Cancer Prevention Study II (352,363 men and 553,593 women) Outcome = mortality	Oropharynx	Men Never smoked (34) Current smokers (196) Former smokers (67) Women Never smoked (73) Current smokers (84) Former smokers (21)

Case-control studies

Study Location/population	Cancer site	Smoking status (cases/controls)
Franceschi et al. 1992 Italy, 1986–1990 Hospital-based study (men aged <75 years)	Tongue	Never smoked (3/153) Current smokers (83/306) Former smokers (15/260)
	Mouth	Never smoked (3/153) Current smokers (78/306) Former smokers (18/260)
Muscat et al. 1996 United States, 1981–1990, hospital-based study (cases matched to controls for gender, age, race, and date of admission)	Oropharynx	Men Never smoked (70/138) Current smokers (459/219) Former smokers (158/262) Women Never smoked (77/167) Current smokers (196/65) Former smokers (49/72)

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

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

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

Table 2.5 Continued

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

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

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

	Cohort studies	
Study Location/population	**Cancer site**	**Cigarettes per day (number of deaths)**
Kahn 1966 United States, veterans, followed for 8.5 years (293,658 men aged 35–84 years) Outcome = mortality	Buccal cavity	Never or occasional smokers only (11) Current smokers 1–9 cigarettes / day (1) 10–20 cigarettes / day (13) 21–39 cigarettes / day (20) ≥40 cigarettes / day (3)
	Pharynx	Never or occasional smokers (4) Current smokers 1–9 cigarettes / day (3) 10–20 cigarettes / day (19) 21–39 cigarettes / day (12) ≥40 cigarettes / day (3)
American Cancer Society (ACS), unpublished data United States, 1982–1996, Cancer Prevention Study II (352,363 men and 553,593 women) Outcome = mortality	Oropharynx	Men Never smoked (34) Current smokers <20 cigarettes / day (23) 20 cigarettes / day (58) 21–39 cigarettes / day (61) ≥40 cigarettes / day (54) Women Never smoked (73) Current smokers <20 cigarettes / day (16) 20 cigarettes / day (34) 21–39 cigarettes / day (16) ≥40 cigarettes / day (18)

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

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

Table 2.6 Continued

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

[§]OR = Odds ratio.

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

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

Study Location/population	Cancer site	Smoking status (number of deaths or cases/controls)
Cohort study		
American Cancer Society, unpublished data United States, 1982–1996, Cancer Prevention Study II (352,363 men and 553,593 women) Outcome = mortality	Oropharynx	Men Current smokers (196) Former smokers <11 years since cessation (37) 11–19 years since cessation (10) ≥20 years since cessation (20) Never smoked (34) Women Current smokers (84) Former smokers <11 years since cessation (9) 11–19 years since cessation (7) ≥20 years since cessation (5) Never smoked (73)
Case-control studies		
Blot et al. 1988 United States, 1984–1985, population cancer registry-based study (Atlanta, Los Angeles, Santa Clara and San Mateo counties south of San Francisco-Oakland, and New Jersey); men and women aged 18–79 years; population-based controls identified by random-digit telephone dialing / Health Care Financing Administration	Oropharynx	Men Current smokers (485 / 239) Former smokers 1–9 years since cessation (64 / 98) 10–19 years since cessation (56 / 114) ≥20 years since cessation (43 / 141) Never smoked (50 / 185) Women Current smokers (258 / 129) Former smokers 1–9 years since cessation (24 / 39) 10–19 years since cessation (10 / 35) ≥20 years since cessation (4 / 26) Never smoked (54 / 202)

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

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

Table 2.7 Continued

Case-control studies		
Study Location/population	**Cancer site**	**Smoking status (number of deaths or cases/controls)**
Franceschi et al. 1992 Italy, 1986–1990, hospital-based study (male cases aged <75 years)	Tongue	Current smokers (83 / 306) Former smokers <10 years since cessation (12 / 122) ≥10 years since cessation (3 / 138) Never smoked (3 / 153) χ^2 *for trend*
	Mouth	Current smokers (78 / 306) Former smokers <10 years since cessation (13 / 122) ≥10 years since cessation (3 / 138) Never smoked (3 / 153) χ^2 *for trend*
La Vecchia et al. 1999 Italian and Swiss hospital-based study, 1984–1997 (men and women aged <75 years)	Oral	Current smokers (441 / 1,456) Former smokers 1–2 years since cessation (28 / 127) 3–5 years since cessation (38 / 195) 6–9 years since cessation (31 / 183) 10–14 years since cessation (12 / 238) ≥15 years since cessation (18 / 424) Never smoked (70 / 1,556)
	Pharynx	Current smokers (459 / 1,456) Former smokers 1–2 years since cessation (31 / 127) 3–5 years since cessation (28 / 195) 6–9 years since cessation (27 / 183) 10–14 years since cessation (26 / 238) ≥15 years since cessation (39 / 424) Never smoked (32 / 1,556)
Schlecht et al. 1999a Brazil, 1986–1989, hospital-based study in metropolitan areas (cases of oropharyngeal cancer; controls matched for gender, 5-year age groups, quarter of admission, and hospital)	Mouth	Current smokers (214 / 256) Former smokers <5 years since cessation (19 / 54) 6–10 years since cessation (8 / 37) 11–15 years since cessation (2 / 21) >15 years since cessation (6 / 47) Never smoked (21 / 180)
	Pharynx	Current smokers (138 / 184) Former smokers <5 years since cessation (12 / 41) 6–10 years since cessation (2 / 19) 11–15 years since cessation (2 / 12) >15 years since cessation (2 / 23) Never smoked (5 / 82)

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

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

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

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

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

Table 2.8 Continued

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

[§]CI = Confidence interval.

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

Table 2.8 Continued

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

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

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

Esophageal Cancer

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

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

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

Conclusions of Previous Surgeon General's Reports

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

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

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

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

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

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

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

Biologic Basis

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

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

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

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

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

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

Epidemiologic Evidence

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

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

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

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

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

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

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

Evidence Synthesis

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

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

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

Conclusions

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

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

Implications

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

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

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

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

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

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

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

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

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

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

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

Table 2.11 Continued

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

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

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

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

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

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

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

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

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

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

Table 2.14 follows on page 130.

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

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

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

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

Table 2.14 Continued

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

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

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

Study Location/population	Smoking status
Kabat et al. 1993 United States, 1981–1990 Hospital controls matched for age, gender, race, and hospital	Squamous cell carcinoma Never smoked Ever smoked Adenocarcinoma Never smoked Ever smoked
Brown et al. 1994 United States, 1986–1989 Population controls matched for age	Adenocarcinoma <1 pack / day (ever) ≥1 pack / day (ever)
Gao et al. 1994 Shanghai, China, 1990–1993 Population controls matched for age and gender	None Current smokers <10 cigarettes / day 10–19 cigarettes / day ≥20 cigarettes / day
Castellsagué et al. 1999 South America, 1986–1992 Pooled analysis of hospital controls matched for age, gender, and hospital	Men Never smoked Ever smoked Women Never smoked Ever smoked
Zambon et al. 2000 Northern Italy, 1992–1997 Hospital controls	Never smoked Current smokers 1–14 cigarettes / day 15–24 cigarettes / day ≥25 cigarettes / day

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

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

Pancreatic Cancer

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

Conclusions of Previous Surgeon General's Reports

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

Biologic Basis

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

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

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

Epidemiologic Evidence

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

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

Evidence Synthesis

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

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

Conclusion

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

Implications

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

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

Study	Population	Outcome	Tobacco exposure
Heuch et al. 1983	16,713 persons Norway 1964–1978	Diagnosis of pancreatic cancer	• Level of cigarette smoking Never smoked Former smokers Current smokers 1–9 cigarettes / day ≥10 cigarettes / day • Tobacco chewing level Never Former or occasional current use Regular use
Zheng et al. 1993	26,030 white male policy-holders of the Lutheran Brotherhood Insurance Society Followed for 20 years (286,731 person-years) United States (nationwide) 1967–1986	Mortality from pancreatic cancer	• Never / former / current smokers • Tobacco use other than cigarettes
Doll et al. 1994	34,439 British male doctors United Kingdom 1951–1991 (40-year follow-up)	Mortality from pancreatic cancer	• Never / former / current smokers • Cigarettes / day
Shibata et al. 1994	13,979 residents of a retirement community outside of Los Angeles Began in 1981 9-year follow-up	Incident pancreatic cancer	• Cigarettes • Never smoked • Quit smoking ≥20 years ago • Recent quitters (<20 years) or current smokers

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

Findings	Risk estimates (95% CI*)		Comments
• Some increased mortality was associated with tobacco use	Men only Observed / expected number of cases Level of cigarette smoking Never smoked Former smokers and 1–9 cigarettes / day Current smokers of ≥10 cigarettes / day Level of tobacco chewing Never used Former or occasional current use Regular current use Odds ratio ≥10 cigarettes / day vs. never smokers Regular chew users vs. never used	 16 / 18.1 16 / 13.6 6 / 6.3 32 / 36.2 12 / 8.2 12 / 11.6 1.13 1.34	Risk estimates were adjusted for region, urban / rural place of residence, age, and gender; p values and 95% CIs were not provided
• 57 outcome events • Significant dose-response relationship	RR† Never used tobacco Used tobacco other than cigarettes Former cigarette smokers Current cigarette smokers <25 cigarettes / day ≥25 cigarettes / day p value for trend <0.01	 1.0 (referent) 0.8 (0.3–2.5) 1.0 (0.4–2.2) 1.4 (0.6–3.2) 3.9 (1.5–10.3)	RRs were adjusted for age and alcohol index
• ". . .clearly related to smoking." (p. 903)	Annual mortality per 100,000 men Nonsmokers Former smokers Current smokers 1–14 cigarettes / day 15–24 cigarettes / day ≥25 cigarettes / day	 16 23 35 30 29 49	Mortality rates were standardized for age and calendar period; p value was not provided
• 65 outcome events	RR Never smoked Quit ≥20 years ago Quit <20 years ago and current smokers	 1.00 (referent) 1.38 (0.73–2.62) 1.20 (0.65–2.20)	RRs were adjusted for gender and age

Table 2.16 Continued

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

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

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

Table 2.16 Continued

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

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

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

Table 2.16 Continued

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

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

Findings	Risk estimates (95% CI)	Comments
• Risk estimate was not significant	Former smokers RR = 1.1 (0.9–1.3)	RRs were adjusted for age
• Significant risk for both male and female current smokers • Significant dose-response relationship for cigarettes / day (men and women) • Significant dose-response relationship for duration of smoking in men only	RR Men Years since cessation <10 years 1.6 (1.2–2.0) 10–19 years 1.3 (1.0–1.5) ≥20 years 1.0 (0.9–1.2) Current smokers 2.1 (1.9–2.4) <10 cigarettes / day 1.8 (1.4–2.5) 10–19 cigarettes / day 1.7 (1.3–2.2) 20 cigarettes / day 2.1 (1.8–2.6) >20 cigarettes / day 2.4 (2.0–2.8) p value for trend = 0.03 Duration of smoking ≤25 years 1.6 (1.1–2.3) >25–35 years 2.4 (2.0–3.0) >35–45 years 2.1 (1.7–2.5) >45 years 2.0 (1.7–2.5) p value for trend = 0.02 Women Years since cessation <10 years 1.3 (1.0–1.8) 10–19 years 1.7 (1.4–2.0) ≥20 years 0.9 (0.8–1.1) Current smokers 2.0 (1.8–2.3) <10 cigarettes / day 1.2 (0.9–1.6) 10–19 cigarettes / day 1.9 (1.6–2.4) 20 cigarettes / day 2.3 (1.9–2.7) >20 cigarettes / day 2.3 (1.9–2.8) p value for trend = 0.001	Death rates were standardized to the CPS-II population; RRs were adjusted for age; race; years of education; family history of pancreatic cancer in first-degree relative; history of gallstones; history of diabetes; BMI; and consumption of alcohol, total red meat, citrus fruits and juices, and vegetables

Table 2.16 Continued

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

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

Table 2.16 Continued

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

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

Findings	Risk estimates (95% CI)		Comments
	Pack-years among current smokers		
	1–8.5 pack-years	0.2 (0.3–5.4)	
	>8.5 pack-years	2.8 (1.3–6.2)	
	p value for trend = 0.01		
	Cigarettes / day		
	1–9 cigarettes / day	1.6 (0.6–4.6)	
	>9 cigarettes / day	2.7 (1.2–6.1)	
	p value for trend = 0.02		
	Time since cessation		
	Current smokers	1.0 (referent)	
	≤5 years	1.3 (0.4–4.6)	
	>5 years	0.5 (0.2–1.9)	
	Never smoked	0.5 (0.2–1.0)	
	p value for trend = 0.03		
• 327 outcome events • No significant associations	Mortality rate ratios		RRs were adjusted for age, alcohol consumption, and smokeless tobacco use
	Never smoked	1.0 (referent)	
	1–2 cigars / day	0.6 (0.3–1.4)	
	≥3 cigars / day	1.6 (1.0–2.5)	
	Years of cigar smoking		
	<25 years	1.5 (0.7–3.3)	
	≥25 years	1.1 (0.7–1.8)	
NR	Median age at diagnosis of pancreatic cancer		
	Never smoked	50 years old	
	Ever smoked	70 years old	
	p = 0.02		

Table 2.16 Continued

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

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

Table 2.16 Continued

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

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

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

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

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

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

Table 2.17 Continued

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

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

Table 2.17 Continued

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

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

Table 2.17 Continued

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

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

Table 2.17 Continued

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

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

Table 2.17 Continued

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

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

Bladder and Kidney Cancers

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

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

Conclusions of Previous Surgeon General's Reports

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

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

Biologic Basis

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

Epidemiologic Evidence

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

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

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

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

Evidence Synthesis

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

Conclusion

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

Implication

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

Cervical Cancer

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

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

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

Conclusions of Previous Surgeon General's Reports

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

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

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

Biologic Basis

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

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

Epidemiologic Evidence

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

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

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

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

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

Evidence Synthesis

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

Conclusion

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

Implication

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

Ovarian Cancer

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

Conclusions of Previous Surgeon General's Reports

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

Biologic Basis

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

Epidemiologic Evidence

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

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

Evidence Synthesis

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

Conclusion

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

Implication

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

Endometrial Cancer

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

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

Because of the strong dependence of endometrial cancer risk on exposure to estrogens, separating direct and indirect causal pathways for the effect of smoking on ovarian cancer risk has been difficult. Women who smoke are more likely to be lean and to enter menopause earlier than nonsmokers (Willett et al. 1983). They are thus more likely to take estrogen therapy after menopause and to have more years of estrogen exposure (Pike et al. 1998). Separating causal paths involving smoking from those involving hormonal factors has consequently been complicated.

Conclusions of Previous Surgeon General's Reports

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

Biologic Basis

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

Epidemiologic Evidence

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

Evidence Synthesis

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

Conclusion

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

Implication

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

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

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

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

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

Table 2.18 Continued

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

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

Stomach Cancer

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

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

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

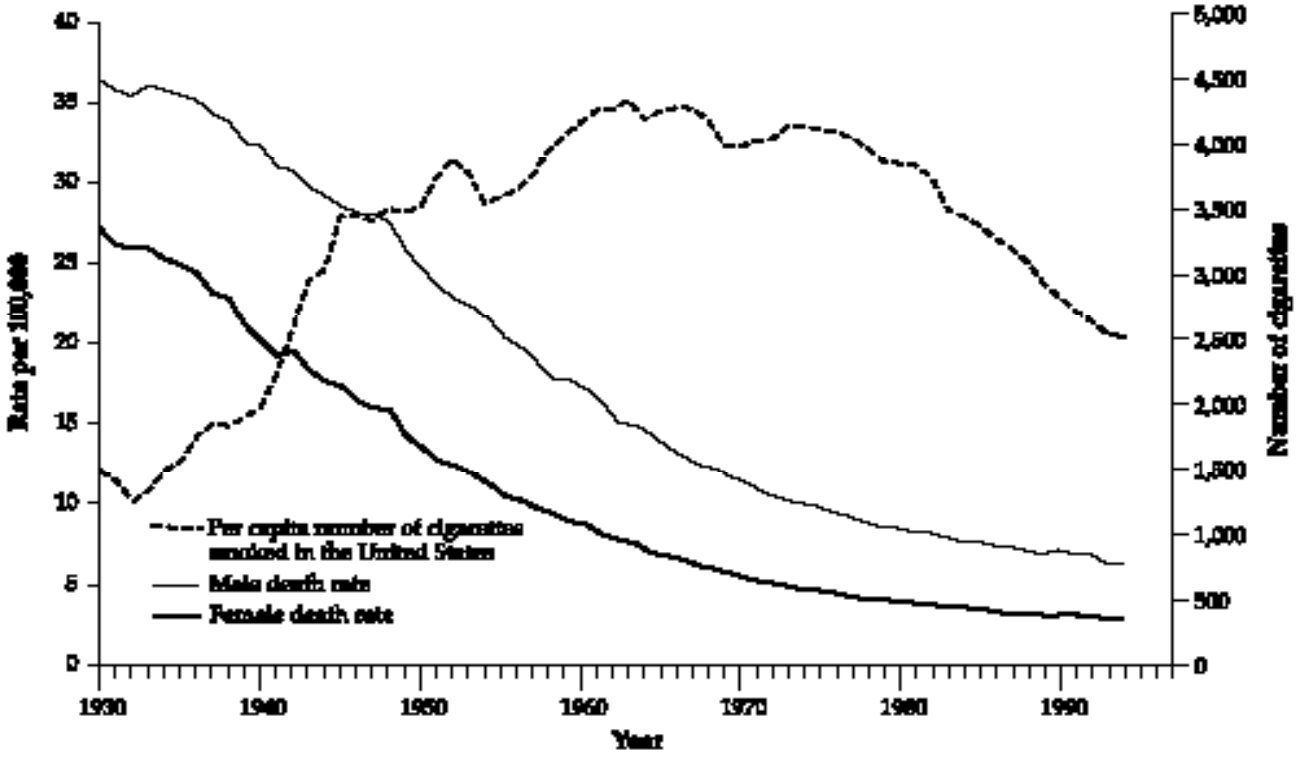
Assessments of the independent contribution of cigarette smoking to the development of stomach cancer are complicated by two factors. First, the background occurrence of stomach cancer decreased globally during much of the twentieth century for reasons unrelated to changes in cigarette smoking. This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

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

Conclusions of Previous Surgeon General's Reports

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

Figure 2.6 Stomach cancer death rates stratified by gender and per capita number of cigarettes smoked in the United States, 1930–1994



Sources: Centers for Disease Control and Prevention, National Center for Health Statistics, U.S. Mortality Volumes 1930–1959, U.S. Mortality public use data tapes 1960–1994; Tobacco Yearbook 1981; Creek et al. 1994; U.S. Department of Agriculture 1996.

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

> No relationship has been established between tobacco use and stomach cancer (USDHEW 1964, p. 229).
>
> No firm relationship between stomach cancer and cigarette smoking has been established (USDHEW 1974, p. 55).
>
> In epidemiological studies, an association between cigarette smoking and stomach cancer has been noted. The association is small in comparison with that noted for smoking and some other cancers (USDHHS 1982, p. 22).

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

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

Biologic Basis

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

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

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

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

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

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

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

H. pylori infections may have differing effects on cancers of the gastric cardia than on noncardia cancers (Fox and Wang 2000). Whereas an *H. pylori* infection is an established risk factor for noncardia stomach cancers, some evidence suggests that *H. pylori* infections actually may be protective against gastric cardia tumors at the gastroesophageal junction (Blaser 1999a,b). Eradication of *H. pylori* results in increased rates of gastroesophageal reflux, a factor contributing to the pathogenesis of Barrett's syndrome and esophageal adenocarcinoma (Labenz et al. 1997; Vicari et al. 1998). Persons who carry particular cagA(+) strains of *H. pylori* experience a marked inflammation of the gastric cardia but have a lower risk of developing adenocarcinoma of either the gastric cardia or the esophagus (Peek et al. 1999; Vaezi et al. 2000).

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

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

Epidemiologic Evidence

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

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

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

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

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

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

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

Evidence Synthesis

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

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

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

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

Conclusions

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

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

Implications

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

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

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

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

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

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

Table 2.19 Continued

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

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

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

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

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

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

Comments
Adjusted for age, area, and hospital; current and former included pipe / cigar smokers; current included former smokers who had quit <5 years before the study
Adjusted for age, income, education, and alcohol intake
Adjusted for age, residence, urban / rural status, and alcohol and vegetable intake
Adjusted for age, education, years lived on farm, and family history of cancer
Adjusted for age; year; season of first hospital visit; family history of gastric cancer; and alcohol, salty food, and fruit intake
Adjusted for age, education, and alcohol consumption
Adjusted for age, income, and education
Adjusted for age, education, years lived on farm, and family history of cancer

Table 2.20 Continued

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

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

Comments
Adjusted for age; year; season of first hospital visit; family history of gastric cancer; and alcohol, salty food, and fruit intake
Adjusted for age, gender, alcohol intake, education, and income
Adjusted for residence; analysis did not control for age, gender, or hospital
Adjusted for age, gender, and hospital
Matched for age, gender, and socioeconomic status; current and former included pipe/cigar smokers; current included former smokers who had quit <5 years before the interview
Adjusted for age, gender, socioeconomic status, and other tobacco use

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

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

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

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

Table 2.21 Continued

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

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

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

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

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

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

Table 2.22 Continued

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

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

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

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

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

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

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

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

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

Comments
Adjusted for age, income, education, and alcohol intake
Adjusted for age, residence, urban / rural status, and alcohol and vegetable intake
Adjusted for age, education, years lived on farm, and family history of cancer
Adjusted for age; excluded prevalent cancer and incomplete data
Adjusted for age, income, education, and alcohol intake
Adjusted for age, education, years lived on farm, and family history of cancer

Table 2.24 Continued

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

Comments
Adjusted for age; excluded prevalent cancer and incomplete data
Adjusted for age, gender, socioeconomic status, and other tobacco use

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

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

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

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

Table 2.25 Continued

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

Colorectal Cancer

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

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

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

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

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

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

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

Conclusions of Previous Surgeon General's Reports

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

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

Biologic Basis

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

Because observational studies consistently show an association between cigarette smoking and adenomatous polyps (IARC 1986; Kikendall et al. 1989; Cope et al. 1991; Monnet et al. 1991; Zahm et al. 1991; Lee et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994b; Peipins and Sandler 1994; Boutron et al. 1995; Martínez et al. 1995; Longnecker et al. 1996; Nagata et al. 1999; Potter et al. 1999; Almendingen et al. 2000; Breuer-Katschinski et al. 2000; Inoue et al. 2000), Giovannucci and others have proposed that cigarette smoking plays a role early in colon and rectum carcinogenesis, likely acting on *APC* genes (Giovannucci et al. 1994a,b; Giovannucci and Martínez 1996). Two large cohort studies found that smoking for two decades or more was associated with large adenomas and that smoking for less than 20 years was associated with small adenomas (Giovannucci et al. 1994a,b). Cigarette smoking for at least three decades also has been associated with an increased risk of colorectal cancer incidence and mortality (Giovannucci et al. 1994a,b; Heineman et al. 1995; Chao et al. 2000). An initiating role of tobacco in the formation of adenomas is further supported by the finding that smokers who quit continue to have an elevated risk of adenoma recurrence after 10 years of smoking cessation (Jacobson et al. 1994). Cigarette smoking has not yet been associated with specific gene mutations or epigenetic changes associated with colorectal cancer.

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

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

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

Animal Models

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

Epidemiologic Evidence

Published studies on cigarette smoking and colorectal adenomatous polyps and cancer cited in this section were identified by searching the MEDLINE database from 1966 through July 2000 using the headings "tobacco," "smoking," "colorectal adenomas," "colorectal neoplasms," "colonic neoplasms," and "rectal neoplasms," and from the reference lists of published original and review articles in English on cigarette smoking and colorectal adenomas and cancer. The association between cigarette smoking and colorectal adenomas and cancer has been evaluated in a number of prospective and case-control studies since the 1960s. This review focuses on published studies that exclude cigar and pipe smokers, specify lifetime nonsmokers, and distinguish current from former smokers. If there are multiple reports from the same prospective cohort, results from the longest follow-up period are reported unless otherwise stated.

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

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

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

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

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

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

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

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

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

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

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

Evidence Synthesis

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

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

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

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

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

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

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

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

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

Conclusion

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

Implications

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

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

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

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Men	
Monnet et al. 1991 Case-control study, France, 1983–1987 (103 men with colorectal adenoma; 108 male hospital controls with normal colonoscopy)	Colorectal adenomas	Never smoked (17 / 33) Current smokers (39 / 43) Former smokers (47 / 32)
Zahm et al. 1991 Cross-sectional study, United States, 1981–1983 (549 white men from the Pattern Makers League of North America at 11 factories, in a flexible sigmoidoscopy screening program)	Adenomatous polyps	Never smoked (7 / 178) Current smokers (12 / 120) Former smokers (12 / 217)
Honjo et al. 1992 Cross-sectional study, Japan, 1989–1990 (115 cases of men with adenomatous polyps of the sigmoid colon, and 930 male controls with a normal colonoscopy)	Adenomatous polyps of the sigmoid colon	Never smoked (13 / 244) Former smokers (33 / 276) Current smokers <25 cigarettes / day (50 / 280) ≥25 cigarettes / day (20 / 130)
Giovannucci et al. 1994b Cohort study, United States, 1986–1992 (Health Professionals Follow-up Study data, 626 new cases of colorectal adenomas, with pack-year information available for 499 cases and 7,968 of the noncases)	Small (<1 cm) and large (≥1 cm) colorectal adenomas	Total pack-years‡ 0 (186 / 4,085) 1–9 (70 / 970) 10–19 (58 / 917) 20–29 (53 / 727) 30–39 (49 / 454) ≥40 (83 / 815)
Nagata et al. 1999 Cohort study with cross-sectional analysis, Japan, 1993–1995 (14,427 men aged ≥35 years, with 181 new cases of colorectal adenoma; smoking information available for 178 of the cases and 12,260 of the noncases)	Colorectal adenomas	Never smoked (23 / 2,036) Current smokers (99 / 6,670) Former smokers (56 / 3,554)

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

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

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Men	
Breuer-Katschinski et al. 2000 Case-control study, Germany, 1993–1995 (94 histologically confirmed colorectal adenomas, 88 hospital controls, and 92 population controls free of adenomas, determined by a colonoscopy)	Colorectal adenomas	Compared with hospital controls Never smoked (NR[§]) Current smokers (NR) Former smokers (NR) Compared with population controls Never smoked (NR) Current smokers (NR) Former smokers (NR)
Inoue et al. 2000 Cross-sectional study, Japan, 1995–1996 (205 histologically confirmed adenomas of the proximal and distal colon, 220 male controls who received a total colonoscopy)	Colorectal adenomas	Never smoked (35/73) Current smokers <25 cigarettes/day (83/51) ≥25 cigarettes/day (46/24) Former smokers (41/72)
	Women	
Giovannucci et al. 1994a Cohort study with cross-sectional analysis, United States, Nurses Health Study (12,143 women who had a first colonoscopy or sigmoidoscopy between 1980 and 1990, with 498 new cases of adenoma)	Small (<1 cm) and large (≥1 cm) adenomas of the left colon and rectum	Total pack-years 0 (164/5,382) 1–9 (52/1,498) 10–19 (55/1,280) 20–29 (46/1,166) 30–39 (56/828) ≥40 (125/1,491)
Nagata et al. 1999 Cohort study with cross-sectional analysis, Japan, 1993–1995 (17,125 women aged ≥35 years with 78 new cases of colorectal adenomas; smoking information was available for 64 cases and 14,105 noncases)	Colorectal adenomas	Never smoked (46/11,679) Ever smoked (18/2,426)

[§]NR = Data were not reported.

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

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Women	
Breuer-Katschinski et al. 2000 Case-control study, Germany, 1993–1995 (88 histologically confirmed colorectal adenomas, 90 hospital controls, and 90 population controls free of adenomas, determined by a colonoscopy)	Colorectal adenomas	Compared with hospital controls Never smoked (NR) Current smokers (NR) Former smokers (NR) Compared with population controls Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Men and women	
Hoff et al. 1987 Cohort study, Norway (159 men and women aged 50–59 years with a 2-year follow-up)	Polyps in the rectum and sigmoid colon	Men Never smoked (2/12) Current smokers (13/42) Former smokers (1/17) Women Never smoked (4/32) Current smokers (2/27) Former smokers (1/6)
Kikendall et al. 1989 Cross-sectional study, United States (Washington, DC; 102 men and postmenopausal women with adenomas at colonoscopy, and 89 colonoscopy-negative controls)	Colonic adenomas	Never smoked (24/31) Current smokers (41/19) Former smokers (33/37) (quit ≥2 years)
Kato et al. 1990b Case-control study, Japan, 1986–1990 (525 colorectal adenomas and 181 cases with multiple adenomas)	Proximal colon (n = 163) Distal colon (n = 351) Rectum (n = 118)	Never smoked (NR) Current smokers (NR) Former smokers (NR) Never smoked (NR) Current smokers (NR) Former smokers (NR) Never smoked (NR) Current smokers (NR) Former smokers (NR)

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

Table 2.26 Continued

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

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

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Men and women	
Longnecker et al. 1996 Case-control study, United States, 1991–1993, southern California HMO-based study of men and women aged 50–74 years undergoing sigmoidoscopy in southern California (488 cases with colorectal adenomatous polyps and 488 controls without polyps, determined by sigmoidoscopy, including white, black, Asian, and Hispanic persons)	Colorectal adenomatous polyps	Never smoked (168/209) Current smokers (97/55) Former smokers (223/224)
Baron et al. 1998 United States, 1984–1988, men and women participating in a multicentered clinical trial of antioxidant vitamins to prevent colorectal adenoma recurrence (260 recurrent adenomas and 449 with no recurrence)	Adenoma recurrence	In right colorectum: Never smoked (NR) Current smokers (NR) Former smokers (NR) In left colorectum: Never smoked (NR) Current smokers (NR) Former smokers (NR)
Terry and Neugut 1998 Case-control study, United States (New York City), 1986–1988, 269 incident cases of colorectal adenoma; 508 hospital controls with normal colonoscopy, with smoking information available for 267 of the cases and 503 of the controls	Colorectal adenomas	Newly diagnosed adenoma Never smoked (97/215) Ever smoked (170/288)

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

Table 2.26 Continued

Study Location/population	Type of adenoma	Smoking status (case/noncase)
	Men and women	
Potter et al. 1999 Case-control study, United States (Minneapolis, Minnesota), 1991–1994, clinic-based study of men and women aged 30–74 years undergoing colonoscopies (527 with adenomatous polyps and 633 controls without polyps, determined by colonoscopy)	Adenomatous polyps	Never smoked (NR) Current smokers (NR) Former smokers (NR)
Almendingen et al. 2000 Case-control study, Norway (87 adenoma cases and 35 hospital and 35 "healthy" controls without polyps [determined by colonoscopy] aged 50–76 years)	Colorectal adenomas	Compared with hospital controls Never smoked (20/15) Current smokers (38/5) Former smokers (29/15) Compared with "healthy" controls Never smoked (20/15) Current smokers (38/7) Former smokers (29/13)

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

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

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

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

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

Table 2.27 Continued

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

[Δ]BMI = Body mass index.

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

Table 2.27 Continued

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

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

Table 2.27 Continued

Study Location/population	Type	Smoking status (deaths or cases)
	Men and women	
Terry et al. 2001 Sweden, 1961–1977 (17,118 same sex twins; 318 cases of colon cancer; 180 cases of rectal cancer)	Colon (Incidence)	Never smoked (196) 1–10 cigarettes / day (42) 11–20 cigarettes / day (15) ≥21 cigarettes / day (2) Former smokers (49)
	Rectal (Incidence)	Never smoked (106) 1–10 cigarettes / day (26) 11–20 cigarettes / day (14) ≥21 cigarettes / day (4) Former smokers (30)

RR	95% CI	Comments
1.0		Adjusted for age, gender, BMI, and physical activity;
1.0	0.7–1.5	excluded those who died prior to assessment and those
1.0	0.6–1.8	with prevalent cancer at baseline; estimates for current
1.7	0.4–7.0	smoking were available only for cigarettes per day; risk
1.1	0.8–1.5	estimates for cigar and pipe smokers were not presented
1.0		
0.9	0.6–1.5	
1.2	0.6–2.4	
5.3	1.9–15.0	
1.0	0.6–1.6	

Table 2.28 Case-control studies on the association between smoking status and the risk of colorectal cancer incidence

Study Location/population	Type	Smoking status (cases/controls)
	Men	
Kune et al. 1992 Australia, 1980–1981 (202 colon cancer cases; 186 rectal cancer cases; 398 population controls)	Colon	Never smoked (60 / 110) Current smokers (46 / 121) Former smokers (96 / 167)
	Rectal	Never smoked (47 / 110) Current smokers (55 / 121) Former smokers (84 / 167)
D'Avanzo et al. 1995 Italy, 1985–1991 (875 colorectal cancer cases; 1,863 hospital controls)	Colorectal	Never smoked (269 / 457) Current smokers (316 / 837) Former smokers (290 / 569)
Le Marchand et al. 1997 United States, 1987–1991, Hawaii (multiethnic: Japanese, Caucasian, Filipino, Hawaiian, Chinese; 197 right colon cancer cases / 197 population controls; 270 left colon cancer cases /270 controls; 221 rectal cancer cases / 221 controls)	Right colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Left colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Rectal	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Women	
Kune et al. 1992 Australia, 1980–1981 (190 colon cancer cases; 137 rectal cancer cases; 329 community controls)	Colon	Never smoked (129 / 197) Current smokers (32 / 65) Former smokers (29 / 67)
	Rectal	Never smoked (91 / 197) Current smokers (26 / 65) Former smokers (20 / 67)
D'Avanzo et al. 1995 Italy, 1985–1991 (709 colorectal cancer cases; 1,016 hospital controls)	Colorectal	Never smoked (558 / 740) Current smokers (101 / 205) Former smokers (50 / 71)

*OR = Odds ratio.
†CI = Confidence interval.
‡NR = Data were not reported.
§Based on a diet rich in cereals and poor in vegetables.
ΔBMI = Body mass index.

OR*	95% CI†	Comments
1.00		Adjusted for age
0.72	NR‡	
1.03	NR	
1.00		
1.03	NR	
1.23	NR	
1.0		Adjusted for age, education, area of residence, family history of intestinal cancer, food consumption score§ and intake of fat, calories, meat, and alcohol
0.6	0.5–0.8	
0.8	0.6–1.0	
1.0		Adjusted for age; family history of colorectal cancer; physical activity; BMI¶; and intake of eggs, fiber, calcium, calories, and alcohol
0.7	0.3–1.6	
1.0	0.5–1.9	
1.0		
0.9	0.4–1.9	
1.4	0.9–2.4	
1.0		
0.8	0.4–1.8	
1.4	0.8–2.3	
1.00		Adjusted for age
0.75	NR	
0.64	NR	
1.00		
0.85	NR	
0.64	NR	
1.0		Adjusted for age, education, area of residence, family history of intestinal cancer, food consumption score and intake of fat, calories, meat, and alcohol
0.7	0.5–0.9	
1.3	0.8–1.9	

Table 2.28 Continued

Study Location/population	Type	Smoking status (cases/controls)
	Women	
Newcomb et al. 1995 United States, 1990–1991 (526 colon cancer cases; 239 rectal cancer cases; 2,303 population controls)	Colon	Never smoked (276 / 1,243) Current smokers (113 / 517) Former smokers (137 / 543)
	Rectal	Never smoked (115 / 1,243) Current smokers (65 / 517) Former smokers (59 / 543)
Le Marchand et al. 1997 United States, 1987–1991, Hawaii (multiethnic: Japanese, Caucasian, Filipino, Hawaiian, Chinese; 164 right colon cancer cases / 164 population controls; 194 left colon cancer cases /194 controls; 129 rectal cancer cases /129 controls)	Right colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Left colon	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Rectal	Never smoked (NR) Current smokers (NR) Former smokers (NR)
	Men and women	
Baron et al. 1994 Stockholm, 1986–1988 (334 colon cancer cases; 210 rectal cancer cases; 496 population controls)	Colon	Never smoked (163 / 233) Current smokers (78 / 125) Former smokers (93 / 138)
	Rectal	Never smoked (101 / 233) Current smokers (51 / 125) Former smokers (58 / 138)
Slattery et al. 1997 United States, 1991–1994, English-speaking members of Kaiser Permanente (1,097 male cases and 892 female cases with first primary colon cancer; 2,410 population controls)	Colon	Men Never smoked (336 / 485) Ever smoked (761 / 805) Women Never smoked (487 / 636) Ever smoked (405 / 484)

OR	95% CI	Comments
1.00		Adjusted for age, BMI, alcohol intake, family history of colon cancer, and sigmoidoscopy; excluded incomplete data
1.33	1.01–1.75	
1.24	0.96–1.59	
1.00		
1.70	1.19–2.41	
1.25	0.88–1.77	
1.0		Adjusted for age; family history of colorectal cancer; physical activity; BMI; and intake of alcohol, eggs, fiber, calcium, and calories
1.1	0.4–2.6	
2.4	1.0–5.6	
1.0		
0.7	0.3–1.5	
1.1	0.6–2.0	
1.0		
1.3	0.5–3.7	
1.6	0.7–3.4	
1.00		Adjusted for age, gender, exercise, BMI, and fat and fiber intake; excluded incomplete data
0.91	0.63–1.31	
0.94	0.66–1.34	
1.00		
0.84	0.55–1.28	
0.88	0.58–1.32	
1.0		Estimates were adjusted for age, BMI, long-term vigorous activity, energy intake, dietary fiber, dietary calcium, family history of colorectal cancer, and use of aspirin and/or nonsteroidal anti-inflammatory drugs
1.26	1.05–1.51	
1.0		
1.08	0.90–1.30	

Table 2.29 Cohort studies on the association between the duration of current smoking and the risk of colorectal cancer incidence or mortality*

Study Location/population	Type	Duration (deaths or cases)
	Men	
Giovannucci et al. 1994b United States, Health Professionals Follow-up Study data (47,935 men; 238 colorectal cancer cases)	Colorectal (Incidence)	Never smoked (84) 1–10 cigarettes / day 1–19 years (0) 20–29 years (9) 30–34 years (8) 35–39 years (14) 40–44 years (26) ≥45 years (43) ≥11 cigarettes / day 1–19 years (3) 20–29 years (5) 30–34 years (3) 35–39 years (10) 40–44 years (13) ≥45 years (20)
Nyrén et al. 1996 Swedish construction workers (134,985 men; 713 colon cancer cases; 505 rectal cancer cases)	Colon (Incidence)	Never smoked (219) 1–10 years (15) 11–20 years (34) 21–30 years (88) 31–40 years (119) ≥41 years (53)
	Rectal (Incidence)	Never smoked (135) 1–10 years (7) 11–20 years (26) 21–30 years (69) 31–40 years (94) ≥41 years (34)
Hsing et al. 1998 United States, Lutheran Brotherhood Insurance (17,633 men; 120 colorectal cancer cases)	Colon (Mortality)	Never smoked (16) 1–19 years (1) 20–29 years (11) ≥30 years (17)

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

RR[†]	95% CI[‡]	Comments
1.00		Adjusted for age; BMI[Δ]; intake of alcohol, fat, fiber, and folate; and family history of colorectal cancer; excluded prevalent cancer, ulcerative colitis, familial polyposis syndrome, and incomplete data
NR[§]	NR	
1.26	0.60–2.63	
1.28	0.60–2.74	
1.18	0.66–2.13	
1.83	1.15–2.92	
1.60	1.06–2.04	
1.87	0.55–6.31	
0.83	0.32–2.17	
0.77	0.23–2.57	
1.15	0.58–2.31	
1.74	0.92–3.28	
2.55	1.49–4.38	
1.00		Adjusted for age; excluded prevalent colon cancer and incomplete vital status data
0.75	0.43–1.30	
0.74	0.51–1.08	
1.03	0.80–1.33	
1.05	0.83–1.33	
0.99	0.72–1.35	
1.00		
0.76	0.35–1.66	
1.01	0.66–1.55	
1.17	0.87–1.57	
1.26	0.96–1.66	
1.08	0.73–1.60	
1.0		Adjusted for age, alcohol use, and area of residence (urban / rural)
1.3	0.2–9.7	
2.4	1.0–5.3	
1.2	0.6–2.4	
	p value for trend = 0.79	

Table 2.29 Continued

Study Location/population	Type	Duration (deaths or cases)
	Men	
Chao et al. 2000 United States, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)	Colorectal (Mortality)	Never smoked (683) <20 years (12) 20–29 years (46) 30–39 years (177) ≥40 years (323)
	Women	
Giovannucci et al. 1994a United States, Nurses Health Study (118,334 women; 586 colorectal cancer cases)	Colorectal (Incidence)	Never smoked (263) 1–10 cigarettes / day 1–19 years (10) 20–29 years (41) 30–34 years (33) 35–39 years (37) 40–44 years (34) ≥45 years (11) ≥11 cigarettes / day 1–19 years (2) 20–29 years (32) 30–34 years (26) 35–39 years (49) 40–44 years (33) ≥45 years (15)
Chao et al. 2000 United States, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer cases)	Colorectal (Mortality)	Never smoked (1,355) <20 years (28) 20–29 years (81) 30–39 years (163) ≥40 years (204)

RR	95% CI	Comments
1.00		Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.24	0.68–2.24	
1.33	0.96–1.84	
1.34	1.11–1.62	
1.31	1.13–1.51	
	p value for trend = 0.17	
1.00		Excluded prevalent cancer, ulcerative colitis, familial polyposis syndrome, and incomplete data; adjusted for age and BMI
0.79	0.40–1.40	
0.98	0.69–1.40	
0.76	0.52–1.10	
0.81	0.57–1.16	
1.03	0.70–1.50	
1.05	0.56–1.99	
0.37	0.11–1.32	
1.06	0.71–1.57	
0.82	0.54–1.24	
1.47	1.07–2.01	
1.63	1.14–2.33	
2.00	1.14–3.49	
1.00		
1.07	0.73–1.58	Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin, multivitamin, and estrogen replacement therapy use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer and incomplete data
1.33	1.05–1.69	
1.41	1.19–1.68	
1.51	1.29–1.76	
	p value for trend = 0.17	

Table 2.30 Cohort studies on the association between the age at initiation of current smoking and the risk of colorectal cancer mortality*

Study Location/population	Type	Smoking initiation (deaths)
	Men	
Heineman et al. 1995 United States, U.S. veterans (248,046 men; 3,812 colon cancer deaths; 1,100 rectal cancer deaths)	Colon	Never smoked (782) Started at ≥25 years (219) 20–24 years (382) 15–19 years (503) <15 years (99)
	Rectal	Never smoked (201) Started at ≥25 years (61) 20–24 years (108) 15–19 years (183) <15 years (30)
Chao et al. 2000 United States, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)	Colorectal	Never smoked (683) Started at ≥20 years (143) 16–19 years (258) <16 years (146)
	Women	
Chao et al. 2000 United States, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer deaths)	Colorectal	Never smoked (1,355) Started at ≥20 years (225) 16–19 years (193) <16 years (54)

*Includes only studies that specified lifetime nonsmokers and distinguished current from former smoking.
†RR = Relative risk.
‡CI = Confidence interval.
§BMI = Body mass index.

RR[†]	95% CI[‡]	Comments
1.0		Adjusted for age, year of questionnaire, calendar time, socioeconomic status, and having a sedentary job
1.1	1.0–1.3	
1.3	1.1–1.5	
1.2	1.1–1.4	
1.4	1.2–1.8	
	p value for trend <0.001	
1.0		
1.2	0.9–1.6	
1.4	1.1–1.7	
1.6	1.3–1.9	
1.5	1.0–2.2	
	p value for trend = 0.006	
1.00		Adjusted for age; race; BMI[§]; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.21	1.01–1.47	
1.36	1.16–1.58	
1.36	1.12–1.64	
	p value for trend = 0.55	
1.00		Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; estrogen replacement therapy; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.36	1.18–1.57	
1.43	1.21–1.67	
1.74	1.31–2.29	
	p value for trend = 0.013	

Table 2.31 Cohort studies on the association between the number of years since or age at smoking cessation and the risk of colorectal cancer incidence or mortality*

Study Location/population	Type	Years since/age at cessation (deaths or cases)
	Men	
Wu et al. 1987 United States, 1981–1985 (11,644 retired men and women; 58 male colorectal cancer cases)	Colorectal (Incidence)	Current smokers (NR§) Years since cessation ≤20 years (NR) >20 years (NR) Never smoked (NR)
Chao et al. 2000 United States, 1982–1996, Cancer Prevention Study II (312,332 men; 2,156 colorectal cancer deaths)	Colorectal (Mortality)	Current smokers (558) Years since cessation <11 (317) 11–19 (293) ≥20 (304) Never smoked (683) Current smokers (558) Age at cessation ≥61 years (104) 51–60 years (235) 41–50 years (280) 31–40 years (205) <31 years (91) Never smoked (683)
	Women	
Wu et al. 1987 United States, 1981–1985 (11,644 retired men and women; 68 female colorectal cancer cases)	Colorectal (Incidence)	Current smokers (NR) Years since cessation ≤20 (NR) >20 (NR) Never smoked (NR)

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

RR[†]	95% CI[‡]	Comments
1.80	0.6–5.2	Adjusted for age; excluded those with pre-existing colorectal cancer
2.63	1.3–5.3	
1.71	0.8–3.6	
1.00		
1.32	1.16–1.49	Adjusted for age; race; BMI[Δ]; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer and incomplete data
1.28	1.11–1.47	
1.24	1.08–1.43	
0.99	0.86–1.13	
1.00		
	p value for trend = 0.001	
1.32	1.16–1.49	
1.21	0.98–1.50	
1.29	1.11–1.51	
1.19	1.03–1.37	
1.08	0.92–1.26	
0.91	0.73–1.13	
1.00		
	p value for trend = 0.001	
1.35	0.7–1.0	Adjusted for age; excluded those with pre-existing colorectal cancer
0.71	0.3–1.5	
1.61	0.8–3.0	
1.00		

Table 2.31 Continued

Study Location/population	Type	Years since/age at cessation (deaths or cases)
	Women	
Chao et al. 2000 United States, 1982–1996, Cancer Prevention Study II (469,019 women; 2,276 colorectal cancer deaths)	Colorectal (Mortality)	Current smokers (476) Years since cessation <11 (317) 11–19 (293) ≥20 (304) Never smoked (1,355) Current smokers (476) Age at cessation ≥61 years (67) 51–60 years (122) 41–50 years (93) 31–40 years (93) <31 years (70) Never smoked (1,355)

RR	95% CI	Comments
1.41	1.26–1.58	Adjusted for age; race; BMI; education; family history of colorectal cancer; exercise; aspirin and multivitamin use; estrogen replacement therapy; and intake of alcohol, vegetables, high-fiber grain foods, and fatty meats; excluded prevalent cancer, pipe/cigar smoking, and incomplete data
1.39	1.18–1.63	
1.10	0.90–1.33	
1.16	0.98–1.37	
1.00		
	p value for trend = 0.038	
1.41	1.26–1.58	
1.50	1.16–1.93	
1.54	1.28–1.87	
1.03	0.83–1.27	
1.15	0.93–1.43	
0.98	0.77–1.25	
1.00		
	p value for trend = 0.038	

Prostate Cancer

Prostate cancer is a leading cause of morbidity and mortality among men in the United States. It is more common in African American men than in white men, and the highest recorded rates in the world are among black men in the United States. In 2003, an estimated 220,900 new cases of prostate cancer were diagnosed, and an estimated 28,900 deaths were expected to occur (ACS 2003). Prostate cancer is the leading cause of cancer incidence among men (ACS 2003).

The risk of prostate cancer increases with age. African American men are at an increased risk, whereas Asian men are at a lower risk than white men. Lower vitamin A consumption and higher animal fat intake may increase the risk (Gann et al. 1994; Le Marchand et al. 1994), while a higher intake of lycopene may decrease the risk (Giovannucci et al. 1995; Giovannucci 1999). Having a vasectomy may be associated with an increased risk of prostate cancer 20 or more years after the procedure (Ross and Schottenfeld 1996). Endocrine factors, including testosterone and insulin-like growth factors, have been implicated in the development of this malignancy (Ross and Schottenfeld 1996; Giovannucci et al. 1997; Chan et al. 1998). Variations in the length of the androgen receptor gene *CAG repeat* may explain part of the excess risk in African American men (Platz et al. 2000).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not addressed the relationship between smoking and prostate cancer.

Biologic Basis

During the last several decades there has been an explosion of epidemiologic studies addressing potential risk factors for this common malignancy, including cigarette smoking. Pathogenic mechanisms that may underlie the relationship between smoking and prostate cancer remain unclear. Carcinogens from tobacco can enter and concentrate in prostate cells (Smith and Hagopian 1981). Compared with men who do not smoke, men who smoke cigarettes have higher circulating levels of hormones formed in the adrenal gland (dehydroepiandrosterone, dehydroepiandrosterone sulfate, cortisol, and androstenedione) as well as testosterone, dihydrotestosterone, and sex hormone-binding globulin (Dai et al. 1988; Khaw et al. 1988; Field et al. 1994). This finding supports a potential mechanism for smoking because prospective epidemiologic studies have shown that testosterone is directly related to prostate cancer incidence and mortality (Nomura et al. 1988; Hsing and Comstock 1993; Gann et al. 1996).

Epidemiologic Evidence

The epidemiologic evidence relating smoking to the risk of prostate cancer has been mixed. Studies addressing disease incidence (which include case-control studies and several cohort studies) show an inconsistent increase in risk (Mishina et al. 1985; Honda et al. 1988; Hayes et al. 1994; van der Gulden et al. 1994), or no association between cigarette smoking and prostate cancer (Weir and Dunn 1970; Ross et al. 1987; Fincham et al. 1990; Talamini et al. 1992). Studies of mortality, largely limited to prospective cohort studies, show an increase in risk directly related to the number of cigarettes smoked. Investigators using different approaches to data analysis have attempted to determine whether this finding reflects a delayed diagnosis and treatment of smokers compared with nonsmokers, residual confounding factors, or a direct effect of tobacco smoke. Two studies found that smokers are more likely than nonsmokers to have their cancers diagnosed at a more advanced stage or histologic grade (Hussain et al. 1992; Daniell 1995).

Hsing and colleagues (1991) analyzed data from the follow-up of nearly 250,000 U.S. veterans and observed increased mortality rates for those who were current smokers at baseline. During 26 years of follow-up, approximately 4,600 men died of prostate cancer. Current smokers had a RR of 1.18 (95 percent CI, 1.09–1.28) compared with men who had never smoked, and the risk increased with the number of cigarettes smoked. Men smoking 40 or more cigarettes per day had a RR of 1.51 (95 percent CI, 1.20–1.90) compared with those who had never smoked. In this cohort, risks were higher during the first eight and one-half years of follow-up than during the remainder of the follow-up period, suggesting that recent smoking influenced the risk of prostate cancer mortality.

In an analysis of data from a follow-up of 348,874 men screened for the Multiple Risk Factor Intervention Trial, Coughlin and colleagues (1996) observed similar results. Compared with those who had never smoked, current smokers had a RR of 1.31 (95 percent CI, 1.13–1.52) for prostate cancer mortality. The risk increased with the number of cigarettes smoked; men smoking more than 25 cigarettes per day had a RR of 1.45 (95 percent CI, 1.19–1.97) compared with those who had never smoked.

The Lutheran Brotherhood Cohort Study also provides data on the association between smoking and prostate cancer. Hsing and colleagues (1990b) followed 17,633 white males for 20 years and documented 149 fatal cases of prostate cancer. The RR of prostate cancer mortality was significantly elevated for current smokers. Compared with men who had never smoked, smokers had a RR of 1.8 (95 percent CI, 1.1–2.9). Data from CPS-II were based on 1,748 deaths during nine years of follow-up of 450,279 men (Rodriguez et al. 1997). Current cigarette smoking was related to prostate cancer mortality in this cohort (RR = 1.34 [95 percent CI, 1.16–1.56]), but trends in risk were not observed with the number of cigarettes smoked per day or with the duration of smoking. Among 43,432 men in a prepaid health plan in northern California, Hiatt and colleagues (1994) observed similar results based on 238 deaths from prostate cancer. Men who smoked one or more packs of cigarettes per day had an adjusted RR that was 1.9 (95 percent CI, 1.2–3.1) compared with those who had never smoked.

The Health Professionals Follow-Up Study examined both incidence and mortality in an analysis of the association between smoking and prostate cancer, offering the possibility of considering issues related to etiology, delay in diagnosis, and mortality (Giovannucci et al. 1999). Lifetime cumulative smoking was unrelated to total prostate cancer incidence. However, men who had quit in the past 10 years were at an increased risk of diagnosis with distant metastatic prostate cancer (RR = 1.56 [95 percent CI, 0.98–2.48]) and fatal prostate cancer (RR = 1.73 [95 percent CI, 1.00–3.01]). Men who currently smoked cigarettes had an elevated risk of prostate cancer mortality; however, this risk was not statistically significant (RR = 1.58 [95 percent CI, 0.81–3.10]). Examining pack-years of cigarettes smoked in the preceding 10 years revealed a significant dose-response relationship with metastatic and fatal prostate cancer (p trend = 0.02). Men who smoked 15 or more pack-years in the preceding 10 years were at a higher risk of distant metastatic prostate cancer (RR = 1.81 [95 percent CI, 1.05–3.11]), and fatal prostate cancer (RR = 2.06 [95 percent CI, 1.08–3.90]) compared with nonsmokers. Within 10 years after smoking cessation, the excess risk was eliminated. In this cohort, the investigators also examined the relationship between smoking and survival after diagnosis. Men who smoked cigarettes had a lower survival rate than nonsmokers.

Several cohort studies do not show a significant increase in risk among cigarette smokers (Table 2.32). The British physicians cohort study found no clear association between smoking and prostate cancer mortality in 1951, 1957, 1966, 1972, 1978, and 1990. The heaviest smokers (smoking ≥25 cigarettes per day) had a RR of 1.24 for fatal prostate cancer compared with men who had never smoked (Doll et al. 1994). A similar association was observed among men followed for 20 years in Sweden (Adami et al. 1996). Current smokers had a RR for prostate cancer mortality of 1.26 (95 percent CI, 1.06–1.50) compared with men who had never smoked. Other studies with a single assessment of smoking status and follow-up periods of up to several decades did not show a clear association between smoking and prostate cancer (Whittemore et al. 1985; Carstensen et al. 1987; Severson et al. 1989).

Other Data

Differential screening and delay in seeking medical care have been hypothesized as possible explanations for the increased risk of prostate cancer mortality among cigarette smokers. In the study by Giovannucci and colleagues (1999), however, screenings for the prostate-specific antigen (PSA) did not differ substantially between groups. Among men younger than 65 years of age, 53 percent of those who had never smoked, 53 percent of the smokers who had quit in the past 10 years, and 50 percent of the current smokers had had at least one PSA test by 1994. For men 65 years of age or older the screening rates were higher: 79 percent of men who had never smoked, 78 percent of those who had quit in the past 10 years, and 70 percent of current smokers.

Smoking may relate to prostate cancer mortality through its impact on tumor characteristics. Two studies have suggested that smokers are more likely to have stage D tumors and to have poorly differentiated tumors (Hussain et al. 1992; Daniell 1995).

Evidence Synthesis

The suggestion of elevated risks for mortality and not for incidence (measured either in case-control studies or in prospective cohort studies) supports an association between smoking and prostate cancer mortality. The association between smoking and prostate cancer mortality rates appears to be reduced within 10 years of smoking cessation. The basis for this association is unclear. It might reflect more advanced disease in smokers, but evidence is limited.

If smoking contributed to the etiology of prostate cancer, an association of smoking with incidence would be anticipated, along with an increase in disease-specific mortality, assuming that cancers in smokers and nonsmokers are similar in clinical features.

Conclusions

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

2. The evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers.

Implications

Smoking cessation may reduce prostate cancer mortality. Further research is needed to refine this temporal relationship and to quantify the benefits of smoking cessation after diagnosis with prostate cancer.

Acute Leukemia

In 2003, an estimated 21,900 deaths attributable to leukemia and an estimated 30,600 new cases, evenly divided between acute and chronic leukemia, were expected to occur, affecting 10 times more adults than children (ACS 2003). In adults, the most common types of leukemia are acute myeloid (approximately 10,500 cases were diagnosed in 2003) and chronic lymphocytic (approximately 7,300 cases were diagnosed in 2003). Rates of acute myeloid leukemia among adults are higher in males than in females. In children, the most common type of leukemia is acute lymphocytic, accounting for 2,200 cases in 2003 (ACS 2003).

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted that smoking has been implicated in the etiology of leukemia but the evidence was not consistent, and a conclusion was not reached regarding a possible causal relationship. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that acute myeloid leukemia has been consistently associated with cigarette smoking.

Biologic Basis

Several known leukemogenic substances are contained in cigarette smoke, including benzene and polonium-210 and lead-210 (which emit ionizing radiation). Both benzene and ionizing radiation (NRC 1990) are known causes of human leukemia that are associated with myeloid forms of leukemia and have little, if any, effect on the incidence of chronic lymphocytic leukemia. Radiation also causes acute lymphocytic leukemia in children (NRC 1990). Benzene, classified as a human carcinogen by IARC (1986), induces leukemia both in humans through occupational exposures and in laboratory animal models of this disease. Cigarette smoke is a major source of benzene exposure in the United States, accounting for roughly half of the exposures (Wallace 1996). Among smokers, 90 percent of benzene exposures come from smoking (Wallace 1996).

Data from human and experimental animal studies support the relationship between smoking and leukemia. Known leukemogens have been identified in cigarette smoke, and specific chromosomal abnormalities have been reported among smokers with leukemia. Sandler and colleagues (1993a) reported a higher frequency of smoking in persons with acute myeloid leukemia with specific chromosomal abnormalities (-7 or 7q-, -Y, +13) than in similar patients without these abnormalities. In acute lymphoblastic leukemia the changes found in chromosomes were t(9;22) and (q34;q11).

Epidemiologic Evidence

A possible association between smoking and risk for leukemia was proposed by Austin and Cole (1986), who recommended further analyses of existing data to clarify the relationship between the amount smoked and specific forms of leukemia. Since then, numerous such analyses and new studies have been reported. By 1993, Siegel had systematically reviewed the literature, which included 21 published studies (including several reports from the follow-up of the same population), and concluded, after applying Hill's causal criteria, that smoking was a cause of leukemia (Siegel 1993). Also in 1993, Brownson and colleagues reported a meta-analysis of published studies. They noted a significant association between current or former smoking and leukemia in general, and a stronger association between smoking and myeloid leukemia than with other subtypes (Brownson et al. 1993). Additional studies with similar findings have been published subsequently.

Both case-control and prospective cohort studies support the relationship between cigarette smoking and acute leukemia risk (Tables 2.33 and 2.34). The case-control approach affords the opportunity to quickly develop a series of cases for investigation and to uniformly classify the cases as to the type of leukemia. The results of case-control studies may be subject to information bias, arising from differential reporting of exposure by cases and controls. The prospective cohort studies do not have this limitation, but those using cause-specific mortality as the outcome measure may be affected by misclassification. In spite of these methodologic limitations, the evidence indicates an increased risk for leukemias in smokers. When risk estimates were provided by type, they tended to be higher for acute myeloid leukemia, usually called acute granulocytic leukemia or acute nonlymphocytic leukemia. A recent, large case-control study that included 807 persons with acute leukemia and 1,593 age- and gender-matched controls showed that the risk was highest among current smokers, and it decreased with years since smoking cessation (Kane et al. 1999).

The association appears stronger among the prospective cohort studies, although not all have shown a positive relationship (Table 2.34). The 20-year follow-up of the British physicians cohort study did not find an association (Doll and Peto 1978); however, with the 40-year follow-up, Doll and colleagues (1994) reported a significant dose-response association among cigarette smokers for myeloid leukemias but not for nonmyeloid leukemias. Men smoking 25 or more cigarettes per day had more than twice the age-standardized mortality rates of those who had never smoked.

In CPS-I, women who smoked had a lower risk of death from leukemia during the follow-up period than those who did not smoke (RR = 0.77) (Garfinkel and Boffetta 1990). A similar gender variation was reported by Friedman (1993) in the follow-up of participants enrolled in the Kaiser Permanente Medical Center multiphasic health check-up study. Among men, the RR of leukemia for current smokers was 2.8 (95 percent CI, 1.2–6.4); the RR for former female smokers compared with women who had never smoked was 0.9 (95 percent CI, 0.4–1.7). By contrast, CPS-II documented a significant positive association between former smoking and leukemia risks in women (RR = 1.34, $p < 0.05$), and a significant dose-response relationship with the amount smoked in both women and men (Garfinkel and Boffetta 1990). These results were based on 327 deaths attributable to leukemia among men and 235 deaths among women.

McLaughlin and colleagues (1989) evaluated smoking and the 26-year risk of mortality from leukemia (based on 1,258 leukemia deaths) among the cohort of U.S. military service veterans for whom there were numerous follow-up reports (Hammond 1966; Kahn 1966; Rogot and Murray 1980; Kinlen and Rogot 1988). In the 26-year follow-up data, these authors found a significant relationship between smoking and all leukemias (with a dose-response association between the number of cigarettes smoked per day and the risk of leukemia). The strongest relationship was for myeloid leukemia (365 cases). The RR for current smokers of more than 20 cigarettes per day compared with persons who had never smoked was 1.95 ($p < 0.01$). In this cohort study, which did not update smoking status after the baseline assessment, risk was

stronger for the first 16 years of follow-up (RR = 1.6 [95 percent CI, 1.3–1.9]) than in the later 10 years (years 15 to 26 of the follow-up) (RR = 1.1 [95 percent CI, 0.9–1.3]) (McLaughlin et al. 1995a). In these data, the overall risk increased with the number of cigarettes smoked per day.

Cohort studies by Linet and colleagues (1991) and by Mills and colleagues (1990) also found a positive dose-response relationship between the number of cigarettes smoked and risk of leukemia. In the Lutheran Brotherhood Cohort Study, Linet and colleagues (1991) reported 74 deaths from leukemia (30 myeloid, 30 lymphatic, and 14 unspecified leukemia cases) among 17,633 white males followed for 20 years. The risk of total leukemia increased with the number of cigarettes smoked per day. Mills and colleagues (1990) followed 34,000 Seventh-Day Adventists for six years and identified 46 histologically-confirmed cases of leukemia. The group that had smoked the highest number of cigarettes in their lifetime had the highest risk of leukemia. These two cohorts were considerably smaller than the U.S. veterans and ACS studies. Other studies supporting a positive dose-response relationship include some of the case-control studies.

Among the prospective studies, the 20-year follow-up of a cohort of construction workers in Sweden shows no relationship between smoking and leukemia (Adami et al. 1998). In this study, 400 cases of leukemia (including 171 myeloid leukemias) were diagnosed during follow-up. Current smokers had a RR for total leukemia of 1.0 (95 percent CI, 0.8–1.2) compared with workers who had never smoked. Similar null results were also observed for myeloid leukemia (RR = 1.0 [95 percent CI, 0.7–1.4]), and there was no evidence of a trend in risks with the number of cigarettes smoked per day.

Evidence Synthesis

A relationship between former or current smoking and the risk of acute myeloid leukemia is supported by evidence of a consistent dose-response relationship with the number of cigarettes smoked per day. The association of the duration of smoking with the degree of risk and an increase in risk among former smokers suggests that the relationship is not dependent on current smoking, but perhaps on the cumulative effects of cigarette smoking. This relationship is observed across diverse populations. The RR for persons who had ever smoked compared with nonsmokers ranged from 1.3 to 1.5. Among those who smoked more than a pack of cigarettes per day the risk increased twofold. In 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and myeloid leukemia (IARC 2002).

Data from human and experimental animal studies provide evidence of a relationship between smoking and leukemia. Known leukemogens have been identified in cigarette smoke, and specific genetic alterations have been reported in smokers with leukemia. Benzene, a known leukemogen (Heath 1990), is found in cigarettes, and is the strongest known chemical leukemogen (Linet and Cartwright 1996). Polonium-210 and lead-210, alpha particle emitters in cigarette smoke, can reach the bone marrow where stem cells are located (Austin and Cole 1986; NRC 1988).

Korte and colleagues (2000) used risk assessment techniques for low-dose extrapolation to assess the proportion of leukemia and acute myeloid leukemia cases that could be attributed to the benzene in cigarettes. On the basis of linear potency models, these authors concluded that benzene in cigarette smoke contributed between 8 and 48 percent of smoking-induced leukemia deaths in total, and from 12 to 58 percent of smoking-induced acute myeloid leukemia deaths.

Conclusions

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

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

Implications

The incidence of leukemia may remain elevated even after smoking cessation. Evidence is limited on the temporal pattern of change in risk after cessation, but a rapid decline in incidence has not been observed. Further research is needed to refine the patterns of risk after smoking cessation.

Table 2.32 Cohort studies on the association between smoking status and behavior and the risk of prostate cancer incidence or mortality

Study	Population/ country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI†)		Number of cases
Whittemore et al. 1985	47,271 men Harvard / Penn alumni United States	1962–1966, 1978	243	NR‡	NR	NR
Carstensen et al. 1987	25,129 men Sweden	1963–1979	194	Former smokers	1.0	44
				Current smokers		
				1–7 g / day	1.1	26
				8–15 g / day	0.8	31
				>15 g / day	0.9	15
Mills et al. 1989a	±14,000 men Seventh-Day Adventists United States	1977–1982	172	Former smokers	1.24 (0.91–1.67)	79
				Current smokers	0.48 (0.16–1.57)	3
Severson et al. 1989	8,006 men Japanese Hawaii	1965–1968, 1986	174	Cigarette smokers		
				Former	0.89 (0.61–1.29)	46
				Current	0.87 (0.61–1.23)	65
Thompson et al. 1989	1,776 men Retirement community United States	1972–1974, 1987	54	Current cigarette smokers	1.3 (0.8–2.3)	NR
Ross et al. 1990	5,106 men Retirement community United States	1981–1988	138	Cigarette smokers		
				Former	0.8	73
				Current	0.9	9

*Includes subsequent follow-up if applicable.
†CI = Confidence interval.
‡NR = Data were not reported.

Table 2.32 Continued

Study	Population/ country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI)		Number of cases
Doll et al. 1994	34,439 male physicians United Kingdom	1951, 1957, 1966, 1972, 1978, 1990	568		annual mortality	
				Never smokers	68	NR
				Cigarette smokers		
				Former	58	NR
				Current	67	NR
				1–14 cigarettes / day	54	NR
				15–24 cigarettes / day	73	NR
				≥25 cigarettes / day	84	NR
				Other smokers		
				Former	54	NR
				Current	64	NR
Hiatt et al. 1994	43,432 men Prepaid health plan United States	1978–1985	224	Former smokers	1.1 (0.8–1.5)	94
				Current smokers		
				<20 cigarettes / day	1.0 (0.6–1.6)	24
				≥20 cigarettes / day	1.9 (1.2–3.1)	25
Le Marchand et al. 1994	8,881 men Random sample Aged ≥45 years Hawaii	1975–1980, 1989	198	Cigarette smokers		
				Low quartile	1.0	NR
				Intermediate quartile (i)	0.9 (0.6–1.4)	NR
				Intermediate quartile (ii)	1.0 (0.7–1.6)	NR
				High quartile	1.0 (0.6–1.6)	NR
Thune and Lund 1994	1,776 men Retirement community United States	1974–1978, 1991	211	Per 10 cigarettes / day	1.08 (0.90–1.30)	NR
Adami et al. 1996	135,006 male construction workers Sweden	1971–1975, 1991	2,368	Former smokers	1.09 (0.96–1.22)	617
				Current smokers	1.11 (1.01–1.23)	1,069
				Cigarettes / day		
				0	1.00	1,348
				1–4	1.06 (0.93–1.20)	282
				5–14	1.10 (0.99–1.22)	459
				15–24	1.14 (0.99–1.31)	239
				≥25	1.00 (0.72–1.38)	38
Engeland et al. 1996	11,863 men Norway	1966–1993	703	Former smokers	0.9 (0.7–1.1)	117
				Current smokers	1.1 (0.9–1.37)	451

*Includes subsequent follow-up if applicable.

Table 2.32 Continued

Study	Population/ country	Period of observation*	Number of prostate cancers	Risk related to nonsmokers (95% CI)		Number of cases
Grönberg et al. 1996	9,680 men Twin register members Sweden	1967, 1970–1989	406	Former smokers Current smokers Tobacco as cigarettes / day (including former smoking) 0 1–9 10–19 ≥20	0.91 (0.68–1.21) 1.00 (0.71–1.39) 1.00 (NR) 1.06 (0.77–1.48) 0.96 (0.65–1.39) 0.72 (0.42–1.15)	92 157 117 112 86 33
Cerhan et al. 1997	1,050 men Rural United States	1982–1993	71	Former smokers Current smokers <20 cigarettes / day ≥20 cigarettes / day	1.2 (0.7–2.1) 1.8 (0.7–2.4) 2.7 (1.2–6.0)	30 6 9
Hakulinen et al. 1997	4,601 men Finland	1962–1993	209	Former smokers Current smokers	0.85 (NR) 1.01 (NR)	48 99
	11,373 men Finland	1972, 1977–1993	109	Former smokers Current smokers	1.26 (NR) 0.96 (NR)	56 36
Tulinius et al. 1997	11,366 men Iceland	1968–1995	524	Compared with never smokers, differences for all smoking categories = p ≥0.1		NR
Veierod et al. 1997	24,051 men Norway	1977–1983, 1992	69	Former smokers Current smokers <10 cigarettes / day ≥10 cigarettes / day	0.6 (0.3–1.1) 0.5 (0.3–1.1) 0.6 (0.3–1.2)	20 11 14
Giovannucci et al. 1999	47,781 men Health professionals United States	1986–1994	1,369	Former smokers <10 years ≥10 years Current smokers	 1.01 (0.87–1.22) 0.94 (0.88–1.02) 1.05 (0.85–1.27)	 174 503 112
Heikkilä et al. 1999	16,481 men Finland	1972–1991	166	Current smokers compared with all others	0.76 (NR)	NR
Parker et al. 1999	1,177 men Iowa United States	1986–1989, 1995	81	Former smokers Current smokers <20 cigarettes / day ≥20 cigarettes / day	1.3 (0.8–2.2) 1.7 (0.8–3.8) 1.9 (0.8–4.5)	42 9 7

*Includes subsequent follow-up if applicable.

Table 2.33 Case-control studies on the association between smoking and the risk of leukemia

Study	Population	Tobacco exposure	Findings
Williams and Horm 1977	7,518 incident invasive cancer cases For each type of cancer, all other cases comprised the control group United States (nationwide)	• Never smoked • Cigarette level 1: 1–400 cigarette-years[†] (up to 20 pack-years[‡]) • Cigarette level 2: 401–800 cigarette-years (>20 but <40 pack-years) • Cigarette level 3: >800 cigarette-years (≥40 pack-years) • Men only for cigars and pipes • Cigar level 1: 1–50 cigar-years[§] • Cigar level 2: >50 cigar-years • Pipe level 1: 1–50 pipe-years • Pipe level 2: >50 pipe-years	• No significant associations were found

*CI = Confidence interval.
[†]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.
[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[§]Cigar-years = The number of years of smoking multiplied by the number of cigars smoked per day.
[Δ]ALL = Acute lymphocytic leukemia.
[¶]NR = Data were not reported.
**CLL = Chronic lymphocytic leukemia.
[††]AGL = Acute granulocytic leukemia.

Risk estimates (95% CI*)		Comments
Men	Relative odds	The number of all leukemia cases was not provided; p values and 95% CIs were not provided
ALL[Δ] cigarette use		
Never smoked	1.00 (referent)	
Level 1	0.40	
Level 2	1.48	
Level 3	0.35	
ALL cigar use		
Never smoked	1.00 (referent)	
Level 1	NR[¶]	
Level 2	8.81	
ALL pipe use		
Never smoked	1.00 (referent)	
Level 1	2.03	
Level 2	2.77	
CLL** cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.36	
Level 2	0.84	
Level 3	0.78	
CLL cigar use		
Never smoked	1.00 (referent)	
Level 1	1.32	
Level 2	1.01	
CLL pipe use		
Never smoked	1.00 (referent)	
Level 1	1.13	
Level 2	0.74	
AGL[††] cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.61	
Level 2	1.35	
Level 3	1.14	
AGL cigar use		
Never smoked	1.00 (referent)	
Level 1	0.81	
Level 2	3.19	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Williams and Horm 1977 (risk estimates continued)			

[Δ]ALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
[††]AGL = Acute granulocytic leukemia.
[‡‡]CGL = Chronic granulocytic leukemia.

Risk estimates (95% CI)		Comments
AGL†† pipe use		None
Never smoked	1.00 (referent)	
Level 1	0.61	
Level 2	0.93	
CGL‡‡ cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.80	
Level 2	NR	
Level 3	3.22	
CGL cigar level		
Never smoked	1.00 (referent)	
Level 1	NR	
Level 2	0.82	
CGL pipe level		
Never smoked	1.00 (referent)	
Level 1	NR	
Level 2	2.13	
Women	Relative odds	
ALL$^{\Delta}$ cigarette use		
Never smoked	1.00 (referent)	
Level 1	1.14	
Level 2	NR	
Level 3	NR	
CLL** cigarette level		
Never smoked	1.00 (referent)	
Level 1	0.84	
Level 2	0.34	
Level 3	0.53	
AGL cigarette level		
Never smoked	1.00 (referent)	
Level 1	1.59	
Level 2	8.76	
Level 3	2.59	
CGL cigarette level		
Never smoked	1.00 (referent)	
Level 1	0.75	
Level 2	3.27	
Level 3	2.59	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Severson 1987	114 incident cases of leukemia (93 with AML[§§]) 133 population controls matched for gender and age Washington state 1981–1984	• Ever smoked • Duration of smoking (years)	• Significant dose-response relationship for duration of smoking with AML
Cartwright et al. 1988	161 cases of acute myeloid leukemia 310 hospital controls matched for gender, age, and hospital Yorkshire, United Kingdom 1979–1986	• Nonsmokers • Smokers	• Marginally significant reduction in risk was associated with smoking
Flodin et al. 1988	111 cases of chronic lymphatic leukemia 431 population controls matched for hospital catchment area Sweden 1975–1984	• Never smoked • Ever smoked	• Ever smoking was a nonsignificant protective factor

[§§]AML= Acute myelocytic leukemia.
[ΔΔ]OR = Odds ratio.
[¶¶]RR = Relative risk.

Risk estimates (95% CI)		Comments
OR[ΔΔ] for AML		None
Never smoked	1.00 (referent)	
Ever smoked	1.78 (1.01–3.15)	
1–9 years	0.93 (0.34–2.51)	
10–19 years	0.79 (0.27–2.29)	
20–29 years	1.70 (0.67–4.27)	
30–39 years	1.80 (0.61–5.35)	
40–49 years	3.03 (1.17–7.83)	
≥50 years	5.28 (1.73–16.19)	
p value for trend <0.001		
RR[¶¶]		Crude RR was reported
Nonsmokers	1.0 (referent)	
Smokers	0.6 (0.4–0.96)	
p value = 0.04		
Rate ratio		Crude rate ratio was reported
Never smoked	1.0 (referent)	
Ever smoked	0.71 (0.4–1.2)	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Kabat et al. 1988	342 male and 220 female leukemia cases 9,349 NCC*** and 9,846 CC††† (no matching) United States (9 cities) 1969–1985	• Never smoked • Former smokers • Current smokers • Men only for pipes / cigars • Cigarettes / day (men with ANLL‡‡‡ only)	• Significant negative association with smoking in several categories • No significant positive association with smoking

ΔALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
***NCC = Noncancer controls.

Risk estimates (95% CI)		Comments
Men	OR	Risk estimates were adjusted for age, duration of smoking, race, gender, education, marital status, type of hospital, and time period
ANLL		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.90 (0.62–1.31)	
CC	1.04 (0.72–1.51)	
Former smokers		
NCC	1.35 (0.90–2.02)	
CC	1.30 (0.87–1.95)	
Current smokers		
NCC	0.63 (0.41–0.97)	
CC	0.91 (0.58–1.41)	
Pipes / cigars only		
NCC	0.67 (0.31–1.44)	
CC	0.57 (0.27–1.21)	
1–14 cigarettes / day		
NCC	0.88 (0.51–1.52)	
CC	1.05 (0.61–1.82)	
15–30 cigarettes / day		
NCC	1.04 (0.69–1.55)	
CC	1.25 (0.83–1.87)	
≥31 cigarettes / day		
NCC	0.74 (0.44–1.25)	
CC	0.88 (0.52–1.47)	
ALL[Δ]		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.45 (0.21–0.94)	
CC	0.52 (0.25–1.09)	
CML[§§§]		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.69 (0.37–1.28)	
CC	0.79 (0.42–1.48)	
CLL**		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.63 (0.33–1.20)	
CC	0.72 (0.37–1.39)	
Women	OR	
ANLL		
Never smoked	1.00 (referent)	
Ever smoked		
NCC	0.74 (0.49–1.12)	
CC	0.99 (0.65–1.50)	

[†††]CC = Cancer controls.
[‡‡‡]ANLL = Acute nonlymphocytic leukemia.
[§§§]CML = Chronic myelogenous leukemia.

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Brownson 1989	909 white leukemia patients Aged ≥20 years 3,636 white controls matched for age Missouri 1984–1987	• Never or ever smoked • Cigarettes / day	• For acute leukemias, cigarette smoking was a positive risk factor • For chronic leukemias, cigarette smoking was a negative risk factor

**CLL = Chronic lymphocytic leukemia.
§§AML= Acute myelocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)		Comments
ANLL[‡‡‡]	OR	ORs were adjusted for age and gender
Ever smoked		
No	1.00 (referent)	
Yes	1.43 (1.07–1.90)	
Cigarettes / day		
Never smoked	1.00 (referent)	
<20 cigarettes / day	1.42 (0.81–2.53)	
≥20 cigarettes / day	1.44 (0.85–1.92)	
ANLL /AML[§§]	OR	
Ever smoked		
No	1.00 (referent)	
Yes	1.42 (1.05–1.90)	
Cigarettes / day		
Never smoked	1.00 (referent)	
<20 cigarettes / day	1.30 (0.67–2.41)	
≥20 cigarettes / day	1.32 (0.82–1.95)	
ANLL / non-AML	OR	
Ever smoked		
No	1.00 (referent)	
Yes	1.59 (0.56–4.61)	
Cigarettes / day		
Never smoked	1.00 (referent)	
<20 cigarettes / day	2.41 (0.48–10.81)	
≥20 cigarettes / day	1.54 (0.35–6.65)	
CLL**	OR	
Ever smoked		
No	1.00 (referent)	
Yes	0.96 (0.71–1.30)	
Cigarettes / day		
Never smoked	1.00 (referent)	
<20 cigarettes / day	0.70 (0.32–1.48)	
≥20 cigarettes / day	0.97 (0.61–1.53)	
CML[§§§]	OR	
Ever smoked		
No	1.00 (referent)	
Yes	0.81 (0.50–1.30)	
Cigarettes / day		
Never smoked	1.00 (referent)	
<20 cigarettes / day	1.08 (0.43–2.58)	
≥20 cigarettes / day	0.29 (0.11–0.73)	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Severson et al. 1990	114 incident cases of leukemia 133 population controls matched for gender and age Washington state 1981–1984	• Ever smoked cigarettes • Pack-years	• Significant risk was associated with ever smoking cigarettes • Significant dose-response relationship with pack-years
Spitz et al. 1990	253 adults with leukemia Cancer controls (number not stated) Texas 1985–1988	• Ever smoked • Never smoked	• No positive associations were found
Brownson et al. 1991	608 men and 523 women with leukemia 1,899 male and 1,742 female hospital controls, frequency matched for age Missouri 1984–1990	• Ever or never smoked • Cigarettes / day	• In men, ever cigarette smoking was a significant risk factor for ANLL • In females, the same relationship was observed, but it was not significant

**CLL = Chronic lymphocytic leukemia.
§§AML= Acute myelocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.
ΔΔΔAANL = Adult acute nonlymphocytic leukemia.

Risk estimates (95% CI)		Comments
OR		Increased risk in smokers appears to be limited to those who inhaled into the chest
Never smoked	1.0 (referent)	
Ever smoked, AANL[ΔΔΔ]	2.1 (1.2–3.8)	
Ever smoked, AML[§§]	2.1 (1.2–3.9)	
AANL		
0.7–19.9 pack-years	1.0 (0.4–2.1)	
20.0–39.9 pack-years	2.5 (1.0–6.4)	
≥40.0 pack-years	3.1 (1.4–7.4)	
p value for trend = 0.0008		
CML[§§§]	OR	There were no adjustments
Never smoked	1.00 (referent)	
Ever smoked	0.81 (0.53–1.25)	
CLL**		
Never smoked	1.00 (referent)	
Ever smoked	0.96 (0.54–1.72)	
AANL / AML		
Never smoked	1.00 (referent)	
Ever smoked	0.75 (0.37–1.54)	
ANLL[‡‡‡] / non-AML		
Never smoked	1.00 (referent)	
Ever smoked	0.62 (0.08–1.28)	
All leukemias		
Never smoked	1.00 (referent)	
Ever smoked	0.78 (0.55–1.12)	
Men	OR	
ANLL		
Never smoked	1.0 (referent)	
Ever smoked	1.5 (1.1–2.0)	
<20 cigarettes / day	1.2 (0.7–2.2)	
≥20 cigarettes / day	1.2 (0.8–1.8)	
CLL		
Never smoked	1.0 (referent)	
Ever smoked	1.0 (0.7–1.4)	
<20 cigarettes / day	0.9 (0.5–1.9)	
≥20 cigarettes / day	0.9 (0.2–3.7)	
CML		
Never smoked	1.0 (referent)	
Ever smoked	1.2 (0.8–1.9)	
<20 cigarettes / day	1.8 (0.9–3.7)	
≥20 cigarettes / day	0.8 (0.4–1.6)	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Brownson et al. 1991 (risk estimates continued)			
Brown et al. 1992	578 white men with leukemia 820 population controls, frequency matched for age, state of residence, and vital status Iowa and Minnesota 1981–1984	• Tobacco users or nonusers • Types of tobacco used • Cigarettes / day • Duration of smoking (years)	• Significant increase in risk for cigarette smokers of the longest duration with CML and CLL

**CLL = Chronic lymphocytic leukemia.
‡‡‡ANLL = Acute nonlymphocytic leukemia.
§§§CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)		Comments
Women	OR	None
ANLL[‡‡‡]		
Never smoked	1.0 (referent)	
Ever smoked	1.4 (1.0–1.9)	
<20 cigarettes / day	1.4 (0.8–2.5)	
≥20 cigarettes / day	1.6 (1.0–2.7)	
CLL**		
Never smoked	1.0 (referent)	
Ever smoked	1.1 (0.7–1.6)	
<20 cigarettes / day	1.1 (0.4–2.1)	
≥20 cigarettes / day	1.0 (0.5–2.0)	
CML[§§§]		
Never smoked	1.0 (referent)	
Ever smoked	0.8 (0.4–1.4)	
<20 cigarettes / day	0.9 (0.3–2.2)	
≥20 cigarettes / day	0.5 (0.2–1.4)	
ANLL	OR	Risk estimates were adjusted for age, state of residence, and alcohol consumption
Type of tobacco used		
Nonusers	1.0 (referent)	
Users	1.4 (0.7–2.9)	
Smokeless only	0.9 (0.2–3.1)	
Pipes / cigars only	0.7 (0.2–2.1)	
Pipes / cigars and smokeless only	1.2 (0.2–5.6)	
Cigarettes only	1.6 (1.0–2.7)	
Cigarettes and other tobacco	1.3 (0.8–2.2)	
<20 cigarettes / day	1.6 (0.9–2.7)	
20 cigarettes / day	1.4 (0.8–2.3)	
>20 cigarettes / day	1.3 (0.7–2.4)	
Duration of smoking		
1–20 years	1.4 (0.8–2.6)	
21–35 years	1.3 (0.7–2.4)	
36–45 years	1.2 (0.6–2.4)	
≥46 years	1.5 (0.8–2.8)	

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Brown et al. 1992 (risk estimates continued)			

[Δ]ALL = Acute lymphocytic leukemia.
**CLL = Chronic lymphocytic leukemia.
[§§§]CML = Chronic myelogenous leukemia.

Risk estimates (95% CI)	Comments
CML[§§§]	OR
Type of tobacco used	
Nonusers	1.0 (referent)
Users	1.7 (0.8–3.8)
Smokeless only	2.1 (0.4–10.7)
Pipes / cigars only	0.6 (0.1–5.1)
Pipes / cigars and smokeless only	2.1 (0.2–18.3)
Cigarettes only	2.1 (0.9–4.9)
Cigarettes and other tobacco	1.4 (0.6–3.6)
<20 cigarettes / day	2.1 (0.8–5.3)
20 cigarettes / day	1.5 (0.6–3.9)
>20 cigarettes / day	2.1 (0.8–5.3)
Duration of smoking	
1–20 years	1.6 (0.6–4.4)
21–35 years	1.5 (0.6–4.0)
36–45 years	1.4 (0.4–4.4)
≥46 years	3.3 (1.2–9.0)
CLL**	OR
Type of tobacco used	
Nonusers	1.0 (referent)
Users	1.6 (1.1–2.3)
Smokeless only	1.9 (0.8–4.3)
Pipes / cigars only	1.6 (0.8–3.2)
Pipes / cigars and smokeless only	1.6 (0.5–5.0)
Cigarettes only	1.6 (1.0–2.5)
Cigarettes and other tobacco	1.6 (1.1–2.5)
<20 cigarettes / day	1.9 (1.2–3.0)
20 cigarettes / day	1.2 (0.7–1.9)
>20 cigarettes / day	1.7 (1.1–2.8)
Duration of smoking	
1–20 years	1.9 (1.2–3.1)
21–35 years	1.3 (0.8–2.1)
36–45 years	1.6 (0.9–2.6)
≥46 years	1.6 (1.0–2.7)
ALL[Δ]	OR
Type of tobacco used	
Nonusers	1.0 (referent)
Users	0.5 (0.2–1.5)
Smokeless only	0.0
Pipes / cigars only	0.8 (0.1–7.2)
Pipes / cigars and smokeless only	0.0
Cigarettes only	0.5 (0.1–1.9)
Cigarettes and other tobacco	0.4 (0.1–1.8)
<20 cigarettes / day	0.2 (0.00–1.5)
20 cigarettes / day	0.9 (0.3–3.2)
>20 cigarettes / day	0.3 (0.1–1.6)

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Brown et al. 1992 (risk estimates continued)			

Risk estimates (95% CI)	Comments
Duration of smoking	
1–20 years	0.4 (0.1–2.0)
21–35 years	0.3 (0.1–1.6)
36–45 years	0.8 (0.1–5.0)
≥46 years	0.7 (0.1–4.3)
Myelodysplasia	OR
Type of tobacco used	
Nonusers	1.0 (referent)
Users	1.4 (0.7–2.9)
Smokeless only	2.7 (0.8–9.4)
Pipes / cigars only	0.8 (0.2–3.9)
Pipes / cigars and smokeless only	1.0 (0.1–8.7)
Cigarettes only	1.6 (0.7–3.5)
Cigarettes and other tobacco	1.2 (0.5–2.8)
<20 cigarettes / day	1.0 (0.4–2.5)
20 cigarettes / day	1.7 (0.7–3.7)
>20 cigarettes / day	1.1 (0.4–2.8)
Duration of smoking	
1–20 years	0.4 (0.1–1.6)
21–35 years	1.4 (0.6–3.6)
36–45 years	1.5 (0.6–3.8)
≥46 years	1.6 (0.7–3.9)
Other	OR
Type of tobacco used	
Nonusers	1.0 (referent)
Users	1.0 (0.5–2.0)
Smokeless only	3.0 (0.9–9.2)
Pipes / cigars only	0.3 (0.0–2.7)
Pipes / cigars and smokeless only	5.2 (1.5–17.8)
Cigarettes only	0.7 (0.3–1.6)
Cigarettes and other tobacco	1.0 (0.5–2.2)
<20 cigarettes / day	0.7 (0.3–1.8)
20 cigarettes / day	0.9 (0.4–2.0)
>20 cigarettes / day	0.9 (0.4–2.0)
Duration of smoking	
1–20 years	0.4 (0.1–1.3)
21–35 years	0.9 (0.4–2.1)
36–45 years	0.7 (0.2–1.0)
≥46 years	1.4 (0.6–3.4)

Table 2.33 Continued

Study	Population	Tobacco exposure	Findings
Mele et al. 1994	Incident adult cases aged ≥30 years: 28 with ALL[Δ]; 55 with RAEB[¶¶¶], preleukemia; 76 with CML[§§§]; and 118 with AML[§§] 1,161 outpatient controls Italy (Rome, Bologna, and Pavia) 1986–1989	• Never smoked • Former smokers • Current smokers • Pack-years	• Significant dose-response relationship with the number of cigarettes/day with AML and RAEB

[Δ]ALL = Acute lymphocytic leukemia.
[§§]AML= Acute myelocytic leukemia.
[§§§]CML = Chronic myelogenous leukemia.
[¶¶¶]RAEB = Refractory anemia with excess of blasts.

Risk estimates (95% CI)		Comments
AML	OR	Risk estimates were adjusted for age, gender, education, and residence outside of study town
Never smoked	1.0 (referent)	
Ever smoked	1.4 (1.0–1.9)	
Former smokers	1.6 (0.9–2.8)	
Current smokers	1.4 (0.8–2.5)	
1–10 pack-years	1.2 (0.6–2.2)	
11–20 pack-years	1.7 (0.8–3.6)	
>20 pack-years	1.7 (0.9–3.0)	
p value for trend = 0.05		
ALL	OR	
Never smoked	1.0 (referent)	
Ever smoked	0.9 (0.5–1.8)	
Former smokers	0.6 (0.2–2.0)	
Current smokers	1.3 (0.5–3.4)	
1–10 pack-years	0.6 (0.2–2.3)	
11–20 pack-years	0.9 (0.2–4.7)	
>20 pack-years	1.3 (0.4–3.7)	
p value for trend = 0.54		
RAEB	OR	
Never smoked	1.0 (referent)	
Ever smoked	1.7 (1.0–3.0)	
Former smokers	1.2 (0.4–3.3)	
Current smokers	2.7 (1.2–6.3)	
1–10 pack-years	1.4 (0.5–4.1)	
11–20 pack-years	2.4 (0.7–7.8)	
>20 pack-years	2.4 (1.0–5.8)	
p value for trend = 0.03		
CML	OR	
Never smoked	1.0 (referent)	
Ever smoked	1.2 (0.8–1.9)	
Former smokers	1.3 (0.7–2.6)	
Current smokers	1.4 (0.7–2.7)	
1–10 pack-years	1.7 (0.8–3.4)	
11–20 pack-years	1.4 (0.5–3.4)	
>20 pack-years	1.0 (0.5–2.1)	
p value for trend = 0.82		

Table 2.34 Cohort studies on the association between smoking and the risk of leukemia

Study	Population	Tobacco exposure	Outcome
Weir and Dunn 1970	68,153 men aged 35–64 years 482,658 person-years of observation California Began in 1954	• Nonsmokers • All smokers • Packs / day	Death from leukemia (all leukemias)
Paffenbarger et al. 1978	50,000 male alumni of Harvard University (entering 1916–1950) and the University of Pennsylvania (attending 1931–1940) Followed for 35 years Boston and Philadelphia	• Cigarette smokers • Cigarette nonsmokers • ≥10 cigarettes / day	Death from lymphatic leukemia, myeloid leukemia, or other leukemias
Kinlen and Rogot 1988	U.S. Veterans Cohort Mostly white men United States (nationwide) 1954–1969	• Type of tobacco • Cigarettes / day	Death from lymphatic leukemia, myeloid leukemia, monocytic leukemia, or unspecified leukemias

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

Findings	Risk estimates (95% CI*)		Comments
• Smokers' risk of dying from leukemia is somewhat greater compared with nonsmokers	All leukemias	RR†	Risks were not stratified by leukemia type; p values and 95% CIs were not provided
	Nonsmokers	1.00 (referent)	
	All smokers	1.32	
	About 1/2 pack or less	0.49	
	About 1	1.73	
	About 1 1/2 packs or more	0.66	
• Significant risk was associated with both cigarette smoking and smoking ≥10 cigarettes/day with myeloid leukemia	Lymphatic leukemia	RR	95% CIs were not provided
	Cigarette nonsmokers	1.00 (referent)	
	Cigarette smokers	1.3 (p = 0.57)	
	≥10 cigarettes/day	2.7 (p = 0.17)	
	Myeloid leukemia	RR	
	Cigarette nonsmokers	1.00 (referent)	
	Cigarette smokers	2.4 (p = 0.03)	
	≥10 cigarettes/day	3.6 (p = 0.03)	
	Other leukemias	RR	
	Cigarette nonsmokers	1.00 (referent)	
	Cigarette smokers	1.3 (p = 0.63)	
	≥10 cigarettes/day	0.6 (p = 0.65)	
• 723 outcome events • Significant dose-response relationship with cigarettes/day and lymphatic and myeloid and monocytic leukemias	Lymphatic leukemia	RR	No adjustments
	Type of tobacco		
	Never smoked	1.00 (referent)	
	Cigarettes	1.58 (1.27–1.95)	
	Former smokers	1.56 (1.17–2.04)	
	Cigars	2.01 (1.00–3.60)	
	Pipes	0.83 (0.17–2.43)	
	Cigarettes/day		
	Never smoked	1.00 (referent)	
	<10 cigarettes/day	1.40 (0.74–2.39)	
	10–20 cigarettes/day	1.76 (1.29–2.34)	
	≥21 cigarettes/day	1.48 (0.97–2.17)	
	χ^2 for trend = 5.02 (p <0.05)		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Kinlen and Rogot 1988 (risk estimates continued)			

‡NR = Data were not reported.

Findings	Risk estimates (95% CI)	Comments
	Myeloid and monocytic leukemia — RR	
	Type of tobacco	
	Never smoked — 1.00 (referent)	
	Cigarettes — 1.72 (1.45–2.03)	
	Former smokers — 1.54 (1.22–1.92)	
	Cigars — 1.78 (0.97–2.98)	
	Pipes — 1.18 (0.48–2.57)	
	Cigarettes / day	
	Never smoked — 1.00 (referent)	
	<10 cigarettes / day — 1.31 (0.78–2.07)	
	10–20 cigarettes / day — 1.75 (0.37–2.21)	
	≥21 cigarettes / day — 1.93 (1.45–2.52)	
	χ^2 for trend = 15.48 ($p < 0.001$)	
	Acute leukemia — RR	
	Type of tobacco	
	Never smoked — 1.00 (referent)	
	Cigarettes — 1.51 (1.19–1.89)	
	Former smokers — 1.15 (0.81–1.59)	
	Cigars — 1.53 (0.66–3.01)	
	Pipes — 0.85 (0.17–2.48)	
	Cigarettes / day	
	Never smoked — 1.00 (referent)	
	<10 cigarettes / day — 1.67 (0.94–2.76)	
	10–20 cigarettes / day — 1.54 (1.09–2.10)	
	≥21 cigarettes / day — 1.40 (0.87–2.11)	
	χ^2 for trend = 2.81	
	Unspecified leukemia — RR	
	Type of tobacco	
	Never smoked — 1.00 (referent)	
	Cigarettes — 0.87 (0.55–1.31)	
	Former smokers — 1.06 (0.63–1.68)	
	Cigars — 0.36 (0.01–2.00)	
	Pipes — NR‡	
	Cigarettes / day	
	Never smoked — 1.00 (referent)	
	<10 cigarettes / day — 0.63 (0.13–1.85)	
	10–20 cigarettes / day — 0.70 (0.32–1.32)	
	≥21 cigarettes / day — 1.40 (0.70–2.50)	
	χ^2 for trend = 0.13	

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
McLaughlin et al. 1989	U.S. Veterans Study (update) 293,658 persons aged 31–84 years (mainly white male World War I veterans) who held active U.S. government life insurance policies in December 1953 Questionnaire administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 26 years of follow-up United States (nationwide)	• Nonsmokers • Ever smoked • Former smokers • Current noncigarette smokers • Current cigarette smokers (cigarettes/day)	Death from leukemia

Findings	Risk estimates (95% CI)		Comments
• Study indicates a positive relationship with smoking, especially for myeloid leukemia	Lymphatic leukemia	RR	95% CIs were not provided
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.09	
	Former smokers	1.21	
	Noncigarette smokers	1.02	
	Current cigarette smokers	1.03	
	<10 cigarettes / day	0.66	
	10–20 cigarettes / day	1.14	
	>20 cigarettes / day	1.10	
	Nonsignificant p value for trend		
	Myeloid leukemia	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.51 (p <0.05)	
	Former smokers	1.31	
	Noncigarette smokers	1.08	
	Current cigarette smokers	1.62 (p <0.01)	
	<10 cigarettes / day	1.48	
	10–20 cigarettes / day	1.45 (p <0.05)	
	>20 cigarettes / day	1.95 (p <0.01)	
	p value for trend = <0.05		
	Acute leukemia	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.27 (p <0.05)	
	Former smokers	1.19	
	Noncigarette smokers	1.01	
	Current cigarette smokers	0.31 (p <0.05)	
	<10 cigarettes / day	1.10	
	10–20 cigarettes / day	1.47 (p <0.01)	
	>20 cigarettes / day	1.16	
	p value for trend = <0.05		
	Other leukemias	RR	
	Nonsmokers	1.00 (referent)	
	Ever smoked	1.31	
	Former smokers	1.59 (p <0.05)	
	Noncigarette smokers	0.61	
	Current cigarette smokers	1.16	
	<10 cigarettes / day	1.31	
	10–20 cigarettes / day	0.98	
	>20 cigarettes / day	1.37	

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Garfinkel and Boffetta 1990	2 cohort studies Cancer Prevention Study (CPS) I 2,387,252 male and 3,318,242 female person-years 1959–1965 CPS-II 1,867,375 male and 2,398,772 female person-years 1982–1986 United States (nationwide)	• Never smoked cigarettes • Ever smoked cigarettes • Former cigarette smokers • Cigarettes / day • Cigar / pipe smokers (men only)	Death from lymphatic leukemia, myeloid leukemia, or other leukemias

Findings	Risk estimates (95% CI)			Comments
• CPS-I: 477 male and 339 female outcome events • CPS-II: 327 male and 235 female outcome events • In male ever smokers, standardized mortality ratio was significantly larger than 1.0 for all leukemia and myeloid leukemia in both CPS-I and CPS-II; no such relationship was found in female ever smokers	Standardized leukemia mortality ratios			The number of expected deaths was calculated by applying the 5-year, age group-specific mortality rate of the nonsmokers to the denominator of the corresponding age group in the exposed categories; 95% CIs were not provided
	Lymphatic leukemia	RR		
		Men	Women	
	CPS-I			
	Ever smoked	1.02	0.80	
	Former smokers	1.25	0.56	
	1–19 cigarettes / day	0.77	0.87	
	≥20 cigarettes / day	0.99	0.83	
	Cigar / pipe smokers	1.12		
	CPS-II			
	Ever smoked	1.24	1.52	
	Former smokers	1.44	1.94 ($p < 0.05$)	
	1–19 cigarettes / day	0.94	0.67	
	≥20 cigarettes / day	0.68	1.13	
	Cigar / pipe smokers	1.23		
	Myeloid leukemia			
	CPS-I			
	Ever smoked	2.44 ($p < 0.05$)	0.61 ($p < 0.05$)	
	Former smokers	2.23 ($p < 0.05$)	0.36	
	1–19 cigarettes / day	2.25 ($p < 0.05$)	0.61	
	≥20 cigarettes / day	2.87 ($p < 0.05$)	0.74	
	Cigar / pipe smokers	1.51		
	CPS-II			
	Ever smoked	1.32 ($p < 0.05$)	1.27	
	Former smokers	1.17	1.33	
	1–19 cigarettes / day	1.65	1.45	
	≥20 cigarettes / day	1.75 ($p < 0.05$)	0.98	
	Cigar / pipe smokers	0.85		
	Other leukemias			
	CPS-I			
	Ever smoked	1.58 ($p < 0.05$)	0.94	
	Former smokers	1.18	1.44	
	1–19 cigarettes / day	1.53 ($p < 0.05$)	0.88	
	≥20 cigarettes / day	1.95 ($p < 0.05$)	0.75	
	Cigar / pipe smokers	1.07		
	CPS-II			
	Ever smoked	1.70	0.79	
	Former smokers	1.63 ($p < 0.05$)	0.88	
	1–19 cigarettes / day	2.17 ($p < 0.05$)	0.79	
	≥20 cigarettes / day	1.75	0.61	
	Cigar / pipe smokers	1.14		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Mills et al. 1990	Seventh-Day Adventist Health Study 34,000 Seventh-Day Adventists California 1977–1982	• Never smoked • Former cigarette smokers • Current cigarette smokers • Greatest number of cigarettes smoked daily • Duration of smoking (years)	Diagnosis of all leukemias and myeloid leukemia

Findings	Risk estimates (95% CI)		Comments
• Significant dose-response relationship with all leukemias, but not with myeloid leukemia	All leukemias	RR	RRs were adjusted for age and gender
	Never smoked	1.00 (referent)	
	Former smokers	2.00 (1.01–3.95)	
	Current smokers	2.10 (0.48–9.23)	
	Greatest number of cigarettes smoked daily		
	Never smoked	1.00 (referent)	
	1–14 cigarettes / day	1.01 (0.34–2.99)	
	15–24 cigarettes / day	2.44 (0.93–6.38)	
	≥25 cigarettes / day	3.00 (1.25–7.22)	
	p value for trend = 0.009		
	Duration of smoking		
	Never smoked	1.00 (referent)	
	<5 years	1.28 (0.39–4.32)	
	5–14 years	1.69 (0.56–5.14)	
	≥15 years	2.55 (1.18–5.53)	
	p value for trend = 0.03		
	Myeloid leukemia	RR	
	Never smoked	1.00 (referent)	
	Former smokers	2.24 (0.91–5.53)	
	Current smokers	2.04 (0.25–16.65)	
	Greatest number of cigarettes smoked daily		
	Never smoked	1.00 (referent)	
	1–14 cigarettes / day	1.94 (0.60–6.27)	
	15–24 cigarettes / day	1.49 (0.32–6.94)	
	≥25 cigarettes / day	3.55 (1.14–11.07)	
	p value for trend = 0.10		
	Duration of smoking		
	Never smoked	1.00 (referent)	
	<5 years	2.39 (0.65–8.77)	
	5–14 years	1.45 (0.31–6.71)	
	≥15 years	2.69 (0.94–7.72)	
	p value for trend = 0.19		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Linet et al. 1991	Lutheran Brotherhood Cohort Study 17,633 white male policy-holders of the Lutheran Brotherhood Insurance Society Followed for 20 years (286,731 person-years) United States (nationwide) 1967–1986	• Type of tobacco • Cigarettes / day	Death from leukemia

Findings	Risk estimates (95% CI)		Comments
• 74 outcome events • No significant relationship with any of the leukemias • Most of the myeloid leukemia risk estimates were less than 1.0	Myeloid leukemia	RR	Poisson regression was used to calculate RRs; risk estimates were adjusted for age
	Type of tobacco used		
	Never	1.0 (referent)	
	Any	0.8 (0.3–1.7)	
	Cigarettes only	0.3 (0.1–1.6)	
	Pipes / cigars only	1.1 (0.2–5.0)	
	Cigarettes and other tobacco	1.0 (0.4–2.2)	
	Cigarettes / day		
	Never smoked	1.0 (referent)	
	Ever smoked	0.8 (0.3–1.8)	
	≤10 cigarettes / day	0.5 (0.2–1.6)	
	11–20 cigarettes / day	0.8 (0.3–2.1)	
	>20 cigarettes / day	1.3 (0.5–3.8)	
	p value for trend = 0.68		
	Lymphatic leukemia	RR	
	Type of tobacco used		
	Never	1.0 (referent)	
	Any	1.4 (0.5–3.5)	
	Cigarettes only	2.7 (0.9–8.3)	
	Pipes / cigars only	0.7 (0.1–6.1)	
	Cigarettes and other tobacco	1.5 (0.6–4.2)	
	Cigarettes / day		
	Never smoked	1.0 (referent)	
	Ever smoked	1.7 (0.6–4.4)	
	≤10 cigarettes / day	1.5 (0.5–4.6)	
	11–20 cigarettes / day	1.7 (0.6–5.2)	
	>20 cigarettes / day	1.9 (0.5–7.2)	
	p value for trend = 0.11		
	Other leukemias	RR	
	Type of tobacco used		
	Never	1.0 (referent)	
	Any	1.5 (0.3–6.8)	
	Cigarettes only	1.5 (0.2–10.3)	
	Pipes / cigars only	NR	
	Cigarettes and other tobacco	NR	
	Cigarettes / day		
	Never smoked	1.0 (referent)	
	Ever smoked	1.7 (0.4–7.6)	
	≤10 cigarettes / day	0.4 (0.0–4.5)	
	11–20 cigarettes / day	2.5 (0.5–12.5)	
	>20 cigarettes / day	3.0 (0.5–18.2)	
	p value for trend = 0.06		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Friedman 1993	Kaiser Permanente study 57,224 never smokers 20,928 former smokers 64,839 current smokers 24 years of follow-up Oakland and San Francisco Began in 1964	• Never smoked • Former smokers • Current smokers • Packs / day (men with acute nonlymphocytic leukemia only)	Diagnosis of leukemia
Doll et al. 1994	34,439 British male doctors United Kingdom 1951–1991 (40 years of follow-up)	• Never smoked • Former smokers • Current smokers • Cigarettes / day	Mortality from myeloid leukemia or nonmyeloid leukemia

Findings	Risk estimates (95% CI)			Comments
• Cigarette smoking was significantly associated with the development of acute nonlymphocytic leukemia in men	Acute nonlymphocytic leukemia	RR		RRs were adjusted for age
		Men	Women	
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	2.3 (0.9–5.7)	1.3 (0.6–2.8)	
	Current smokers	2.8 (1.2–6.4)	0.9 (0.4–1.7)	
	<1 pack / day	1.0 (referent)		
	1–2 packs / day	1.5 (0.6–3.6)		
	>2 packs / day	1.6 (0.5–5.1)		
	p value for trend = 0.31			
	Acute myeloid leukemia	RR		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	1.6 (0.6–4.7)	1.4 (0.6–3.1)	
	Current smokers	2.0 (0.8–5.0)	0.9 (0.4–1.8)	
	Chronic myeloid leukemia	RR		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	0.5 (0.0–4.2)	1.0 (0.2–4.5)	
	Current smokers	3.5 (0.9–13.0)	0.6 (0.2–2.2)	
	Chronic lymphocytic leukemia	RR		
	Never smoked	1.0 (referent)	1.0 (referent)	
	Former smokers	1.0 (0.5–1.8)	0.6 (0.1–1.7)	
	Current smokers	0.8 (0.5–1.5)	0.6 (0.3–1.3)	
• "...(myeloid leukemia) showed a marginally significant relation with the amount smoked." (p. 903)	Annual mortality per 100,000 men			Mortality rates were standardized for age and calendar period; p value was not provided
	Myeloid leukemia	Number		
	Nonsmokers	4		
	Former smokers	8		
	Current smokers	7		
	1–14 cigarettes / day	3		
	15–24 cigarettes / day	9		
	≥25 cigarettes / day	10		
	Nonmyeloid leukemia	Number		
	Nonsmokers	14		
	Former smokers	9		
	Current smokers	12		
	1–14 cigarettes / day	16		
	15–24 cigarettes / day	8		
	≥25 cigarettes / day	13		

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Engeland et al. 1996	26,000 men Norway 1966–1993	• Never smoked • Former smokers • Current smokers	Diagnosis of leukemia
Engeland et al. 1997	502,496 cancer cases Norway 1953–1993	• Ever / never smoked	Diagnosis of leukemia before or after diagnosis of another smoking-associated cancer (SAC)
Nordlund et al. 1997	26,000 women Sweden 1963–1989	• Never smoked • Former smokers • Current smokers • Cigarettes / day • Age at smoking initiation	Diagnosis of leukemia
Tulinius et al. 1997	11,580 women 11,366 men Iceland 1968–1995	• Never smoked • Former smokers • Cigarettes / day	Diagnosis of leukemia (all leukemias)

Findings	Risk estimates (95% CI)			Comments
• No significant associations	Men	RR		No adjustments
	Never smoked	1.0 (referent)		
	Former smokers	0.9 (0.4–1.9)		
	Current smokers	0.6 (0.4–1.2)		
	Women	RR		
	Never smoked	1.0 (referent)		
	Former smokers	0.3 (0.0–2.2)		
	Current smokers	1.3 (0.7–2.5)		
• Significantly increased mortality among men and women who smoked for developing leukemia before developing other SACs	Standardized incident ratios for smokers (observed / expected)			Estimates of the expected number were based on gender-specific incidence rates from the entire Norwegian population during 8 time periods
		Men	Women	
	Leukemia before another SAC	1.6 (1.2–2.0)	1.9 (1.2–2.8)	
	Leukemia after another SAC	1.3 (1.0–1.6)	1.3 (0.9–2.0)	
• No significant risks		RR		RRs were adjusted for age and place of residence
	Never smoked		1.00 (referent)	
	Former smokers		1.03 (0.32–3.29)	
	Current smokers		1.24 (0.71–2.18)	
	1–7 cigarettes / day		1.52 (0.80–2.91)	
	8–15 cigarettes / day		0.93 (0.33–2.59)	
	≥16 cigarettes / day		0.69 (0.09–4.99)	
	Age at smoking initiation			
	≤19 years old		1.25 (0.38–4.16)	
	20–23 years old		1.56 (0.85–2.86)	
	p value for trend = 0.154			
• Significant risk associated with smoking 15–24 cigarettes / day		RR		RRs were adjusted for age
	Never smoked		1.0 (referent)	
	Former smokers		2.08 (0.68–6.35)	
	1–14 cigarettes / day		1.14 (0.34–3.78)	
	15–24 cigarettes / day		3.96 (1.52–10.3)	
	≥25 cigarettes / day		NR	

Table 2.34 Continued

Study	Population	Tobacco exposure	Outcome
Adami et al. 1998	334,957 male construction workers Sweden 1971–1991	• Never smoked • Former smokers • Current smokers • Cigarettes / day • Duration of smoking (years) • Pipe tobacco • Snuff dipping	Diagnosis of leukemia

Findings	Risk estimates (95% CI)		Comments
• No significant association • No indication of a dose-response relationship	Myeloid leukemias	RR	RRs were adjusted for age
	Never smoked	1.0 (referent)	
	Former smokers	0.7 (0.5–1.2)	
	Current smokers	1.0 (0.7–1.4)	
	1–14 cigarettes / day	1.3 (0.9–1.7)	
	≥15 cigarettes / day	0.8 (0.5–1.3)	
	Duration of smoking		
	Former smokers		
	1–10 years	0.6 (0.3–1.3)	
	11–20 years	1.0 (0.6–1.9)	
	≥21 years	0.7 (0.3–1.4)	
	Current smokers		
	1–10 years	0.8 (0.4–1.7)	
	11–20 years	0.7 (0.4–1.3)	
	21–30 years	1.4 (0.8–2.2)	
	≥31 years	1.2 (0.8–1.9)	
	Pipe tobacco		
	<30 g / week	1.0 (0.6–1.7)	
	≥30 g / week	1.2 (0.8–1.7)	
	Ever dipped snuff	1.0 (0.7–1.4)	
	Acute leukemias	RR	
	Never smoked	1.0 (referent)	
	Former smokers	0.8 (0.5–1.3)	
	Current smokers	1.1 (0.8–1.6)	
	1–14 cigarettes / day	1.4 (1.0–2.0)	
	≥15 cigarettes / day	1.1 (0.7–1.8)	
	Duration of smoking		
	Former smokers		
	1–10 years	0.7 (0.3–1.5)	
	11–20 years	0.7 (0.3–1.5)	
	≥21 years	1.0 (0.5–2.0)	
	Current smokers		
	1–10 years	1.4 (0.8–2.7)	
	11–20 years	0.7 (0.4–1.5)	
	21–30 years	1.5 (0.9–2.4)	
	≥31 years	0.9 (0.5–1.5)	
	Pipe tobacco		
	<30 g / week	1.0 (0.6–1.8)	
	≥30 g / week	1.1 (0.7–1.7)	
	Ever dipped snuff	1.0 (0.7–1.4)	

Liver Cancer

There are strong geographic variations in liver cancer incidence around the world. Although liver cancer is a relatively infrequent cause of cancer mortality in the United States, it is a leading cause of cancer deaths in the world (London and McGlynn 1996). In the United States, less than 1.5 percent of incident cancers are primary cancers of the liver and bile ducts. However, cancer of the liver ranks eighth (by deaths) on a worldwide basis, with three-quarters of the cases occurring in developing countries where hepatitis B and aflatoxin ingestion are prevalent causal exposures (Parkin et al. 1993). In the United States, an estimated 17,300 new cases of liver cancer and 14,400 deaths attributed to this cancer were expected to occur in 2003 (ACS 2003). Liver cancer is more common among men than women, in part reflecting the greater alcohol intake by men. Liver cancer incidence and mortality rates have increased since the 1980s in the United States (McKean-Cowdin et al. 2000). Hypotheses for this increase include the increasing frequency of hepatitis C virus and hepatitis B virus (HBV) infections.

Interpretation of the relationship between smoking and liver cancer is complicated by the potential for confounding by alcohol and HBV infections. First, alcohol intake is an established risk factor and smokers tend to drink more than nonsmokers, and this exposure has not been measured routinely in all studies that include information on smoking history. Second, chronic HBV infections are recognized as a major cause of this malignancy (IARC 1988). As for alcohol, not all epidemiologic studies that have addressed smoking have also assessed the hepatitis status of study participants. Hence, the unconfounded contribution of smoking to risks for liver cancer has been difficult to assess. Considerable epidemiologic evidence indicates, however, that smokers are at an increased risk for this cancer.

Conclusions of Previous Surgeon General's Reports

The 1990 Surgeon General's report (USDHHS 1990) noted an association between smoking and hepatocellular cancer that persisted after controlling for potentially confounding lifestyle factors including alcohol intake. That report also noted that HBV infections may modify the effects of smoking on the risk of liver cancer. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that smoking might be a contributing factor to the development of liver cancer.

Biologic Basis

Circulating carcinogens from tobacco smoke are metabolized in the liver, thus exposing the liver to many absorbed carcinogens. A long-term exposure to these carcinogens may therefore lead to cellular damage in the liver and the development of cancer. Carcinogens may act directly on the genes of the hepatocytes.

Epidemiologic Evidence

Epidemiologic data come from a wide range of studies in both low- and high-incidence countries (Table 2.35). Many of these studies have evaluated smoking, alcohol, and viral causes of liver cancer thoroughly, although some of the larger cohort studies have not controlled for each of these causal agents in assessing smoking's effect. Cigarette smoking was directly related to the risk of liver cancer as the number of cigarettes smoked per day increased in some case-control studies (Yu et al. 1983; Trichopoulos et al. 1987b; Kuper et al. 2000) but not in others (Tanaka et al. 1992).

In a cohort study of U.S. veterans, Hsing and colleagues (1990a) noted a significant trend in increased risks with an increasing number of cigarettes smoked, but their analysis did not control for alcohol consumption or hepatitis viral status. On the other hand, Doll and colleagues (1994) did not observe a trend in risk with higher levels of cigarette smoking in the 40-year report of the British physicians cohort study, and concluded that smoking is not related to liver cancer. In a 12-year cohort study of 14,397 residents of Taiwan aged 40 years and older, cigarette smoking was positively related to mortality from liver cancer (Liaw and Chen 1998). Among men, 110 deaths from liver cancer were identified, and for current smokers the RR was 2.2 (95 percent CI, 1.4–3.6) compared with persons who had never smoked. These authors adjusted for alcohol consumption and the presence of HBV surface antigens.

For persons smoking more than a pack a day, the RR for liver cancer has been 2 or more in both case-control and cohort studies, compared with the risk for persons who had never smoked (Yu et al. 1983; Hsing et al. 1990a; Doll et al. 1994; Kuper et al. 2000). However, not all studies have found an effect of this magnitude (Tanaka et al. 1992; Chiesa et al. 2000; Mori et al. 2000a). This inconsistency may be in part due to the study design and to the relative contribution of HBV infection to the risk of malignancy. For example, Lam and colleagues (1982) observed a RR of 3.3 (95 percent CI, 1.0–13.4) among current smokers, but the association was confined to those who were HBV-negative. Similarly, Trichopoulos and colleagues (1980, 1987b) observed significant associations among HBV-negative persons. In contrast, in a cohort of HBV-positive men and women in China, Tu and colleagues (1985) observed a RR of 4.6. One explanation for the varying results is the dominant role of hepatitis viral infection and the extent to which its effects have been considered in the studies on smoking. The higher RRs that were observed in several studies of persons who were negative for HBV compared with those who were positive suggest that this explanation is plausible.

Evidence Synthesis

A substantial body of epidemiologic evidence supports a relationship between smoking and liver cancer, but a positive association was not found in all studies considered. The metabolism in the liver of the many carcinogens from tobacco smoke leads to an exposure of hepatocytes to these carcinogens. The strength of an association between cigarette smoking and liver cancer varies according to HBV infection status, with stronger associations among those who are negative for HBV. In many of the studies, risk increases with the number of cigarettes smoked per day. Although confounding by alcohol and HBV infection status may bias the findings of some studies, controlling for these causes does not remove the strong association between smoking and liver cancer seen in several of the studies summarized in this report. Finally, in 2002, IARC concluded that there is now sufficient evidence for a causal association between cigarette smoking and cancer of the liver (IARC 2002).

Conclusion

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

Implications

The global burden of liver cancer may increase if smoking increases around the world. Further research is needed to resolve the relationship of smoking to liver cancer with further consideration of the history of hepatitis infection and alcohol use.

Table 2.35 Studies on the association between smoking and the risk of liver cancer

Study	Location	Cases
	Case-control studies	
Trichopoulos et al. 1980	Greece	79
Lam et al. 1982	Hong Kong	107
Stemhagen et al. 1983	United States	265
Yu et al. 1983	United States	78
Hardell et al. 1984	Sweden	102
Filippazzo et al. 1985	Italy	120
Kew et al. 1985	South Africa	240
Austin and Cole 1986	United States	86
Trichopoulos et al. 1987b	Greece 1976–1984	194
La Vecchia et al. 1988	Italy	151
Lu et al. 1988	Taiwan	131
Yu et al. 1988	United States	165

*RR = Relative risk.
†CI = Confidence interval.
‡HBV = Hepatitis B virus.
§HBsAg = Hepatitis B surface antigen.

RR* (95% CI†) compared with never smokers	Comments
5.5 (2.0–15.6)	The association was confined to persons who were HBV‡-negative
3.3 (1.0–13.4)	The association was confined to persons who were HBV-negative
Men: 0.7 (0.4–1.1) Women: 1.0 (0.6–1.7)	None
Current ≤1 pack / day: 1.2 (0.6–2.5) >1 pack / day: 2.6 (1.0–6.7)	RR in heavy smokers (>1 pack / day) compared with light smokers (≤1 pack / day) = 1.8 (0.1–4.6); RR for the >1 pack / day low-alcohol intake group = 1.8 (0.7–5.0)
1.1 for current and former smokers (no CI was reported)	RR was calculated from smokers (73.5%) and 66% of the never smokers (controls)
0.8 (0.4–1.5)	None
<1.0 (no CI was reported) for heavy smokers; compared with nonsmokers; no current HBV = 1.3 for heavy smokers compared with nonsmokers	Heavy smoking = ≥20 cigarettes / day
1.0 (0.5–1.8)	None
7.3 for smokers of ≥30 cigarettes / day	The association was confined to persons who were HBV-negative; slope for a trend with the number of cigarettes smoked was significantly higher in persons negative for HBsAg§ than the corresponding slope for persons positive for HBsAg
0.9 (0.6–1.5)	None
Odds ratio = 1.33 for smokers compared with nonsmokers; χ^2 for trend = 0.88 ($p > 0.05$) adjusted for gender and HBsAg	Smoking behaviors, duration in years, or number of cigarettes smoked per day were not associated with hepatocellular carcinoma in the multivariate models
3.3, $p < 0.05$	None

Table 2.35 Continued

Study	Location	Cases
	Case-control studies	
Tanaka et al. 1992	Japan	204
Kuper et al. 2000	Greece 1995–1998	333
	Cohort studies	
Oshima et al. 1984	Japan	20
Tu et al. 1985	China	70
Shibata et al. 1986	Japan	22
Kono et al. 1987	Japan	51
Hsing et al. 1990a	United States veterans	289
Doll et al. 1994	United Kingdom	76
McLaughlin et al. 1995a	United States veterans	363
Liaw and Chen 1998	Taiwan	Men: 110 Women: 18
Mori et al. 2000a	Japan	22

[‡]HBV = Hepatitis B virus.
[§]HBsAg = Hepatitis B surface antigen.
[Δ]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

RR* (95% CI†) compared with never smokers	Comments
Current smokers: 1.5 (0.9–2.5) Former smokers: 1.6 (0.9–2.8)	There was no significant trend in risks with pack-years[Δ] smoked
Current smokers <2 packs / day: 1.2 (0.8–1.9) ≥2 packs / day: 1.6 (0.9–2.9)	Risks were strongest in persons without both HBsAg[§] and antibodies to hepatitis C virus (RR = 2.8 [1.1–6.9] for smokers of ≥2 packs / day; trend p = 0.03)
5.8 (1.0–34.2)	None
4.6 (p <0.05)	HBV[‡]-positive cohort
Standard mortality ratio (observed / expected) = >4.8 (p <0.001) among cigarette smokers in fishing area	There was no clear dose-response relationship; risks were insignificant after adjusting for shahi drinking
Current compared with never and former smokers 1–19 cigarettes / day: 1.14 (0.59–2.20) ≥20 cigarettes / day: 1.04 (0.49–2.23)	There was no association with smoking
Cigar / pipe smokers: 3.1 (2.0–4.8) Cigarettes Current smokers: 2.4 (1.6–3.5) Former smokers: 1.9 (1.2–2.9)	Risks increased with the number of cigarettes / day: <10 (2.2); 10–20 (2.0); 21–39 (2.9); >39 (3.8 [1.9–8.0]); there was a strong dose-response relationship (p <0.001); did not control for alcohol intake or HBV status
2.0 for persons who smoked ≥25 cigarettes / day	There was no significant trend for the number of cigarettes smoked per day
Current smokers: 1.8 (1.4–2.3) Former smokers: 1.5 (1.2–2.0)	The mortality study did not control for alcohol or viral status
Men Current smokers: 2.2 (1.4–3.6)	Results were adjusted for alcohol intake and HBsAg status; risks increased with more years of smoking, and decreased with an older age at initiation
2.10 (0.61–7.23)	Results were adjusted for age and gender; a small number of cases precluded an informative analysis of the interactions

Adult Brain Cancer

Brain cancer incidence is higher in men than in women. In 2003, an estimated 18,300 new cases (10,200 among men and 8,100 among women), and an estimated 13,100 deaths attributed to brain cancer were expected to occur (ACS 2003).

The systematic epidemiologic study of brain cancer is hampered by the grouping of clinicopathologic entities and by problems with the accurate diagnosis of intracranial lesions. Further, it often is difficult to distinguish primary from secondary or metastatic lesions. Risk factors for brain cancers include working in petrochemical, rubber, and agricultural industries. Radiation exposure also has been related to the risk of brain cancer (NRC 1990; Preston-Martin and Mack 1996).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not reviewed brain cancer and smoking.

Biologic Basis

Exposure to nitroso compounds has been related to the risk of brain cancer, stimulating interest in cigarette smoke as a source of exposure. Two major subcategories of nitroso compounds include nitrosamines, which require metabolic activation, and nitrosamides, which do not. The nitrosamides, particularly nitrosoureas, are effective nervous system carcinogens in many species (Preston-Martin and Mack 1996). Nitrosamides have been shown to damage DNA by the production of adducts. The major sources of exposure to nitrosamines in the United States are tobacco smoke, cosmetics, automobile interiors, and cured meats.

Epidemiologic Evidence

Both case-control and cohort studies have evaluated the relationship between smoking and cancer of the brain. In the 26-year follow-up of the U.S. veterans cohort (Hsing et al. 1991), no relationship was observed between smoking and mortality from brain cancer. In a population-based case-control study in Los Angeles County, California, that included 94 women with intracranial gliomas, no relationship was observed between cigarette smoking and the risk of brain cancer (Blowers et al. 1997). In a comparable study from the San Francisco Bay area that included 434 adults with incident glioma, men but not women were at an increased risk of cancer if they had smoked unfiltered cigarettes. Among the men, those who reported using filter-tipped cigarettes had no increase in risks compared with men who had never smoked (RR = 0.8 [95 percent CI, 0.5–1.2]), and those who smoked unfiltered cigarettes had an increased RR of 1.8 (95 percent CI, 0.9–3.4) (Lee et al. 1997). Among the women, an increased risk was not observed, although the prevalence of smoking unfiltered cigarettes was substantially lower. An Australian case-control study also failed to show any relationship between smoking and glioma in women, but did show a suggestive relationship in men (Ryan et al. 1992). On the basis of 416 cases (166 women and 250 men), Hurley and colleagues (1996) reported that men who had smoked had a RR for glioma of 1.64 (95 percent CI, 1.10–2.45) compared with men who had never smoked, while for women who had smoked the RR was 0.99 (95 percent CI, 0.62–1.62) compared with women who had never smoked. In this study, there was no evidence of an increase in risk among either women or men with increased durations of smoking or pack-years of smoking.

Eight other studies, all smaller than those reviewed above, have also failed to find an association between smoking and glioma (Musicco et al. 1982; Ahlbom et al. 1986; Burch et al. 1987; Brownson et al. 1990; Hochberg et al. 1990; El-Zein et al. 1999; Bondy et al. 2001; Zheng et al. 2001). In several of these studies, controls were limited to hospitalized patients—a potential source of bias when evaluating smoking-related risks (Musicco et al. 1982; Burch et al. 1987). Ahlbom and colleagues (1986) studied 78 cases and observed no association between smoking and astrocytoma when using population controls (RR = 1.2 [95 percent CI, 0.6–2.5]). Musicco and colleagues (1982) observed a nonsignificant increase in risk when comparing heavy smokers with persons who had never smoked (RR = 1.5, p = 0.71). Burch and colleagues (1987) compared 215 cases with 215 hospital controls, and observed an overall RR of 1.44 (95 percent CI, 0.94–2.21) comparing smokers of plain cigarettes with

nonsmokers, and a RR of 0.98 (95 percent CI, 0.66–1.46) comparing smokers of filter-tipped cigarettes with nonsmokers. There was a significant increase in risk with an increased amount smoked for those smoking plain cigarettes ($p = 0.026$) but not for those smoking filter-tipped cigarettes ($p = 0.64$).

Evidence Synthesis

Overall, the epidemiologic evidence shows no consistent relationship between smoking and glioma. Duration of smoking, the number of cigarettes smoked per day, and pack-years of smoking have been evaluated in different studies. None of these measures of exposure shows a strong or consistent relationship.

Conclusion

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

Implications

Epidemiologic research using both case-control and cohort designs has not found an association between smoking and brain cancer in adults. Any new studies on this topic will need to have large sample sizes and careful characterizations of the tumors.

Breast Cancer

Breast cancer is the most frequently diagnosed nonskin cancer among women (ACS 2003). In 2003, an estimated 212,600 new cases and 40,200 deaths attributed to breast cancer were expected to occur. From 1996–2000, the average annual age-adjusted population incidence rate of breast cancer per 100,000 in the United States was 140.8 in white women, 121.7 in black women, 97.2 in Asian / Pacific Islander women, 89.8 in Hispanic women, and 58.0 in American Indian /Alaska Native women (Ries et al. 2003). The possibility that cigarette smoking is associated with breast cancer has been a topic of substantial research, given the high prevalence of exposure to this harmful agent, the high incidence of breast cancer, and the relative difficulty of modifying many established breast cancer risk factors.

The relationship between active smoking and breast cancer has been investigated since 1960 (MacMahon and Feinleib 1960) in many large, well-designed epidemiologic studies (Palmer and Rosenberg 1993; Terry and Rohan 2002). Most of these studies have found overall associations close to the null: some RRs for the association with smoking have been modestly inverse, whereas some have been modestly positive. Investigators have hypothesized that smoking may have antiestrogenic effects as well as carcinogenic effects on breast tissue, and thus may exert countervailing influences on breast cancer risks (Palmer and Rosenberg 1993). If both of these effects have a role in breast cancer development, the increase in risk may become apparent only when women are classified according to characteristics related to their susceptibility to the antiestrogenic or carcinogenic effects. In the absence of such stratification, the hypothesized effects of cigarette smoke might be expected to lead to null findings overall in a single study and to inconsistency across studies, depending on the characteristics of the participants.

Conclusions of Previous Surgeon General's Reports

The 2001 Surgeon General's report on women and smoking (USDHHS 2001) reviewed the scientific data on the association between cigarette smoking and breast cancer, concluding that "Thus, active smoking does not appear to appreciably affect breast cancer risk overall. However, several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS[2] exposure affects risk" (p. 217). A more detailed review of the evidence is

[2]ETS = Environmental tobacco smoke.

provided in this section, including evidence on the above three points. Since the 2001 report, IARC has concluded that the evidence is indicative of no association between smoking and breast cancer (IARC 2002).

Biologic Basis

Because smokers have a higher incidence of cancers at sites that do not have direct contact with cigarette smoke, including the cervix, pancreas, and bladder (USDHHS 1982), researchers have hypothesized that constituents of cigarette smoke may reach distant tissues, including breast tissue. Biomarkers have now provided evidence supporting this hypothesis. Mutagens from cigarette smoke have been found in the nipple aspirates of nonlactating women (Petrakis et al. 1980), indicating that mutagenic tobacco smoke components do reach breast tissue. Thus, prolonged exposure to these substances may initiate and promote benign and malignant breast disease. In a small case-only study, Perera and colleagues (1995) found DNA adducts characteristic of cigarette smoke in four out of seven breast tumors from smoking women, but not in any of the tumors from eight nonsmokers. In a larger case-only study, Li and colleagues (1996) similarly found such adducts in breast tissues of all current smokers (17 out of 17) and in some (5 out of 8) former smokers, even 18 years after smoking cessation. They found the same adducts in 4 out of 52 nonsmokers. The data from former smokers suggest that smoking-induced DNA damage might persist for a long time.

Whereas the research described above suggests that breast tissue of smokers is exposed to tobacco-smoke carcinogens, some researchers (MacMahon et al. 1982) have proposed that smokers would have a reduced risk of breast cancer, based on a hypothesis that breast cancer is an estrogen-related disease and that cigarette smoking has antiestrogenic effects. However, the biologic foundations underlying both of the postulated mechanisms of this hypothesis (carcinogenic exposure and antiestrogenic effects) are not firmly established.

Empirical support for the hypothesis that cigarette smoking exerts antiestrogenic effects and therefore might lower the risk for breast cancer comes from several sources, including laboratory studies of rodents and studies of hormones in smokers and nonsmokers. Rats exposed to cigarette smoke develop fewer mammary tumors than do unexposed rats (Davis et al. 1975; Dalbey et al. 1980), although this finding may be the result of differences in weight or survival. Findings from this animal model also are interpreted in light of the uncertain relevance of the mammary tumor model in rodents for breast cancer in humans. For instance, mammary cancer in rats is prolactin-dependent (Kleinberg 1987), and the lower risk of tumors may reflect a lowering of prolactin levels from long-term exposure to tobacco smoke (Ferry et al. 1974; Andersson 1985).

Smoking has also been hypothesized as affecting estrogen levels. Researchers are uncertain about how smoking might affect the biology of estrogen-related events in women not taking oral estrogens. However, several possible mechanisms have been proposed. Polycyclic aromatic hydrocarbons in tobacco smoke may induce cytochrome P-450 enzymes that metabolize sex hormones (Conney 1967; Lu et al. 1972). Michnovicz and colleagues (1986) suggested that smoking increases the 2-hydroxylation of the estradiol metabolic pathway, thus decreasing the availability of active estrogens to tissues. Cigarette smoking leads to an early menopause, and disturbances in estrogen-dependent processes before menopause could be due to a toxic impact on the developing graafian follicle (Mattison 1980). Also, the lower body weight of smokers would result in lower estrone and estradiol levels than nonsmokers of similar age. Finally, smoking increases the levels of the adrenal androgen hormones androstenedione and dihydroepiandrosterone (Baron et al. 1990; Law et al. 1997), which could explain some (but hardly all) of the hormone effects.

Whereas initial comparisons of estrogen levels between smokers and nonsmokers documented differences, more recent studies have generally shown similar levels. Among premenopausal women, studies of urinary excretion of estrogens have tended to yield different findings from studies of plasma levels of reproductive hormones. MacMahon and colleagues (1982) were among the first to examine estrogens and smoking, and reported that premenopausal women who smoked had lower urinary excretions of estrone, estriol, and estradiol during the luteal phase of the menstrual cycle than women who had never smoked. Former smokers did not manifest this pattern, however, nor were there differences in urinary excretion during the follicular phase of the menstrual cycle. Michnovicz and colleagues (1986) found results similar to those of MacMahon and colleagues for both the luteal and follicular phases. In another study of premenopausal women, Westhoff and colleagues (1996) found that smokers had, on average, lower levels of midcycle and luteal-phase urinary estradiol levels than nonsmokers.

However, comparisons of endogenous serum estrogen levels between smokers and nonsmokers have clearly shown that among both premenopausal and postmenopausal women smokers do not have lower levels of the major estrogens than nonsmokers (Baron et al. 1990; Law et al. 1997; USDHHS 2001). Three studies of premenopausal women (Longcope and Johnston 1988; Key et al. 1991; Thomas et al. 1993) found no differences in plasma concentrations of reproductive hormones between smokers and nonsmokers. Although the study conducted by Thomas and colleagues (1993) consisted of a small number of women (26 smokers, 24 nonsmokers), it was more detailed than other similar studies. These researchers took multiple blood samples from participants over the course of a menstrual cycle, equally timed from the date of the previous cycle, and also examined the effects of smoking on luteinizing hormone pulsatility, enabling them to explore possible differences in the length of the follicular and luteal phases between smokers and nonsmokers. Thomas and colleagues (1993) concluded that smoking did not result in major alterations in cyclicity; secretion of gonadotropins, estradiol, and progesterone; metabolism of estradiol; or secretion of androgens. They noted that these data confirm those of Longcope and Johnston (1988) and Key and colleagues (1991), suggesting that the antiestrogenic properties of cigarette smoking act through mechanisms other than alterations in hormone levels.

Several studies have examined hormone levels in postmenopausal women (Friedman et al. 1987; Trichopoulos et al. 1987a; Khaw et al. 1988; Longcope and Johnston 1988; Kabat et al. 1997). Again, some studies measured hormone levels in urine; others measured levels in plasma. None found lower levels of circulating estrogens among women who smoked compared with women who did not smoke. It is possible that a failure to detect differences in estrogen levels between smoking and nonsmoking women who are postmenopausal could be due to limitations in measurement, because estrogen levels in postmenopausal women are often at the limits of detection. Differences in postmenopausal estrogen levels between smokers and nonsmokers could be due, at least in part, to body fat levels. Smokers tend to be leaner than nonsmokers, and in postmenopausal women, an important source of estrogen is the peripheral conversion of androgen precursors that occurs in fat cells.

The interpretation of differences in estrogen levels between smokers and nonsmokers, and relating them to differences in the risk of breast cancer, is complex because the effects of specific estrogens likely vary by organ site, and smoking may affect only specific estrogens (Rohan and Baron 1989). For example, Michnovicz and colleagues (1986) proposed that smoking may shift the metabolism of estrone and estradiol toward the production of catechol estrogens. This shift would leave estrogen and estradiol concentrations unchanged, but would increase catechol estrogen production at the expense of estriol. If the breast were equally sensitive to estriol and catechol estrogens, this change would not affect breast cancer risk, although it would affect organs that react differently to estriol and catechol estrogens. The estrogenic hormone dependence of breast cancer is not well defined. It is clear, however, that the estrogen dependence of breast cancer is not as marked as that of endometrial cancer, and any antiestrogenic effects of smoking might be unimportant with respect to this weaker estrogen-related disease (Rohan and Baron 1989).

Epidemiologic Evidence

This section discusses all studies of active and passive smoking in relation to breast cancer that were considered in a 1993 epidemiologic review (Palmer and Rosenberg 1993), and any additional epidemiologic studies on this topic published from September 1992 to the end of 1999, identified through a MEDLINE search. Several additional relevant reports beyond this inclusive review are also cited. A review of the observational epidemiologic literature was then used to identify articles in the fields of biology, pathology, and endocrinology that examined the biologic basis for potential positive and negative causal links between exposure to cigarette smoking and breast carcinogenesis.

Cigarette Smoking and Breast Cancer Risk

Palmer and Rosenberg (1993) reviewed all of the studies on smoking and breast cancer published in the scientific literature before September 1992 (Tables 2.36, 2.37, 2.38, and 2.39). They excluded studies of prevalent breast cancer, studies providing insufficient methodologic detail (e.g., those lacking CIs or definitions of the reference categories [all of the studies excluded for this reason had fewer than 300 cases]), and case-control studies in which patients with smoking-related diagnoses were included in the control series. These studies, with likely overestimates of the prevalence of smoking in the general population represented by the control groups, would have found spuriously reduced RR estimates if smoking truly did increase the risk for breast cancer. For each of the 19 studies deemed

informative, Palmer and Rosenberg (1993) provided detailed qualitative summaries in the four tables in their review, noting where the data were available in individual studies, RR estimates for former and current smokers overall stratified by age at commencement of smoking, and for the highest categories of smoking intensity or duration.

In four case-control studies included in this review (Rosenberg et al. 1984; Baron et al. 1986; Stockwell and Lyman 1987; Palmer et al. 1991), controls were selected from among hospital patients or cancer registry patients, and only patients with conditions judged to be unrelated to cigarette smoking were included (Table 2.36). All of these studies were large (all had more than 1,700 cases; one [Stockwell and Lyman 1987] had more than 5,000 cases), and controlled for many of the known risk factors for breast cancer including age at menarche, age at birth of first child, and parity. Two of the four studies also controlled for alcohol consumption, obesity, menopausal status, and other potential confounding factors as they are risk factors for breast cancer and are associated with smoking (Rosenberg et al. 1984; Palmer et al. 1991). Relative risk estimates for the heaviest current smoking categories (i.e., one or more packs per day) were close to 1.0, ranging from 0.93 to 1.3. None of these four studies showed a dose-response gradient of risk with the number of cigarettes smoked per day.

In seven other case-control studies (O'Connell et al. 1987; Adami et al. 1988; Rohan and Baron 1989; Chu et al. 1990; Ewertz 1990, 1992; Palmer et al. 1991; Field et al. 1992), the general community was used as a source of controls (Table 2.37). All of these studies controlled for major reproductive risk factors; some also controlled for alcohol consumption and obesity. The estimated RR for heavy smoking was 0.57 in the smallest study (O'Connell et al. 1987); in the other studies, estimates ranged from 0.75 to 1.59, with no evidence of dose-response relationships.

Three studies of screened populations (Brinton et al. 1986; Meara et al. 1989; Schechter et al. 1989) compared women with incident cases (detected after the first screening) of breast cancer with women who were screened the same number of times without any detection of breast cancer (Table 2.38). All of the studies adjusted for reproductive risk factors and obesity, and one study (Meara et al. 1989) also adjusted for alcohol consumption. These studies generally found ORs between 1.2 and 1.3 for heavy smokers and long-term smokers, compared with women who had never smoked. Meara and colleagues (1989) found higher ORs but CIs were wide.

All five cohort studies (Table 2.39) (Hiatt and Fireman 1986; Hiatt et al. 1988; London et al. 1989; Schatzkin et al. 1989; Vatten and Kvinnsland 1990) controlled for obesity and alcohol consumption in addition to reproductive factors. Relative risk estimates for the heaviest current smoking categories ranged from 0.86 to 1.19. The largest study (London et al. 1989), which assessed repeated measures of smoking during follow-up, found that the RR comparing those currently smoking 25 or more cigarettes per day with women who had never smoked was 1.02.

Palmer and Rosenberg (1993) concluded their 1993 review by stating that the existing body of epidemiologic evidence neither supported the hypothesis that cigarette smoking has a net effect of reducing the risk of breast cancer nor supported the hypothesis that cigarette smoking increases the risk of breast cancer, even among specific subgroups of women who might be assumed to be at an especially high risk from the carcinogenic effects of smoking, such as heavy smokers who began smoking as teenagers.

Since 1993, additional large, well-designed case-control studies of smoking and breast cancer (Table 2.40) have provided detailed analyses of the amount smoked, duration of smoking, and (in two of the three studies) years since smoking cessation. The largest study (Baron et al. 1996) is a population-based, case-control study with 6,888 cases and 9,529 controls from Maine, Massachusetts, New Hampshire, and Wisconsin, conducted from 1988–1991. This study investigated the effects of smoking among women at very high levels of exposure: heavy smokers, long-term smokers, and those who began smoking very early in life. The current understanding of the processes of breast cell development and differentiation has led some scientists to hypothesize that the timing of exposure to tobacco smoke relative to the stage of breast tissue development may be an important determinant of susceptibility to the carcinogenic effects of smoking. Exposure at very young ages and before a first pregnancy may more strongly increase the risk of breast cancer than exposure at older ages, because breast cells are undifferentiated before pregnancy and are therefore believed to be more susceptible to mutagenesis.

In this large study, the number of cigarettes usually smoked per day was not related to risk for breast cancer. Very heavy smokers (those who smoked >2 packs per day) were not at a higher risk than lifetime nonsmokers; the OR was 1.09 (95 percent CI, 0.79–1.49). Duration of smoking was also unassociated with risk; among women who had smoked cigarettes for more

than 50 years compared with women who had never smoked, the OR was 1.07 (95 percent CI, 0.84–1.37). Risk of breast cancer was also not related to the duration of smoking among heavy smokers (>2 packs per day), to the average amount smoked per day among long-term smokers (>20 years), or to pack-years of smoking. There was no overall relationship between age at initiation of smoking and risk of breast cancer. Women who began smoking at an early age (before 15 years of age) were not at an increased risk compared with women who had never smoked; the OR was 1.13 (95 percent CI, 0.97–1.31). This finding was true even among women who began smoking at an early age and who usually smoked more than 20 cigarettes per day (OR = 1.04 [95 percent CI, 0.81–1.33]). No evidence was found of an effect of smoking within subgroups of the study population. The ORs for current and former smokers within high- and low-risk strata for the various covariates, including menopausal status, family history status, history of benign breast disease, and alcohol intake, were all close to 1.0. Thus, in this large population-based study, the researchers found little evidence that cigarette smoking either increases or decreases the risk for breast cancer. Neither early age at smoking initiation, heavy smoking, nor long-term smoking demonstrated an association with an altered risk. This study had several important methodologic strengths that enhanced the validity of the findings. First, the large sample size permitted estimates of the effects of higher exposures with considerable precision. Second, the population-based design of the study, together with a high response rate (>80 percent for both cases and controls), made major response biases unlikely. Finally, substantial confounding of the findings is unlikely, because the RR estimates presented by Baron and colleagues (1996) were adjusted for the main known breast cancer risk factors, with little change over those adjusted only for the matching factors of age and geographic area.

In 1998, Gammon and colleagues published results from another large population-based, case-control study of women under the age of 55 years. This study consisted of 2,199 cases and 2,009 controls surveyed during 1990–1992 from central New Jersey; Seattle, Washington; and Atlanta, Georgia. The objective was similar to that of Baron and colleagues (1996): to examine the effects of smoking on the risk for breast cancer among women at extreme exposure levels, those who were heavy smokers as teenagers or those who were long-term smokers. Similar to Baron and colleagues, Gammon and colleagues (1998) found little evidence for increased breast cancer risk associated with smoking in their large study. Risk was significantly reduced among current smokers who reported smoking for more than 21 years (OR = 0.70 [95 percent CI, 0.52–0.94]), compared with women who had never smoked. Risk was also reduced for women who began smoking at 15 years of age and younger among both current smokers (OR = 0.59 [95 percent CI, 0.41–0.85]) and former smokers (OR = 0.76 [95 percent CI, 0.50–1.15]). Gammon and colleagues found no significant effect modification by selected hormone-related characteristics including menopausal status, oral contraceptive use, hormone replacement therapy use, body size as an adult, and usual alcohol consumption. They also found no significant heterogeneity in breast cancer risk in relation to the age at beginning smoking.

In a national case-control study of breast cancer in the United Kingdom conducted among young women aged 35 years and younger, Smith and colleagues (1994) found no effects of cigarette smoking on the risk for breast cancer. The RR comparing women who had smoked for 10 or more years with women who had never smoked was 1.0 (95 percent CI, 0.79–1.25), whereas the RR comparing women who had started smoking at 16 years of age or younger was 1.11 (95 percent CI, 0.87–1.43).

The most recent combined analyses on smoking and breast cancer were reported in 2002 by the Collaborative Group on Hormonal Factors in Breast Cancer (2002). Data were analyzed at the individual level from 53 studies, including 58,515 cases and 95,067 controls; information on both tobacco and alcohol was included in all of these studies. The analysis of the risk associated with smoking was limited to the 22,255 cases and 40,832 controls who reported drinking no alcohol. Compared with lifetime nonsmokers, the pooled RR for breast cancer was 0.99 for current smokers and 1.03 for former smokers. Only one study found a significantly increased risk (Figure 2.7).

In conclusion, hypotheses that women with higher levels of exposure to cigarette smoking (i.e., heavy smokers and those who have been smoking since an early age) would have elevated risks of breast cancer have not been supported by data from large studies. The weight of the epidemiologic evidence supports the conclusion that smoking is not associated with breast cancer risk. This null relationship is consistent with the two hypothesized mechanisms, antiestrogenic effects and carcinogenic exposures, that imply countervailing consequences of smoking that both increase and decrease the risk for breast cancer.

Genotype-Smoking Interactions

Recent advances in molecular biology and genetics, in terms of both scientific understanding of and technological applications to large populations, have enabled epidemiologists to examine the relationship between smoking and breast cancer in subgroups of women hypothesized to differ with respect to genetic susceptibility to the carcinogenic or antiestrogenic effects of cigarette smoke. Some of the genes involved in the metabolism of carcinogens play a role in the risks for various human cancers, including breast cancer, and reviews of the growing literature on these genes, known as metabolic susceptibility genes, have been published (Idle et al. 1992; Daly et al. 1994; Hirvonen 1995; Raunio et al. 1995; Rothman 1995; Vineis 1995). By definition, these genes function only in the context of interactions with the environment, because the substrates of their gene products are xenobiotic chemicals (foreign to the biologic system) or their metabolites (Garte et al. 1997).

Cigarette smoking results in exposure to aryl aromatic amine carcinogens that are metabolized and detoxified by the cytochrome P-4501A2 (*CYP1A2*) and *NAT1* and *NAT2* genes. The *NAT2* gene has four major alleles (Lin et al. 1993; Hunter et al. 1997). Persons who are homozygous for any combination of the three slow acetylator alleles have a slow acetylation phenotype (slow acetylators), whereas those who have at least one copy of the rapid acetylator allele have a rapid acetylation phenotype (rapid acetylators) (Lin et al. 1993; Hunter et al. 1997). Women who are rapid acetylators are hypothesized to be less vulnerable to potential carcinogenic effects on the breast from smoking than women who are slow acetylators, because members of the former group more rapidly metabolize or "clear" the toxic agents from their tissues. Approximately 50 percent of whites and a lower proportion of African Americans inherit a polymorphism in the *NAT2* gene that leads to decreased acetylator activity (i.e., *NAT2*-"slow" genotype) (Bell et al. 1993; Lin 1996). The *NAT1* enzyme participates in *N*-acetylation of a variety of carcinogenic arylamines, as does the *NAT2* enzyme. However, the link between *NAT1* alleles and enzyme function has not been directly established, and investigations are ongoing to determine the functional importance of *NAT1* gene variants (Deitz et al. 1997; Grant et al. 1997; Hughes et al. 1998; Millikan et al. 1998).

In a case-control study of 304 cases and 327 controls, Ambrosone and colleagues (1996) found that among premenopausal women, being a slow acetylator did not strengthen the effect of smoking on the risk for breast cancer. In fact, risk associated with smoking increased more sharply among rapid acetylators than among slow acetylators, although all ORs were imprecise. Among postmenopausal women, Ambrosone and colleagues (1996) found an association between smoking and breast cancer risk only among women with the *NAT2*-slow genotype. Among women who were slow acetylators, those in the highest category of number of cigarettes smoked per day (>20) were at an increased risk for breast cancer (OR = 4.4 [95 percent CI, 1.3–14.8]), but there were only 11 cases and 5 controls in this high-exposure stratum. The response rates among cases and controls were low, raising concerns about selection biases with regard to smoking status. These methodologic problems may explain, in part, why the finding of an interaction between smoking and slow acetylator genotype has not been replicated in subsequent larger studies. Results from a case-control study nested within the Nurses Health Study cohort with 466 incident cases and 466 matched controls (Hunter et al. 1997) suggest that current smoking was associated with a slight increase in the risk for breast cancer among women with the *NAT2* slow genotype, but this same slight increase was also observed among women with the rapid acetylator genotype. The OR comparing currently smoking women with the slow acetylator genotype to women with the rapid acetylator genotype who had never smoked was 1.4 (95 percent CI, 0.7–2.6); the OR comparing currently smoking women with the rapid acetylator genotype to women who had never smoked with this same "low risk" genotype was 1.2, thus providing no evidence of a genotype-smoking interaction.

To examine the specific hypothesis that smoking before a first pregnancy is an especially strong risk factor for breast cancer, Hunter and colleagues (1997) limited analyses to parous women with complete information on early-life smoking. Women with the rapid acetylator genotype who ever smoked before their first pregnancy were at an increased risk relative to women with the rapid acetylator genotype who had never smoked (OR = 1.7 [95 percent CI, 1.0–2.6]), but there was no dose-response relationship with the duration of smoking before a first pregnancy. Similarly, among women with the slow acetylator genotype, there was an increased risk for breast cancer among women who had smoked for one to five years before their first pregnancy (OR = 2.0 [95 percent CI, 1.1–3.8]), relative to the reference group of women with the rapid acetylator genotype who had never smoked, but the risk of breast cancer was not increased among women who had smoked for five or more years before their first pregnancy (OR = 0.9 [95 percent CI, 0.6–1.5]). Again, there

was no evidence for a genotype-smoking interaction in this analysis.

The Carolina Breast Cancer Study, a population-based case-control study of breast cancer among white and African American women living in North Carolina, found no main effect of smoking (OR = 1.0 for current smokers [95 percent CI, 0.7–1.4], and OR = 1.3 for former smokers [95 percent CI, 0.9–1.8], both relative to lifetime nonsmokers) (Millikan et al. 1998). These results were not modified by the presence of either the *NAT2* or the *NAT1* gene. Among postmenopausal women, those who had smoked within the past three years and had the *NAT1*10* genotype had an OR of 9.0 (95 percent CI, 1.9–41.8) and those with the *NAT2* rapid genotype had an OR of 2.8 (95 percent CI, 0.4–8.0) compared with nonsmokers.

Other research into potential gene-environment interactions has considered genes related to polycyclic aromatic hydrocarbons, which are carcinogens found in cigarette smoke. The *CYP1A1* gene product is involved in the metabolism of these hydrocarbons and is polymorphic, although the exact functional importance of the polymorphisms is unclear (Cosma et al. 1993; Kawajiri et al. 1993; Crofts et al. 1994; Landi et al. 1994; Wedlund et al. 1994; Jacquet et al. 1996; Zhang et al. 1996; Persson et al. 1997; Ishibe et al. 1998). Studies of potential gene-environment interactions have been small and results have been inconsistent. Ambrosone and colleagues (1995) found an interaction between smoking and the *CYP1A1* genotype only among light smokers (for whom the OR comparing the high-risk to low-risk genotype was 5.22 [95 percent CI, 1.16–23.56]); however, among heavy smokers, the high-risk genotype was not associated with an increased risk (OR = 0.86 [95 percent CI, 0.24–3.09]). This somewhat contradictory finding (that no increased risk was found in the subgroup of heavy smokers, despite an increase among light smokers) was based on a small number of cases and noncases in the relevant strata; for instance, the OR of 5.22 was based on only seven cases and three controls in the high-risk genotype stratum.

To date, the largest study of the *CYP1A1* genotype, smoking, and a risk for breast cancer was conducted among 900 women (cases and controls combined) nested within the Nurses Health Study cohort (Ishibe et al. 1998). In this study, current smokers with a high-risk variant at the *MspI* nucleotide had an OR of 7.36 (95 percent CI, 1.39–39.0) relative to lifetime nonsmokers with a low-risk variant; the corresponding OR for a variant at the exon 7 nucleotide was 1.51 (95 percent CI, 0.55–4.13). The OR of 7.36 was based on nine cases and two controls in the high-risk stratum. On the basis of the low prevalences of the high-risk genotypes in *CYP1A1*, Ishibe and colleagues (1998) estimated that only 2.5 percent of breast cancer cases that occurred in the Nurses Health Study cohort over a five-year period could be attributed to the combination of cigarette smoking and a high-risk genotype.

The gene *GSTM1* is also involved in the metabolism of carcinogens, including polycyclic aromatic hydrocarbons (Mannervik and Danielson 1988; Nebert 1991). Ambrosone and colleagues (1995) found that the null effect of cigarette smoking was not modified by the high-risk *GSTM1* genotype.

Scientists are continuing to pursue research into how genetic factors might interact with cigarette smoking to determine a risk for breast cancer, but so far few clear patterns have emerged. Currently, it is not possible to differentiate subgroups of women who are genetically "susceptible" to the carcinogenic effects of cigarette smoking from those women who are not.

Brunet and colleagues (1998) have pursued a different line of genetic research, speculating that the antiestrogenic effects of smoking might be especially potent in women at very high risk of breast cancer; that is, those who carry mutations in the *BRCA1* or *BRCA2* gene. It has been estimated that the risk for breast cancer associated with mutations in either gene exceeds 80 percent by the time a carrier reaches 70 years of age (Easton et al. 1995; Tonin et al. 1995), although some researchers have estimated the risk to be lower (Struewing et al. 1997). Some factors that are believed to influence penetrance (i.e., frequency of expression of a genotype) include parity (Narod et al. 1995) and, with respect to the *BRCA2* gene, the position of the mutation (Gayther et al. 1997). Brunet and colleagues (1998) speculated that cigarette smoking, because of its hypothesized antiestrogenic effects, also may be associated with a lower penetrance. In their case-control study of women in Canada who were carriers of *BRCA1* or *BRCA2* gene mutations (186 cases, 186 controls), the risk of breast cancer in smokers was about half of that in nonsmokers. The reduction in risk associated with smoking was significant for a carrier of *BRCA1* mutations who had smoked the equivalent of four or more pack-years in her life (OR = 0.47 [95 percent CI, 0.26–0.86]). For *BRCA2* gene carriers the magnitude of reduction was somewhat greater (OR = 0.39 [95 percent CI, 0.10–1.49]). There was evidence of a dose-response trend: the degree of breast cancer protection associated with cigarette smoking increased with the number of pack-years smoked. The OR was 0.65 for women with four or fewer pack-years of smoking and 0.46 for those with more than four pack-years of smoking.

Contrasting findings were reported by Couch and colleagues (2001) who carried out a retrospective cohort study of women from high-risk breast cancer families. Of the sisters and daughters in the families, those who had smoked had an increased risk of breast cancer compared with those who had never smoked (RR = 2.4 [95 percent CI, 1.2–5.1]). These studies differ substantially in design, and the case-control approach of Brunet and colleagues (1998) is subject to several potential sources of bias (Baron and Haile 1998).

Passive Smoking, Active Smoking, and Breast Cancer Risk

The involuntary inhalation of tobacco smoke by nonsmokers has also been examined as a risk factor for breast cancer. Exposure to secondhand smoke and breast cancer risk has been considered relevant to understanding active smoking and breast cancer risk because passive exposure involves a lower dose of the same agents inhaled by the active smoker. The literature on passive smoking and breast cancer was reviewed in the 2001 Surgeon General's report with the conclusion that "the totality of the evidence does not support an association between smoking and the risk for breast cancer" (USDHHS 2001, p. 13). Recently, epidemiologists have also investigated the relationship between active and passive exposures to cigarette smoke and breast cancer, and attempted to use a truly "unexposed" reference group; that is, women who have been neither active smokers nor exposed passively to another's cigarette smoke. According to some researchers (Morabia et al. 1996), only by comparison with such a truly unexposed group will the effects of active smoking be assessed without bias.

The studies of passive smoking and breast cancer contrast somewhat with the findings of the far larger number of studies of active smoking that are consistent in showing no relationship of active smoking with breast cancer. Morabia and colleagues (1996) hypothesized that this apparent contradiction stemmed from the failure of most studies to separate passive smokers from the "unexposed" reference group when assessing the effects of active smoking. They tested this hypothesis in a population-based, case-control study conducted among women living in Geneva, Switzerland. The researchers obtained a detailed lifetime history of exposure to active and passive smoking from all participants, and defined their unexposed reference group as those women never regularly exposed to either passive or active smoking. Passive smokers were women who reported having been exposed to secondhand smoke at least one hour per day for at least 12 consecutive months during their lifetime.

The study included 244 cases and 1,032 controls, with 126 cases and 620 controls who were never active smokers. Among these never active smokers, only 28 cases and 241 controls were also never passive smokers, forming the referent "unexposed" group. The ORs comparing ever active smokers with the referent group were 2.2 for smoking an average of 1 to 9 cigarettes per day, 2.7 for 10 to 19 cigarettes per day, and 4.6 for 20 or more cigarettes per day. Among current active smokers the dose-response trend was even stronger. The ORs did not vary in magnitude when women were stratified according to whether they began smoking before or after their first pregnancy. To examine the effect of removing passive smokers from the reference group, Morabia and colleagues (1996) computed the ORs after considering all never active smokers (including those exposed to secondhand smoke) as the reference group, as in most other studies. The ORs corresponding to the three categories of active smoking given above were reduced in magnitude from 2.2, 2.7, and 4.6 to 1.2, 1.7, and 1.9, respectively. Using this same reference group, Morabia and colleagues (1996) also found an association of breast cancer risk with passive smoking.

A caution that must be raised in reference to this study relates to potential confounding. In this study of women living in Geneva, Switzerland, those with a higher formal education smoked more than women with lower educational levels, unlike the situation in the United States where the prevalence of smoking is now higher in lower socioeconomic groups. Women of a higher socioeconomic status tend to have higher risks for breast cancer because of a higher prevalence of reproductive risk factors (e.g., later age at first birth and lower parity). Thus the findings of elevated risks associated with active and passive smoking in this study of Swiss women could be confounded, in part, by the known reproductive risk factors. Although Morabia and colleagues (1996) controlled for some of these known factors (e.g., age at menarche and at first live birth), as well as for family history of breast cancer, body mass index, and alcohol consumption, there may have been residual confounding because of the control for factors in relatively crude categories and the omission of some factors from the model (e.g., parity, postmenopausal hormone use, and age at menopause). Failure to fully adjust for the higher risks associated with a higher socioeconomic status in this study could explain, in part, the relatively high ORs comparing active smokers and the unexposed control group.

Cigarette Smoking and Breast Cancer Hormone Receptor Status

It is not yet clear if breast cancers with a different hormone receptor status represent etiologically distinct forms of the disease with different risk factor profiles. Researchers have hypothesized that breast cancer tumors that have both estrogen and progesterone receptors (ER-positive / PR-positive) are most closely related to risk factors that are likely mediated by endogenous hormones, whereas tumors without these receptors (ER-negative / PR-negative) would be unrelated to these risk factors (Kelsey et al. 1993; Potter et al. 1995). Receptor status-discordant tumors might exhibit intermediate risk factor profiles. It is not clear from this hypothesis, however, whether smoking, because of its antiestrogenic properties, should decrease the risk of ER-positive / PR-positive tumors, increase the risk of ER-negative / PR-negative tumors, or do both. Findings have been inconsistent.

Several studies have examined whether smoking increases the risk of breast cancers with a particular ER status. A case-control study of Japanese women (1,154 cases, 21,714 controls) found a slightly elevated OR for all breast cancers combined associated with ever smoking (Yoo et al. 1997). This OR elevation was confined to PR-positive tumors (OR = 1.73 [95 percent CI, 1.22–2.45]) and was not observed in PR-negative tumors (OR = 1.06 [95 percent CI, 0.73–1.54]). In this study, there was no difference in estrogen receptor status (OR = 1.42 for ER-positive tumors, 1.33 for ER-negative tumors). However, estrogen receptor status was known for only 40 percent of the cases, and progesterone receptor status was known for only 39 percent of the cases.

In a cohort study reported by London and colleagues (1989), heavy smoking was associated with a small increase in the risk of ER-positive tumors (OR = 1.38 [95 percent CI, 1.04–1.84]). Smoking was not associated with either ER-positive or ER-negative tumors in a case-control analysis by McTiernan and colleagues (1986). In another study, researchers found an increased risk of ER-negative tumors among smokers (Cooper et al. 1989).

Each of the above-cited studies examined active smoking in relation to ER status, without removing passive smokers from the reference group (of lifetime nonsmokers). Morabia and colleagues (1998b) examined the relationship between passive smoking, active smoking, and ER status in their previously described case-control study of women in Geneva, Switzerland, again using a reference group of never active, never passive smokers. They divided smokers into three mutually exclusive categories: ever passive, ever active with fewer than 20 cigarettes per day on average, and ever active with 20 or more cigarettes per day on average. They found elevated ORs for both ER-negative and ER-positive tumors in each of the three smoking categories, relative to the reference group. The ORs were slightly higher for the ER-negative tumors, but the numbers of ER-negative cases in the various smoking strata were small, and thus the ORs were imprecise.

Cigarette Smoking and Breast Cancer Mortality

All of the previously discussed studies have examined the relationship between cigarette smoking and breast cancer incidence. Calle and colleagues (1994) examined smoking as a predictor of breast cancer mortality in CPS-II. During the six-year follow-up period, these researchers found that women who were current smokers at baseline were more likely to die of breast cancer than lifetime nonsmokers (RR = 1.26 [95 percent CI, 1.05–1.50]), whereas former smokers were slightly less likely to die of breast cancer than lifetime nonsmokers (RR = 0.85 [95 percent CI, 0.70–1.03]). The association of current smoking with risk for fatal breast cancer increased with a greater number of cigarettes smoked per day, as well as with the total number of years of smoking. The ORs for 1 to 9, 10 to 19, 20 to 29, 30 to 39, and 40 or more cigarettes smoked per day were 0.58, 1.19, 1.32, 1.44, and 1.74, respectively, all relative to lifetime nonsmokers. The ORs for breast cancer mortality for less than 10, 10 to 19, 20 to 29, 30 to 39, and 40 or more years of smoking were 1.10, 1.04, 1.10, 1.26, and 1.38, respectively, again all relative to lifetime nonsmokers.

Because the weight of the epidemiologic evidence does not support a strong etiologic relationship between smoking and breast cancer incidence, these findings on breast cancer mortality likely reflect a poorer survival experience among smokers who develop breast cancer, which might be expected for several reasons. First, smokers are more likely than nonsmokers to have comorbid conditions, such as respiratory and cardiovascular diseases, that could deleteriously affect survival. Second, smokers do not seek a screening mammography as often as nonsmokers, and therefore their disease might tend to be diagnosed at later stages. Data from the 1987 National Health Interview Survey Cancer Control Supplement indicate that current smokers are less likely than lifetime nonsmokers to receive screening mammograms and that the screening disadvantage is greatest among heavy smokers. In contrast, former smokers are more likely to receive

mammograms than lifetime nonsmokers (Calle et al. 1994). These differences in screening behavior support the possibility that the results observed by Calle and colleagues (1994) are due in part to later diagnoses among current, and especially heavy, smokers and to earlier diagnoses among former smokers.

Evidence Synthesis

Since the 1960s many large, well-conducted studies of the relationship between active cigarette smoking and breast cancer have been completed, as have laboratory studies of the relationship between smoking and ovarian hormone levels. The epidemiologic evidence provides no support for an overall relationship, neither causal nor protective, between active cigarette smoking and breast cancer. The studies have been conducted in diverse populations around the world and involved thousands of participants.

Evidence for an increased susceptibility to the carcinogenic effects of cigarette smoking on the breast in subgroups of women (e.g., defined by genotype, menopausal status, age at starting smoking) has been inconsistent. The inconsistency in RRs for subgroup analyses among the various studies is not surprising given the small numbers of women in the relevant strata of many of these analyses. For some subgroups, an initial finding from one study regarding an elevated risk in a particular subgroup of women (e.g., Ambrosone and colleagues' 1996 report of a strong positive relationship between smoking and breast cancer among women with the slow acetylator *NAT* genotype) has not been replicated in subsequent studies. Similarly, Brunet and colleagues (1998) observed that women with mutations in *BRCA1* or *BRCA2* genes who smoked had a significantly lower risk of breast cancer than women with such mutations who did not smoke, but this observation was not replicated in the study conducted by Couch and colleagues (2001).

In light of the evidence showing no overall association between active smoking and breast cancer, passive smoking would also be expected not to be associated with breast cancer risks, assuming that the same mechanisms apply to both active and passive smoking. Although most studies of smoking and breast cancer did not remove passive-only smokers from the reference group of lifetime nonsmokers (Morabia and colleagues [1996] were the first to do so), one would still expect to find a dose-response gradient in analyses of active smoking because active smokers are also the most heavily exposed passive smokers. The hypothesis put forth by Morabia and colleagues (1996, 1998a) and Wells (1991, 1998), that the true (positive) relationship between active smoking and breast cancer will become apparent only when passive-only smokers are removed from the reference group, implicitly assumes that the effects of passive-only smoking are at least as great as those from active smoking. Consider a hypothetical, but realistic, study that shows a RR of 1.0 comparing current smokers who have smoked for 10 or more years and the reference group of never active smokers. If the argument is made that the "true" RR is 2.0, and that it will not become apparent unless passive-only smokers are removed from the reference group, then there is an assumption that the RR of current smokers who have smoked 10 or more years compared with passive-only smokers is 1.0, or, equivalently, that the risk conveyed by passive smoking alone is equal to that conveyed by long-term active smoking. This comparability of risks seems implausible on a biologic basis.

Conclusions

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

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

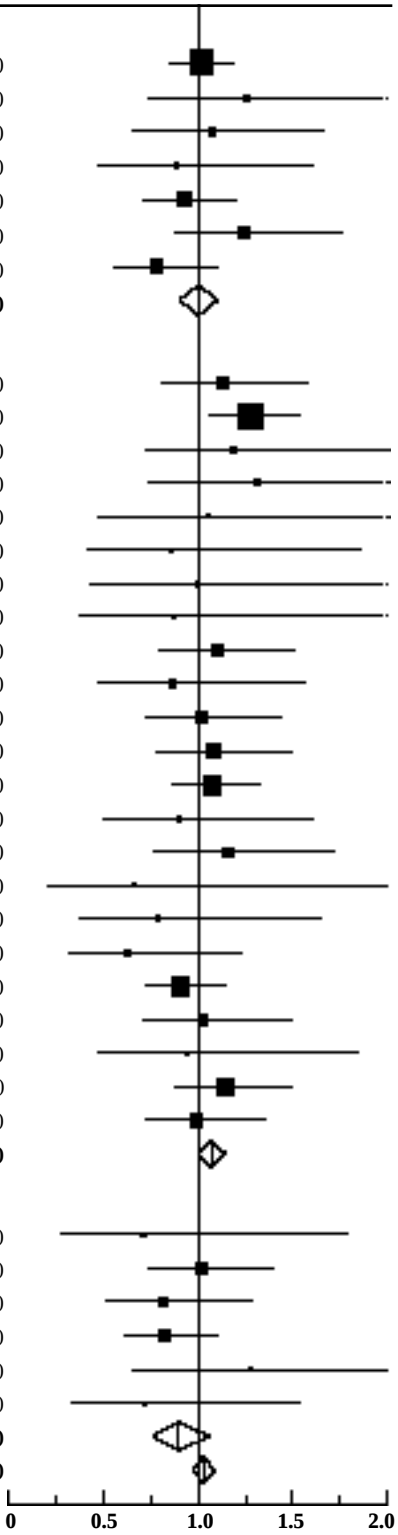
3. Whether women who are at a very high risk of breast cancer because of mutations in *BRCA1* or *BRCA2* genes can lower their risks by smoking has not been established.

Implications

In contrast to evidence for many other chronic diseases, epidemiologic evidence suggests that cigarette smoking does not contribute to the burden of breast cancer. It would be false to tell women that they will prevent breast cancer if they quit smoking. Similarly, no woman should ever be advised to smoke to lower her breast cancer risk, given the lack of evidence and the extremely high health risks for other diseases known to be associated with smoking.

Figure 2.7 Results on tobacco consumption and breast cancer in women who reported drinking no alcohol

Study (country)	Number of cases/controls	% ever smoked (cases/controls)	Relative risk of breast cancer in ever smokers vs. never smokers (SE)*
Cohort studies:			
Willett et al. 1987 (USA)	1,224 / 5,599	49 / 49	1.01 (0.07)
Friedenreich et al. 1993 (Canada)	181 / 662	35 / 35	1.25 (0.23)
Feigelson et al. 2001 (USA)	213 / 922	34 / 33	1.07 (0.19)
van den Brandt et al. 1995 (Netherlands)	119 / 504	27 / 30	0.89 (0.23)
Gapstur et al. 1992 (USA)	679 / 2,765	25 / 26	0.93 (0.10)
Million Women Study Collaborative Group 1999 (UK)	324 / 1,291	50 / 44	1.24 (0.15)
Other‡	1,923 / 7,655	4 / 5	0.78 (0.12)
All cohort studies	**4,663/19,398**	**25/26**	**1.00 (0.04)**
Case-control, population controls:			
Harvey et al. 1987 (USA)	649 / 872	29 / 26	1.12 (0.14)
Chu et al. 1989 (USA)	1,817 / 1,821	49 / 43	1.28 (0.08)
Enger et al. 1999 (USA)	336 / 317	50 / 48	1.18 (0.20)
Siskind et al. 1989 (Australia)	248 / 514	32 / 29	1.31 (0.26)
Rohan and McMichael 1988 (Australia)	188 / 213	35 / 32	1.06 (0.31)
Ewertz 1991 (Denmark)	227 / 198	59 / 57	0.88 (0.27)
Bowlin et al. 1997 (USA)	153 / 208	37 / 34	0.99 (0.32)
Rosenberg et al. 1990 (Canada)	114 / 211	40 / 42	0.88 (0.31)
Sneyd et al. 1991 (New Zealand)	538 / 1,058	43 / 41	1.09 (0.13)
White et al. 1994 (USA)	211 / 286	42 / 42	0.87 (0.21)
Longnecker et al. 1995b (USA)	578 / 590	53 / 52	1.02 (0.13)
Smith et al. 1994 (UK)	655 / 662	47 / 45	1.08 (0.13)
Longnecker et al. 1995a (USA)	1,507 / 2,247	39 / 39	1.07 (0.09)
Rookus and van Leeuwen 1994 (Netherlands)	247 / 247	52 / 51	0.90 (0.21)
Yang et al. 1992 (Canada)	505 / 517	48 / 44	1.15 (0.17)
Primic-Zakelj et al. 1995 (Slovenia)	115 / 128	29 / 30	0.67 (0.38)
Rossing et al. 1996 (USA)	152 / 181	52 / 49	0.79 (0.26)
Swanson et al. 1997 (USA)	353 / 241	59 / 68	0.63 (0.21)
Magnusson et al. 1999 (Sweden)	1,311 / 1,312	32 / 33	0.91 (0.08)
McCredie et al. 1998; Hopper et al. 1999 (Australia)	774 / 518	38 / 36	1.03 (0.15)
Kropp et al. 2001 (Germany)	168 / 251	46 / 52	0.94 (0.25)
Johnson et al. 2000 (Canada)	974 / 1,110	42 / 40	1.14 (0.11)
Other§	2,851 / 3,567	11 / 13	0.99 (0.12)
All case-control, population controls	**14,671/17,269**	**36/35**	**1.07 (0.03)**
Case-control, hospital controls			
Meara et al. 1989 (UK)	154 / 171	44 / 53	0.71 (0.30)
La Vecchia et al. 1987; Ferraroni et al. 1998 (Italy)	831 / 1,025	31 / 31	1.01 (0.12)
(France)Δ	492 / 923	18 / 24	0.82 (0.16)
La Vecchia et al. 1989 (Italy)	980 / 1,034	28 / 30	0.82 (0.10)
Katsouyanni et al. 1994 (Greece)	219 / 462	21 / 24	1.28 (0.29)
Other¶	245 / 550	20 / 26	0.72 (0.25)
All case-control, hospital controls	**2,921/4,165**	**27/29**	**0.89 (0.06)**
All studies	**22,255/40,832**	**33/30**	**1.03 (0.02)**



*SE = Standard error.
†CI = Confidence interval.
‡Hiatt and Bawol 1984; Mills et al. 1989b; Land et al. 1994; Thomas et al. 1997.
§Lee et al. 1987; Adami et al. 1988; Yuan et al. 1988; Ursin et al. 1992; Wang et al. 1992; Morabia et al. 1996; Viladiu et al. 1996; Gao et al. 2000.
ΔLe et al. 1986; Richardson et al. 1989; Clavel-Chapelon et al. 1997.
¶Ferraroni et al. 1993; Levi et al. 1996.
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Table 2.36 Case-control studies on the association between smoking and the risk of breast cancer that used hospital or cancer registry controls

Study	Population	Cases	Controls
Rosenberg et al. 1984	Hospital patients in the United States, mostly from the northeast 1976–1982	2,160	717; cancers of the ovary, colon, rectum, and lymphoreticular system; malignant melanoma
Baron et al. 1986	Hospital patients in New York 1957–1965	1,741	2,118; nonmalignant conditions, excluding diseases of the respiratory or circulatory system
Stockwell and Lyman 1987	Florida cancer registry 1981	5,246	3,921; cancers (colorectal and endocrine; malignant melanoma)
Palmer et al. 1991	Hospital patients in northeastern United States 1982–1986	1,955	805; cancers (colorectal, bone, and connective tissue; malignant melanoma; lymphoma)

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

Measure of cigarette smoking	RR* (95% CI†) compared with never smokers	Comments
Former smokers	1.1 (0.8–1.3)	Controlled for geography, age, education, age at menarche, age at first pregnancy, parity, BMI§, alcohol intake, oral contraceptive use, estrogen use, benign breast disease, and family history
Current smokers	1.1 (0.9–1.3)	
1–14 cigarettes / day	1.3 (0.9–1.8)	
15–24 cigarettes / day	1.0 (0.8–1.4)	
≥25 cigarettes / day	1.1 (0.8–1.6)	
1–14 pack-years‡	0.91 (0.75–1.10)	Controlled for age, marital status, number of pregnancies, and BMI
≥15 pack-years	0.93 (0.76–1.13)	
Former smokers	1.0 (0.8–1.1)	Controlled for age, race, and marital status
Current smokers		
<20 cigarettes / day	1.3 (1.1–1.5)	
20–40 cigarettes / day	1.2 (1.0–1.5)	
>40 cigarettes / day	1.3 (1.0–1.8)	
Former smokers	1.1 (0.9–1.4)	Controlled for age, age at menopause, age at menarche, age at first birth, parity, family history, benign breast disease, oral contraceptive use, education, alcohol intake, and BMI
Current smokers	1.3 (1.1–1.6)	
≥25 cigarettes / day	1.2 (0.9–1.8)	
Age started		
<16 years	1.8 (1.0–3.4)	

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.37 Case-control studies on the association between smoking and the risk of breast cancer that used healthy controls drawn from population sources

Study	Population	Cases	Controls
O'Connell et al. 1987	North Carolina hospital patients 1977–1978	276	1,519 from community
Adami et al. 1988	Swedish cancer registry Aged <45 years only 1984–1985	422	527 from population register
Rohan and Baron 1989	Australian cancer registry 1982–1984	451	451 from electoral rolls
Chu et al. 1990	Cancer and Steroid Hormone Study U.S. cancer registries 1980–1982	4,720	4,682 from random-digit telephone dialing
Ewertz 1990	Denmark Population-based 1983–1984	1,480	1,332 from age-stratified population sample
Palmer et al. 1991	Canada Cases from tertiary care hospital 1982–1986	607	1,214 from neighbors matched for age
Field et al. 1992	New York state Population-based 1982–1984	1,617	1,617 from driver's license lists

*RR = Relative risk.
†CI = Confidence interval.
‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
§Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.
ΔBMI = Body mass index.

Measure of cigarette smoking	RR* (95% CI†) compared with never smokers	Comments
Former smokers	1.16 (0.80–1.69)	Controlled for age, race, oral contraceptive use, estrogen use, and alcohol intake
Current smokers		
1–20 cigarettes / day	0.75 (0.52–1.09)	
>20 cigarettes / day	0.57 (0.30–1.08)	
≥20 cigarettes / day	1.1 (0.7–1.8)	Controlled for age, age at menarche, age at first pregnancy, menopause, education, benign breast disease, family history, oral contraceptive use, and alcohol intake
≥20 years' duration	1.2 (0.8–1.7)	
Age started		
<15 years	1.3 (0.7–2.5)	
Former smokers	1.04 (0.73–1.48)	Controlled for family history, menopausal status, BMI[Δ], alcohol intake, benign breast disease, and the practice of self-examination
Current smokers	1.37 (0.95–1.96)	
1–15 cigarettes / day	1.15 (0.72–1.86)	
>15 cigarettes / day	1.59 (0.99–2.57)	
Ever smokers	1.2 (1.1–1.3)	Controlled for age, reproductive factors, family history, benign breast disease, and estrogen replacement therapy
Former smokers	1.1 (1.0–1.3)	
Current smokers	1.2 (1.1–1.3)	
≥25 cigarettes / day	1.2 (1.1–1.4)	
≥40 pack-years[‡]	1.1 (0.9–1.4)	
Age started		
<17 years	1.1 (1.0–1.2)	
Former smokers	0.98 (0.80–1.24)	Controlled for age and place of residence
Current smokers	0.93 (0.78–1.10)	
≥500 cigarette-years[§]	0.91 (0.69–1.18)	
≥20 cigarettes / day	0.75 (0.56–1.00)	
Age started		
<15 years	0.87 (0.42–1.77)	
Former smokers	1.0 (0.7–1.3)	Controlled for age, age at menopause, age at menarche, age at first birth, family history, benign breast disease, BMI, oral contraceptive use, education, and alcohol intake
Current smokers	1.1 (0.9–1.4)	
≥25 cigarettes / day	1.2 (0.9–1.6)	
Age started		
<16 years	1.7 (1.0–2.9)	
Ever smokers	1.03 (0.9–1.19)	Controlled for birth year, race, menopausal status, age at first birth, family history of breast cancer, and alcohol intake
>2 packs / day	1.16 (0.68–1.96)	
≥40 years' duration	1.04 (0.84–1.29)	
≥40 pack-years	1.05 (0.81–1.35)	
Age started		
<14 years	1.15 (0.51–2.61)	

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.38 Case-control studies on the association between smoking and the risk of breast cancer conducted among screening program participants

Study	Population	Cases	Controls	Measure of cigarette smoking	RR* (95% CI†) compared with never smokers
Brinton et al. 1986	U.S. screening program 1977–1980	1,547	1,930	Ever smokers	1.20 (1.0–1.4)
				Current smokers	1.18 (0.9–1.4)
				Former smokers	1.24 (1.0–1.5)
				≥40 years' smoking	1.26 (0.9–1.7)
				≥40 cigarettes / day	1.15 (0.8–1.6)
				Age started	
				<17 years	1.30 (1.0–1.6)
Meara et al. 1989	Edinburgh (UK) screening program	118	118	Former smokers	0.99 (0.42–2.33)
				Current smokers	
				1–14 cigarettes / day	1.75 (0.65–4.72)
				≥15 cigarettes / day	2.90 (1.16–7.25)
Schechter et al. 1989	Canadian screening program 1981–1987	317	951	Ever smokers	1.1 (0.9–1.6)
				>500 cigarette-years‡	1.2 (0.9–1.9)

*RR = Relative risk.
†CI = Confidence interval.
‡Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.

Comments
Controlled for age; results were unchanged after adjusting for body mass index (BMI), age at menarche, age at first birth, family history, benign breast biopsies, and exogenous hormone use
Controlled for age, menopausal status, age at first pregnancy, age at menarche, family history, oral contraceptive use, BMI, alcohol intake, and socioeconomic status
Controlled for age, age at menarche, age at first birth, parity, age at menopause, family history, benign breast disease, oral contraceptive use, estrogen use, height, weight, ethnicity, breast self-examination, mammograms, education, and marital status

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.39 Cohort studies on the association between smoking and the risk of breast cancer

Study	Population	Cases	Measure of cigarette smoking	RR* (95% CI†) compared with never smokers
Hiatt and Fireman 1986	California health plan members; 84,172 women aged 20–84 years, followed for 8–16 years	1,363	Former smokers Current smokers 1–2 packs / day >2 packs / day	1.21 (1.02–1.42) 1.22 (1.05–1.43) 1.19 (0.88–1.60)
Hiatt et al. 1988	California health plan members; 68,674 women examined 1978–1984, followed for up to 6 years	303	Former smokers Current smokers ≥2 packs / day	0.65 (0.47–0.89) 1.15 (0.47–2.83)
London et al. 1989	Nurses Health Study participants; 117,557 enrolled in 1976, aged 30–55 years, followed for 10 years	1,788	Former smokers Current smokers 15–24 cigarettes / day ≥25 cigarettes / day Age started <17 years	1.08 (0.96–1.20) 0.99 (0.85–1.15) 1.02 (0.86–1.22) 1.07 (0.91–1.25)
Schatzkin et al. 1989	Framingham Heart Study; 2,636 women aged 31–64 years, followed for up to 32 years	143	10–19 cigarettes / day ≥20 cigarettes / day	1.1 (0.7–2.0) 1.0 (0.6–1.7)
Vatten and Kvinnsland 1990	Residents of 3 counties in Norway; 24,329 women followed for 11–14 years; aged 35–51 years at the beginning of this study	242	Current smokers of >10 cigarettes / day vs. former smokers and never smokers	0.86 (0.62–1.19)

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

Comments
Controlled for age, race, education, age at menarche, parity, marital status, body mass index (BMI), and alcohol intake; results were unchanged when age at menopause was controlled
Controlled for age, race, BMI, and alcohol intake
Controlled for age, age at first birth, parity, menopausal status, age at menarche, family history, oral contraceptive use, benign breast disease, alcohol intake, and BMI
Controlled for age, parity, menopausal status, education, BMI, height, and alcohol intake
Controlled for age, occupation, and BMI; reference category included former smokers

Source: Palmer and Rosenberg 1993. Reprinted with permission.

Table 2.40 Large case-control studies on the association between smoking and the risk of breast cancer published after 1993

		OR* compared with never smokers (adjusted)					
		Ever smokers		Current smokers		Former smokers	
Study	Total number of cases and controls	OR	95% CI†	OR	95% CI	OR	95% CI
Smith et al. 1994	755 / 755	1.01	0.81–1.26	NR‡	NR	NR	NR
Baron et al. 1996	6,888 / 9,529	NR	NR	1.0	0.92–1.09	1.10	1.01–1.19
Gammon et al. 1998	2,199 / 2,009	NR	NR	0.82	0.67–1.01	0.99	0.81–1.21

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

OR compared with never smokers (adjusted)								
Number of years of smoking			**Cigarettes per day**			**Number of years since quitting**		
Years	**OR**	**95% CI**	**Amount smoked**	**OR**	**95% CI**	**Years**	**OR**	**95% CI**
1–9	1.09	0.80–1.47	≤15	0.96	0.76–1.23	NR	NR	NR
≥10	1.00	0.79–1.25	≥16	1.16	0.89–1.50	NR	NR	NR
≤10	0.96	0.83–1.10	≤10	1.04	0.95–1.14	≤3	1.39	1.14–1.68
11–20	1.02	0.90–1.15	11–20	1.07	0.98–1.17	4–10	1.23	1.08–1.40
21–30	1.12	1.00–1.25	21–30	1.06	0.90–1.24	11–20	1.08	0.95–1.20
31–40	1.12	1.00–1.25	31–40	1.04	0.87–1.24	21–30	0.94	0.81–1.10
41–50	1.01	0.89–1.15	>40	1.09	0.79–1.49	>30	0.92	0.75–1.12
>50	1.07	0.84–1.37	NR	NR	NR	NR	NR	NR
Current Smokers			Current Smokers					
≤8	0.63	0.34–1.15	<10	0.69	0.47–1.02	NR	NR	NR
9–14	0.98	0.68–1.41	10–19	0.91	0.65–1.28	NR	NR	NR
15–21	0.92	0.68–1.23	20	0.78	0.58–1.04	NR	NR	NR
>21	0.70	0.52–0.94	>20	0.95	0.66–1.38	NR	NR	NR
Former Smokers			Former Smokers					
≤8	0.98	0.76–1.28	<10	0.96	0.70–1.31	0.5–5	1.02	0.73–1.43
9–14	0.98	0.71–1.35	10–19	1.21	0.84–1.74	6–10	0.95	0.67–1.34
15–21	0.91	0.57–1.44	20	0.84	0.61–1.16	11–15	1.01	0.70–1.44
>21	1.27	0.58–2.77	>20	1.05	0.66–1.68	>15	0.97	0.67–1.40

Summary

A systematic review of new epidemiologic evidence adds new inferences for a causal relationship between smoking and a number of cancers. This report draws several new conclusions. Specifically, it concludes that evidence is sufficient to infer a causal relationship between smoking and cancers of the cervix, kidneys, pancreas, and stomach. Also, it infers a causal relationship between smoking and acute myeloid leukemia. Although there is evidence that smoking is not related to the risk of developing prostate cancer, this report also concludes that it is probable that smoking contributes to a higher mortality rate from prostate cancer. Finally, this report concludes that active smoking is not causally related to breast cancer.

Conclusions

Lung Cancer

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

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

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

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

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

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

Laryngeal Cancer

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

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

Oral Cavity and Pharyngeal Cancers

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

Esophageal Cancer

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

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

Pancreatic Cancer

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

Bladder and Kidney Cancers

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

Cervical Cancer

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

Ovarian Cancer

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

Endometrial Cancer

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

Stomach Cancer

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

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

Colorectal Cancer

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

Prostate Cancer

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

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

Acute Leukemia

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

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

Liver Cancer

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

Adult Brain Cancer

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

Breast Cancer

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

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

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

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