

FIGURE 8.—Mean annual incidence rates per 100,000 population for males of bronchogenic carcinoma by cell type, Olmsted County, MN, 1935–79, by decade

SOURCE: Beard et al. (1985).

a reduced effect. Statistical methods are used with epidemiologic data to describe interactions. Either an additive or a multiplicative scale may be used to measure interaction statistically (Saracci 1987). For two exposures, on an additive scale, the sum of the two independent relative risks reduced by one is compared with the relative risk observed when both exposures are present. On a multiplicative scale, the comparison relative risk value is the product of the two independent relative risks. For public health purposes, a positive departure from additivity is considered to represent synergism (Saracci 1987). As the extent of interaction increases, the proportion of the excess cases attributable to the interaction also increases (Saracci 1987).

This Section briefly reviews the current evidence on host characteristics and environmental agents that may modify the risk of cigarette smoking.

Familial Factors

The 1964 Report considered and dismissed the “constitutional hypothesis” that predilections to cigarette smoking and to lung cancer share a common genetic origin. The Report did consider that genetic factors might determine susceptibility for a minority of cases. Subsequent epidemiologic studies have provided empirical evidence of possible genetic or familial determinants of susceptibility (Tokuhata and Lilienfeld 1963a, 1963b; Samet, Humble, Pathak 1986; Ooi et al. 1986). For example, in a recent case-control study in New Mexico (Samet, Humble, Pathak 1986), a parental history of lung cancer was associated with a fivefold increase in lung cancer risk, after adjustment for cigarette smoking. Clinical studies of selected families have also indicated familial aggregation (Brisman et al. 1967; Lynch et al. 1982; Goffman et al. 1982).

Research has not yet identified the mechanisms underlying the familial aggregation of lung cancer. In 1973, Kellermann, Shaw, and Luyten-Kellerman (1973) reported the promising observation that patients with lung cancer had a higher degree of inducibility of aryl hydrocarbon hydroxylase than did control subjects. Because this enzyme converts polycyclic aromatic hydrocarbons to more active carcinogens and because enzyme concentrations are under genetic control, this observation suggested a possible genetic determinant of lung cancer risk. However, not all subsequent studies have been confirmatory, and the inheritance of inducibility in humans has not yet been fully described (Mulvihill and Bale 1984).

Other Host Factors

Acquired host characteristics have also been examined as determinants of lung cancer risk including pulmonary tuberculosis, chronic bronchitis, COPD, disorders associated with interstitial fibrosis of the lung, and peripheral pulmonary scars. However, the evidence related to these disorders is incomplete and frequently is derived from case series rather than from epidemiologic investigations. Recent epidemiologic evidence, however, has indicated increased lung cancer risk for smokers with COPD compared with unaffected smokers (Peto et al. 1983; Samet, Humble, Pathak 1986; Skillrud, Offord, Miller 1986).

Occupational Exposures

Diverse agents inhaled in the workplace have been shown to cause lung cancer. Interaction between occupational exposures and smoking was the focus of the 1985 Report of the Surgeon General (US DHHS 1985). That Report concluded that “For the majority of American workers who smoke, cigarette smoking represents a greater cause of death and disability than their workplace environment.” The Report also highlighted the limitations of the evidence on interactions between smoking and occupational exposures.

Little new information has become available since the 1985 Report. The evidence remains strongest for interactions of smoking with exposure to radon decay products and with exposure to asbestos (Saracci 1987). For both exposures, the preponderance

of the evidence indicates synergism (Doll and Peto 1985; National Research Council 1988), although the results of some individual investigations are inconsistent with synergism.

Ambient Air Pollution

The 1964 Report noted that lung cancer mortality rates tended to be higher in urban than in rural locations. Air pollution was considered a plausible explanation for these differences. The association of lung cancer with atmospheric pollution derives biological plausibility from the presence of carcinogens in polluted air and has some support from epidemiologic data. However, epidemiologic investigation of ambient air pollution as a risk factor for lung cancer has been hampered by methodological problems, including the necessity of considering cigarette smoking and the difficulty of assessing pollution exposure (NIH 1986). Recent epidemiologic investigations have not shown strong effects of air pollution (Samet et al. 1987; Buffler et al. 1988); and Doll and Peto (1981), in their review of the causes of cancer, estimated that only 1 to 2 percent of lung cancer was related to air pollution.

Indoor Air Pollution

As the hazards posed by ambient air pollution from conventional fossil fuels have diminished in some countries, the relevance of indoor air quality for health has become increasingly apparent. Studies of time-activity patterns demonstrate that residents of more developed countries, including the United States, spend on average little time outdoors (Spengler and Sexton 1983; Samet, Marbury, Spengler 1987). Indoor spaces may be polluted by entry of contaminants from outdoor air and by indoor sources including those related to human activity, such as tobacco smoking, building materials, combustion devices, personal care and other household products, and other sources. A trend of reduced building ventilation in the aftermath of the energy problems of the 1970s may have worsened indoor air quality.

Two pollutants in indoor air have been causally linked to lung cancer: environmental tobacco smoke (ETS) (US DHHS 1986a) and radon (National Research Council 1988). The evidence on ETS and cancer was comprehensively reviewed in the 1986 Report (see Section on Involuntary Smoking in this Chapter).

Radon is an inert gas that is formed from radium during the natural decay of uranium. The predominant source of radon in indoor air is the soil beneath structures. Radon diffuses through the ground into basement and crawl spaces, and then throughout the air in a home, or crosses cracks and other penetrations in homes on concrete slabs to enter the indoor environment. Radon daughters are invariably present in indoor air and a wide range of concentrations has been observed in homes (Samet et al. 1988). Some homes have levels comparable to those measured in uranium mines, but the majority of homes probably have levels that are currently considered acceptable.

Radon decays into short-lived particulate decay products. Two of the decay products emit alpha particles, which are highly effective in damaging cells because of their high energy and high mass. When these alpha emissions take place within the lung, the

epithelial lining of the tracheobronchial tree may be damaged and lung cancer may ultimately result. Extensive epidemiologic data from studies of uranium and other underground miners have established a causal association between exposure to radon daughters and lung cancer (National Research Council 1988). The committee on the Biological Effects of Ionizing Radiation (BEIR) IV concluded that the studies of miners indicated synergism between cigarette smoking and radon decay products (National Research Council 1988). The evidence, however, was not considered adequate to determine if the interaction was multiplicative or submultiplicative.

To date, epidemiologic investigations of domestic radon daughters as a risk factor for lung cancer have been limited and preliminary (Samet et al. 1988). However, it is assumed that radon decay products are carcinogenic in the indoor environment as they are in the mining environment. Dosimetric analyses indicate equivalent carcinogenicity in the domestic and mining environments (National Research Council 1988). Thus, radon must be considered one of the most important factors interacting with cigarette smoking. All smokers are exposed to radon, some at unacceptable levels. Quantitative estimates of the contribution of radon to lung cancer are variable. The estimates vary with the underlying assumptions and the risk model employed (Samet et al. 1988).

Although cigarette smoking is by far the major cause of lung cancer, radon must also be considered a cause of the disease. The public health burden of radon-related lung cancer is substantially increased by the synergism between cigarette smoking and radon exposure.

Diet

Diet has recently been considered as potentially influencing the risk of lung cancer in smokers. Nutrients of particular interest include preformed vitamin A, carotene, vitamin E, and vitamin C (Colditz, Stampfer, Willett 1987).

An enlarging body of experimental and epidemiologic evidence supports the hypothesis that the risk for certain cancers varies inversely with consumption of preformed vitamin A or beta-carotene, its precursor (Peto et al. 1981; National Academy of Sciences 1982; Colditz, Stampfer, Willett 1987). The biological plausibility of this hypothesis derives from the known effects of vitamin A deficiency on the differentiation of epithelial surfaces, from in vitro and in vivo models, which show that retinoids can suppress the development of malignancy, and from possible anticarcinogenic activity of beta-carotene, the principal dietary precursor of vitamin A (Peto et al. 1981; National Academy of Sciences 1982). The epidemiologic evidence indicates a protective effect of dietary vitamin A intake from vegetable sources, but not of preformed vitamin A, which is derived from meat and dairy sources, and vitamin supplements. Clinical trials on vitamin A and lung cancer risk are in progress.

Vitamins E and C are antioxidants, which might have anticancer effects. To date, the epidemiologic data on these vitamins are sparse and inconclusive (Colditz, Stampfer, Willett 1987).

Smoking Cessation

Cessation of cigarette smoking results in a gradual decrease in lung cancer risk. Several of the prospective and retrospective epidemiologic studies have demonstrated a reduction in lung cancer risk over time following smoking cessation. One example is provided from the U.S. Veterans study (Kahn 1966) (Figure 9).

Other recent studies have continued to confirm the benefit of smoking cessation for lung cancer risk (Lubin et al. 1984b; Alderson, Lee, Wang 1985; Pathak et al. 1986; Higgins, Mahan, Wynder 1988). For example, Lubin and colleagues (1984b) described the pattern of reduction in risk following smoking cessation in a case-control study that

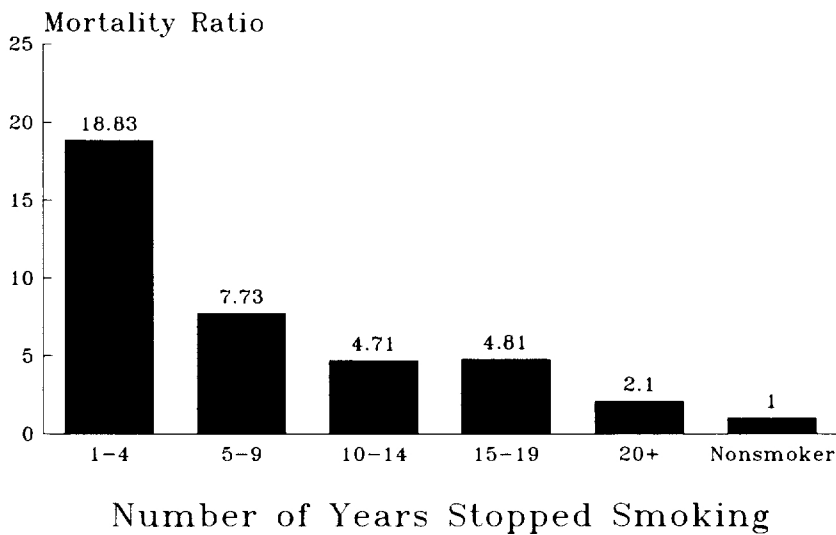


FIGURE 9.—Lung cancer mortality ratio for male former smokers

SOURCE: U.S. Veterans (Kahn 1966).

involved 7,181 lung cancer patients and 11,006 controls. For men and women in this study who had smoked for less than 20 years and had not smoked for 10 years, the risks of lung cancer were approximately the same as those of lifelong nonsmokers. On the basis of the study of British physicians, Peto and Doll (1984) have suggested that the effect of cigarette smoking cessation is to fix the age-specific risk of lung cancer at the rate achieved at the time of cessation, based on the smoking history up to that time. According to this analysis, the former smoker's relative risk of lung cancer declines as the background rate for lung cancer rises with age.

Therefore, smoking cessation is clearly beneficial in reducing the risk of lung cancer compared with continued smoking; but cessation may not reduce the risk to the levels of a lifetime nonsmoker even after many years of cessation. (See Table 2, Chapter 3.)

Laryngeal, Oral, and Esophageal Cancer

The 1964 Surgeon General's Report concluded that cigarette smoking was causally related to laryngeal cancer in men and that pipe smoking was causally related to lip cancer (US PHS 1964). Subsequent reports reviewed the accumulating epidemiologic evidence that established that cancers of the larynx, oral cavity, and esophagus are caused by smoking in both men and women. The mortality ratios for these cancers are similar for smokers whether they smoke cigars, pipes, or cigarettes. A strong dose-response relationship exists, and the risk decreases with cessation, compared with continued smoking. Recent studies have confirmed these findings (Blot et al. 1988; Elwood et al. 1984; Schottenfeld 1984). (See Chapter 3.)

Alcohol consumption is also a risk factor for oral, pharyngeal, laryngeal, and esophageal cancer. The combination of alcohol and smoking produces a synergistic increase in risk. In one study (Schottenfeld 1984), for all upper airway cancers combined, the risk was 8.6 for those smoking 30 or more cigarettes per day in combination with 20 oz of alcohol consumed per week.

Bladder and Kidney Cancer

A relationship between smoking and bladder cancer was noted in the 1964 Surgeon General's Report. The 1979 Report concluded that cigarette smoking acts independently and probably acts synergistically with other risk factors to increase the risk of bladder cancer. The 1982 Surgeon General's Report concluded that cigarette smoking is a contributory factor for both bladder and kidney cancer. Cigarette smoking is estimated to account for 30 to 40 percent of bladder cancer (US DHHS 1982).

Recent studies have confirmed earlier findings. For bladder cancer, in both men and women, cigarette smokers have a relative risk of 2 to 3. A dose-response relationship has been demonstrated, and the risk of bladder cancer decreases following smoking cessation (McLaughlin et al. 1984; Hartge et al. 1987; Zahm, Hartge, Hoover 1987).

There is a positive association between smoking and kidney cancer, with relative risks ranging from 1 to more than 5. The increased risk of kidney cancer due to cigarette smoking is found for both males and females, and there is a dose-response relationship, as measured by the number of cigarettes smoked per day.

Pancreatic Cancer

The first Surgeon General's Report did not examine the relationship between smoking and cancer of the pancreas. Several subsequent reports of the Surgeon General have noted that cigarette smoking is a contributory factor for pancreatic cancer.

The major prospective epidemiologic studies have consistently shown an increased risk of pancreatic cancer among both male and female cigarette smokers. The mortality ratio for cigarette smokers compared with nonsmokers is generally in the range of 2 to

Laryngeal, Oral, and Esophageal Cancer

The 1964 Surgeon General's Report concluded that cigarette smoking was causally related to laryngeal cancer in men and that pipe smoking was causally related to lip cancer (US PHS 1964). Subsequent reports reviewed the accumulating epidemiologic evidence that established that cancers of the larynx, oral cavity, and esophagus are caused by smoking in both men and women. The mortality ratios for these cancers are similar for smokers whether they smoke cigars, pipes, or cigarettes. A strong dose-response relationship exists, and the risk decreases with cessation, compared with continued smoking. Recent studies have confirmed these findings (Blot et al. 1988; Elwood et al. 1984; Schottenfeld 1984). (See Chapter 3.)

Alcohol consumption is also a risk factor for oral, pharyngeal, laryngeal, and esophageal cancer. The combination of alcohol and smoking produces a synergistic increase in risk. In one study (Schottenfeld 1984), for all upper airway cancers combined, the risk was 8.6 for those smoking 30 or more cigarettes per day in combination with 20 oz of alcohol consumed per week.

Bladder and Kidney Cancer

A relationship between smoking and bladder cancer was noted in the 1964 Surgeon General's Report. The 1979 Report concluded that cigarette smoking acts independently and probably acts synergistically with other risk factors to increase the risk of bladder cancer. The 1982 Surgeon General's Report concluded that cigarette smoking is a contributory factor for both bladder and kidney cancer. Cigarette smoking is estimated to account for 30 to 40 percent of bladder cancer (US DHHS 1982).

Recent studies have confirmed earlier findings. For bladder cancer, in both men and women, cigarette smokers have a relative risk of 2 to 3. A dose-response relationship has been demonstrated, and the risk of bladder cancer decreases following smoking cessation (McLaughlin et al. 1984; Hartge et al. 1987; Zahm, Hartge, Hoover 1987).

There is a positive association between smoking and kidney cancer, with relative risks ranging from 1 to more than 5. The increased risk of kidney cancer due to cigarette smoking is found for both males and females, and there is a dose-response relationship, as measured by the number of cigarettes smoked per day.

Pancreatic Cancer

The first Surgeon General's Report did not examine the relationship between smoking and cancer of the pancreas. Several subsequent reports of the Surgeon General have noted that cigarette smoking is a contributory factor for pancreatic cancer.

The major prospective epidemiologic studies have consistently shown an increased risk of pancreatic cancer among both male and female cigarette smokers. The mortality ratio for cigarette smokers compared with nonsmokers is generally in the range of 2 to

3. A detailed review of the epidemiology of pancreatic cancer was written by Gordis and Gold (1984).

For those in the MRFIT Study who smoked 40 or more cigarettes a day, the mortality ratio for pancreatic cancer was 2.3 compared with nonsmokers. Other recent studies (Mack et al. 1986; Whittemore et al. 1985) report that cigarette smoking is strongly and consistently related to pancreatic cancer. Most epidemiologic studies show a dose-response relationship between cigarette smoking and pancreatic cancer for both men and women and a gradual decline in the risk of developing pancreatic cancer following smoking cessation (US DHHS 1982; Mack et al. 1986).

Autopsy studies report hyperplastic changes in the pancreatic duct cells and atypical changes in their nuclei among cigarette smokers compared with nonsmokers. The pancreas is probably exposed to tobacco carcinogens or carcinogenic metabolites present in bile or blood (US DHHS 1982).

Stomach Cancer

The 1964 Surgeon General's Report reviewed smoking and stomach cancer and, on the basis of the limited evidence available at that time, concluded that there was no relationship between smoking and stomach cancer. Evidence from prospective and retrospective studies available more recently has shown a small but consistent increase in mortality ratios, averaging approximately 1.5 for smokers compared with nonsmokers. Dose-response relationships have been demonstrated for the number of cigarettes smoked per day. The 1982 Surgeon General's Report concluded that cancer of the stomach is associated with cigarette smoking.

Cervical Cancer

Cancer of the uterine cervix was not reviewed in the 1964 Surgeon General's Report. The 1982 Report of the Surgeon General reviewed the studies published up to that time and concluded that further research was necessary to define whether there was an association between cigarette smoking and cervical cancer.

There are several risk factors for cervical cancer including early and frequent coitus, multiple sexual partners, pregnancy at an early age, and the presence of sexually transmitted diseases. Some of these risk factors may also be associated with smoking.

Winkelstein and coworkers (1984) reviewed 12 studies dealing with smoking and cervical cancer, and in most studies there was a positive relationship that could not be explained by other risk factors. Two studies published in 1985 confirmed these findings (Clarke et al. 1985; Greenberg et al. 1985).

Baron and coworkers (1986) reported on a case-control study of 1,174 patients with cervical cancer. Cigarette smoking was associated with a statistically significant increase in risk for cervical cancer. LaVecchia and associates (1986) in Italy studied the relationship between cigarette smoking and the risk of cervical neoplasia in a case-control study of 183 women with intraepithelial neoplasia. Cigarette smoking was associated with an increased risk of intraepithelial neoplasia and invasive cancer. This association could not be totally explained by potential confounding factors. In a case-

control study of 480 patients with cervical cancer, there was a 50-percent excess risk of cancer among cigarette smokers (Brinton et al. 1986). This excess risk persisted after adjustment for sexual practices associated with smoking such as age at first intercourse and number of sexual partners. There was a twofold excess risk of cervical cancer for women who smoked more than 40 cigarettes per day. The dose-response relationship persisted after adjusting for several variables. There was no increased risk of cervical cancer among former smokers.

The finding of nicotine and cotinine in the cervical secretions of cigarette smokers (Sasson et al. 1985) and of mutagenic mucus in the cervix of smokers (Holly et al. 1986) complements the epidemiologic findings.

In summary, more than 15 epidemiologic studies have consistently shown an increased risk for cervical carcinoma in cigarette smokers compared with nonsmokers. Supportive clinical studies provide a plausible biological basis for the relationship. The available data confirm an association between cigarette smoking and carcinoma of the uterine cervix.

Endometrial Cancer

Several studies have reported that endometrial cancer is less frequent among women who smoke cigarettes than among nonsmokers (Baron et al. 1986). Cigarette smoking exerts an antiestrogenic effect that may explain this inverse association. The public health significance of this association is limited because of the overall adverse impact of cigarette smoking on morbidity and mortality.

Coronary Heart Disease

The 1964 Surgeon General's Report (US PHS 1964) noted that male cigarette smokers have higher death rates from CHD than nonsmokers. Subsequent reports concluded that cigarette smoking can cause death from CHD and that smoking is one of the major independent risk factors for heart attack, manifested as fatal and nonfatal myocardial infarction and sudden cardiac death. Smoking also increases the risk of heart attack recurrence among survivors of a myocardial infarction (US DHEW 1979). The 1980 Report (US DHHS 1980) noted the increased risk of CHD among women who smoke. It also described the synergistic interaction between smoking and oral contraceptive use that substantially increases CHD risk. The 1983 Report (US DHHS 1983) stated that cigarette smoking is a major cause of CHD and noted the decreased risk of CHD among former smokers compared with current smokers.

Epidemiology

The findings from several prospective studies involving more than 20 million person-years of observation in North America, Northern Europe, and Japan have been remarkably similar: cigarette smokers are at increased risk for fatal and nonfatal myocardial infarction and for sudden death. Overall, smokers have a 70 percent greater

CHD death rate, a two- to fourfold greater incidence of CHD, and a two- to fourfold greater risk for sudden death than nonsmokers (US DHHS 1983).

Although women experience lower CHD rates than men, cigarette smoking is a major determinant of CHD in women. In a recent prospective study of 119,404 female nurses, smoking accounted for approximately one-half of the coronary events (Willett et al. 1987). Cigarette smoking produces a greater relative CHD risk in men and women under 50 years of age than in those over 50 years of age (Glover, Kuber et al. 1982; Rosenberg, Miller et al. 1983).

Dose-response relationships between cigarette smoking and CHD mortality have been demonstrated for several measures of exposure to cigarettes, including the number of cigarettes smoked per day, the depth of inhalation, the age at which smoking began, and the number of years of smoking (US DHHS 1983). Smoking cigarettes with reduced yields of tar and nicotine has not been found to reduce CHD risk (Kaufman et al. 1983).

Coronary Heart Disease Risk Factors

The risk of experiencing a heart attack is multifactorial (US DHHS 1983). The presence of one or more of the major CHD risk factors, cigarette smoking, hypercholesterolemia, and hypertension, identifies individuals at high or very high risk. These risk factors interact synergistically to greatly increase CHD risk (Figure 10). The risk of CHD associated with cigarette smoking is comparable to that associated with the other major CHD risk factors.

The risk of CHD is greatly increased among diabetic men and women who smoke cigarettes (Suarez and Barrett-Connor 1984; Stamler, Wentworth, Neaton 1986), and the sex differences in CHD are substantially reduced among diabetics. Among the MRFIT screenees free of a history of heart attack, there were 5,245 diabetics and 350,977 nondiabetic men aged 35 to 57 years at the time of enrollment (Suarez and Barrett-Connor 1984). The CHD death rate was much higher among diabetics than among nondiabetics. Smokers had higher CHD death rates than nonsmokers among both diabetics and nondiabetics. Six-year CHD mortality was 4.0/1,000 for nonsmokers who were nondiabetic and 23.2/1,000 for diabetics who smoked at least 36 cigarettes per day.

Hyperlipoproteinemia is a primary cause of premature coronary atherosclerosis and heart attacks. Cigarette smoking substantially increases the risk of CHD among individuals with genetic familial hyperlipidemias. Williams and coworkers (Williams et al. 1986; Hopkins, Williams, Hunt 1984) studied four large Utah pedigrees with familial hypercholesterolemia. They noted a substantially increased risk of CHD within the high-risk pedigrees in relation to cigarette smoking.

Miettinen and Gylling (1988) have recently completed a long-term followup of 96 patients with familial hypercholesterolemia. Cigarette smoking was a significant predictor of coronary mortality after adjustment for disease history, sex, and various metabolic parameters.

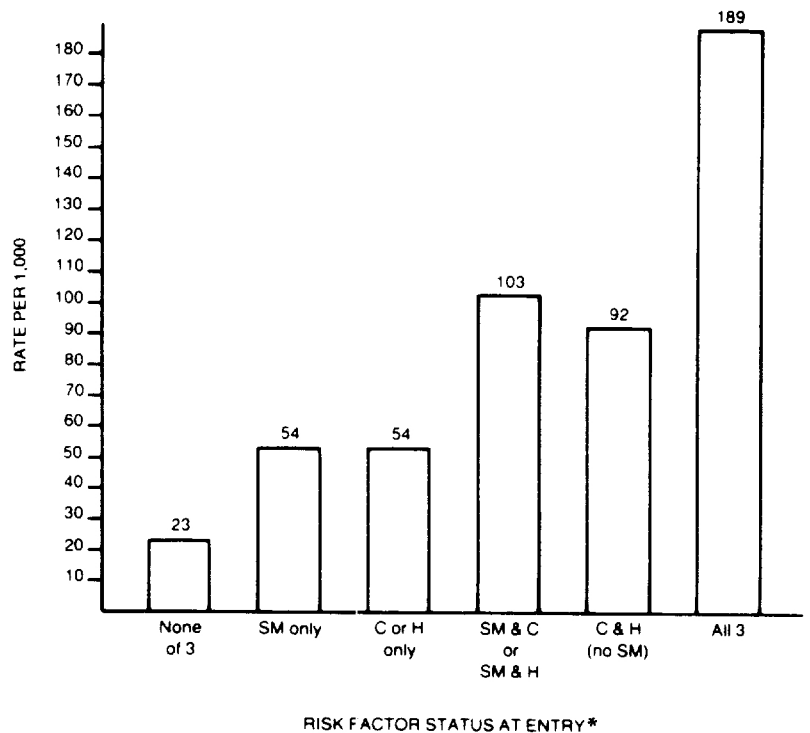


FIGURE 10.—Major risk factor combinations, 10-year incidence of first major coronary events, males aged 30 to 59 years at entry, Pooling Project

Definitions of the three major risk factors and their symbols: hypercholesterolemia (C), ≥ 250 mg/dl; elevated blood pressure (H), diastolic pressure ≥ 90 mm Hg; cigarette smoking (SM), any current use of cigarettes at entry.

NOTE: All rates were age-adjusted by 10-year age groups to the U.S. white male population, 1980.

SOURCE: Pooling Project Research Group (1978).

Pathophysiological Mechanisms

Autopsy studies indicate that cigarette smoking has a significant positive association with atherosclerosis (US DHHS 1983). Studies have noted the strongest relationship of cigarette smoking with aortic atherosclerosis, but smokers also show increased coronary atherosclerosis compared with nonsmokers (US DHHS 1983). Smokers undergoing coronary angiography have more coronary artery disease than nonsmokers (Pearson 1984). Cigarette smokers who continue to smoke following transluminal coronary angioplasty may be more likely to require repeat angioplasty than nonsmokers (Galan et al. 1988).

Cigarette smoking exerts both acute and chronic adverse coronary effects (US DHHS 1983; Holbrook et al. 1984). It contributes to acute ischemic and occlusive events through several possible mechanisms: an imbalance between myocardial oxygen supply and demand, coronary artery spasm, a hypercoagulable state, increased platelet adhesiveness and aggregation, and a decreased ventricular fibrillation threshold (US

DHHS 1983; Martin et al. 1984; Fitzgerald, Oates, Nowak 1988). Cigarette smoking also contributes to the development of coronary atherosclerosis. Possible mechanisms for this chronic effect include: repetitive endothelial injury, a decreased high-density lipoprotein (HDL)/low-density lipoprotein (LDL) cholesterol ratio, abnormalities in the synthesis of thromboxane A2 and prostacyclin, and increased neutrophil elastase activity (Holbrook, in press; Nowak et al. 1987; Weitz et al. 1987).

Clinical Correlations

Cigarette smoking has an adverse effect on individuals with symptomatic or asymptomatic CHD. Compared with nonsmokers, smokers having a positive exercise test (Rautaharju et al. 1986; Gordon et al. 1986) or a history of coronary bypass surgery (Vlietstra et al. 1986; Kemp et al. 1986) face a worse prognosis. Smokers who have angina pectoris have a higher risk of death than nonsmokers (Hubert, Holford, Kannel 1982) and have a poorer long-term prognosis after a myocardial infarction (Ronnevik, Gundersen, Abrahamsen 1985; Kuller et al. 1982). Continuing to smoke increases the likelihood of recurrent acute myocardial infarction and sudden death (Hallstrom, Cobb, Ray 1986). Smoking may also cause silent ischemic disturbances in patients with stable angina pectoris (Deanfield et al. 1986).

Cigarette smoking interferes with the efficacy of medication used to treat CHD such as propranolol, atenolol, and nifedipine (Deanfield et al. 1984).

Smoking Cessation

Prospective epidemiologic studies have documented a substantial reduction in CHD death rates following smoking cessation (US DHHS 1983). While some studies have shown a benefit within 2 years after quitting, other studies have suggested that the former smoker's CHD risk gradually decreases over a period of several years (Cook et al. 1986). For heavier smokers, the residual CHD risk is proportional to the total lifetime exposure to cigarettes.

Cerebrovascular Disease (Stroke)

In the United States stroke is the third leading cause of death. It is also a major cause of morbidity, with more than 400,000 Americans suffering nonfatal strokes each year (Harrison's Principles of Internal Medicine 1987).

There are two major types of cerebrovascular disease: (1) cerebral infarction due to occlusion of a vessel by an embolus or thrombosis, and (2) cerebral hemorrhage, including subarachnoid and parenchymal. The terms cerebrovascular accident and stroke are nonspecific and usually refer to clinical syndromes.

A stroke may be caused by disease of the extra- or intracranial blood vessels. Embolization from the heart or extracranial arteries is also an important cause of stroke. The stroke can result from hemorrhage from a blood vessel or from occlusion of an artery because of atherosclerosis, thrombosis, or embolization. In the Framingham study, atherothrombotic brain infarction accounted for the majority of strokes (Wolf,

Dawber et al. 1978). Improved diagnostic methods have provided a better categorization of the causes of stroke. Epidemiologic studies have shown that hypertension is the most important risk factor for stroke (US DHHS 1983).

The 1964 Report of the Surgeon General stated that the large epidemiologic studies of Hammond and Horn (1958) and Dorn (1958) had found a moderate increase in the mortality rate from cerebrovascular disease in cigarette smokers compared with non-smokers.

The 1971 Report (US DHEW 1971) reviewed six major prospective epidemiologic studies. Cigarette smokers in these studies experienced increased stroke mortality compared with nonsmokers. The 1980 Report (US DHHS 1980) noted that women who smoke have an increased risk of subarachnoid hemorrhage. The 1983 Report (US DHHS 1983) reviewed the data associating cigarette smoking with stroke and found an increased risk for stroke among smokers that was most evident in younger age groups. It also noted that women cigarette smokers experience an increased risk for subarachnoid hemorrhage and that the concurrent use of both cigarettes and oral contraceptives greatly increased this risk.

Since the release of the 1983 Surgeon General's Report the relationship between cigarette smoking and stroke has been clarified in several large studies involving men and women.

The risk of stroke was evaluated in a prospective study of 8,006 Japanese-American men living in Hawaii (Abbott et al. 1986). After 12 years of followup, cigarette smokers had two to three times the risk of thromboembolic or hemorrhagic stroke compared with nonsmokers. The increased risk was independent of other risk factors such as hypertension and CHD. Those smokers who stopped smoking during the course of the study experienced more than a 50-percent reduction in the risk of stroke compared with continuing smokers.

The impact of cigarette smoking on stroke incidence was assessed prospectively in the Framingham Study of 4,255 men and women (Wolf et al. 1988). This cohort was followed for 26 years, and the diagnoses were confirmed by clinical examination. Cigarette smoking made a significant, independent contribution to the risk of stroke. The risk increased as the number of cigarettes smoked increased. Smoking cessation resulted in a significant decrease in stroke risk so that 5 years after stopping smoking the risk was at the level of nonsmokers.

The relationship between cigarette smoking and the risk of stroke was evaluated in a prospective study of 118,539 middle-aged women who were followed for 8 years (Colditz, Bonita, Stampfer 1988). Compared with nonsmoking women, those who smoked 1 to 14 cigarettes per day had a relative risk of fatal and nonfatal stroke of 2.2. Those who smoked 25 or more cigarettes per day had a relative risk of fatal and nonfatal stroke of 3.7. In this latter group of women, the relative risk of subarachnoid hemorrhage was 9.8. The contribution of cigarette smoking to increased stroke risk was independent of other risk factors. Smoking cessation resulted in a prompt decrease in stroke risk; the relative risk of stroke in women who had stopped smoking for 2 years was 1.4, compared with women who had never smoked. The authors of this study also reviewed eight prospective cohort studies and seven case-control studies involving

women, and concluded that most of these studies had shown a positive association between cigarette smoking and stroke (Table 3).

In the ongoing study of approximately 1.2 million persons (CPS-II), cigarette smokers under the age of 65 years experienced increased risks of death from stroke. For men and women (current smokers), the relative risks of death from stroke were 3.7 and 4.9, respectively. The relative risks for those over age 65 years were 1.9 and 1.5 for men and women, respectively (Chapter 3).

Cigarette smoking was associated with decreased cerebral blood flow in a recent clinical study involving 192 normal volunteers (Rogers, Meyer et al. 1983). In a subsequent study of 268 normal volunteers, abstinence from cigarette smoking improved cerebral perfusion (Rogers, Meyer et al. 1985).

As already noted in this Chapter, cigarette smoking increases the risk for CHD, and consequently for congestive heart failure, both of which increase the risk for stroke. Data from the Medical Research Council study on the treatment of mild hypertension illustrate the impact of cigarette smoking on the efficacy of drug therapy and stroke incidence (Medical Research Council Working Party 1985). Nonsmokers receiving propranolol to control hypertension experienced a reduction in stroke incidence, while cigarette smokers did not.

Wolf and coworkers (1988) recently reviewed the association between cigarette smoking and stroke and concluded that it is causal. These investigators noted that the causal connection is supported by all of the traditional epidemiologic criteria; these include an increased risk for stroke among smokers compared with nonsmokers that is independent of other risk factors, a dose-response relationship, and a decrease in stroke risk with smoking cessation (Abbott et al. 1986; Wolf et al. 1988; Colditz, Bonita, Stampfer 1988). The aforementioned recent clinical studies also confirm that cigarette smoking increases the risk for stroke. Thus, current evidence indicates that cigarette smoking is a cause of stroke and that smoking cessation reduces the risk for stroke.

Atherosclerotic Peripheral Vascular Disease

Lower extremity arterial vascular disease causes substantial mortality and morbidity; the complications may include intermittent claudication, tissue ischemia and gangrene, and ultimately, loss of the limb.

The 1964 Surgeon General's Report commented that little is known about the relationship of smoking to peripheral arteriosclerosis. Subsequent reports have described the evidence establishing that cigarette smoking is a cause of and the most powerful risk factor for atherosclerotic peripheral vascular disease and that smoking cessation is the most important intervention in the management of this problem (US DHEW 1971, 1979; US DHHS 1983).

Cigarette smoking is directly related to the extent of atherosclerotic disease involving large and small arteries in the lower extremity (Criqui et al. 1985). Cigarette smoking also causes peripheral vasoconstriction. Epidemiologic and clinical studies have clearly demonstrated that cigarette smokers have a higher prevalence than nonsmokers

TABLE 3.—Summary of studies of cigarette smoking and stroke in women

First author	Cohort size	Type of stroke	No. of cases	Relative risk	Comments
Prospective cohort studies					
Colditz	118,539	All	274	2.2 (95% CI, 1.5–3.3) 2.7 (95% CI, 1.9–3.7) 3.7 (95% CI, 2.7–5.1)	1–14 cigarettes/day 15–24 cigarettes/day ≥25 cigarettes/day
Salonen	4,334	Infarction Other	21 38	1.4 (90% CI, 0.4–5.0) 0.8 (90% CI, 0.3–2.2)	
Tanaka	1,681	Hemorrhage Infarction	30 81	2.1 (NS) 1.0 (NS)	Included 780 men
Sacco	2,421	Subarachnoid hemorrhage	22	1.6	Relative risk was 2.9 for heavy smokers
Vessey	17,000	Subarachnoid hemorrhage Nonhemorrhagic	13 33	3.0 1.4	
Doll	6,194	Cerebral thrombosis	68	0.5 for 15–24 cigarettes/day	Risk tended to decrease with amount smoked
Layde	46,000	Subarachnoid hemorrhage	20		Smokers had higher risk of fatal subarachnoid hemorrhage
Petitti	16,759	Subarachnoid hemorrhage Other	11 23	5.7 (90% CI, 1.8–17.8) 4.8 (90% CI, 2.3–9.8)	
Wolf	2,421	All	238	1.6 (p<0.025)	
Case-control studies					
Taha		Subarachnoid hemorrhage	124	2.6 for aneurysm	Based on 68 female cases
Bell		Subarachnoid hemorrhage	134	3.7 (90% CI, 2.3–5.9)	
Collaborative study		Hemorrhage Thrombosis	192 140		Smoking doubled risk No increased risk
Abu-Zeid		Hemorrhage Thrombosis	137 410	1.4 (NS) 2.4 (p<0.001)	Included men
Bonita		Subarachnoid hemorrhage	70	4.7 (95% CI, 2.9–7.6)	Dose-response relationship not significant
Bonita		Not subarachnoid hemorrhage	53	2.6 (95% CI, 1.4–4.6)	
Herman		Stroke	25	1.2 (95% CI, 0.7–2.3)	Included 78 men

NOTE: CI, confidence interval; NS, not significant.

SOURCE: Colditz, Bonita, Stampfer (1988).

of both symptomatic and asymptomatic lower extremity arterial disease (US DHHS 1983).

In the Lipid Research Clinic prevalence study (Pomrehn et al. 1986), 48 percent of individuals with claudication were current cigarette smokers compared with 30 percent of the controls. Smoking was twice as frequent among individuals developing leg pain, compared with those not developing leg pain, during the exercise test. In the Framingham Study, the risk of developing intermittent claudication was directly and strongly related to cigarette smoking (Kannel and Shurtleff 1973).

Diabetes mellitus and cigarette smoking are the key risk factors for lower extremity arterial disease and subsequent amputation. Peripheral neuropathy and lower extremity arterial disease and infection predispose individuals with diabetes to gangrene and amputation (Herman, Teutsch, Geiss 1987). Diabetics have a sixteenfold increased risk of lower extremity amputation compared with nondiabetics; about 50 percent of the lower extremity amputations in the United States are performed on diabetics. Approximately 31,000 American diabetics undergo such surgery each year. The disease tends to be more progressive and occurs at younger ages in diabetic smokers than in nonsmokers.

In a study in Sweden, practically all diabetic patients under the age of 60 years with gangrene were cigarette smokers (Lithner 1983). The prevalence of lower extremity arterial disease was evaluated for diabetic subjects. One-third of the smokers had evidence of peripheral vascular disease compared with only 16 percent of the nonsmokers. Diabetics who stopped smoking for at least 2 years had a 30 percent lower prevalence of lower extremity arterial disease than those who continued to smoke.

Epidemiologic studies in a Rochester, MN, population (Zimmerman et al. 1981) demonstrated that for 1,073 residents over the age of 30 who were diagnosed with diabetes mellitus between 1945 and 1969, about 8 percent of men and 7 percent of women had clinical evidence of peripheral vascular disease at the time that diabetes was diagnosed. The annual incidence of lower extremity arterial disease among the diabetics was 21/1,000 for men and 17.6/1,000 for women; about 20 percent had gangrene and 36 percent had intermittent claudication. Among diabetics with lower extremity arterial disease, 77 percent of men and 43 percent of women had been cigarette smokers compared with 55 percent of normal control men and 36 percent of normal control women.

Effective treatment of diabetes mellitus and smoking cessation are the two most important interventions to prevent the development of atherosclerotic peripheral vascular disease.

Atherosclerotic Aortic Aneurysm

The 1964 Report of the Surgeon General commented on the increased mortality rates for aortic aneurysm in cigarette smokers compared with nonsmokers. The 1969 Report concluded that there is a close association between cigarette smoking and death caused by aortic aneurysm. The 1983 Report summarized the epidemiologic data and noted that the mortality rate for abdominal aortic aneurysm was 2 to 8 times greater in cigarette smokers than in nonsmokers. As already noted, pathology studies have shown a sig-

nificant association between cigarette smoking and atherosclerosis that is most striking in the aorta (US DHHS 1983).

Chronic Obstructive Pulmonary Disease

In the 1950s, increasing morbidity and mortality from chronic respiratory conditions prompted clinical and epidemiologic investigations of the etiology of chronic bronchitis, emphysema, and related disorders. A variety of terms have subsequently been applied to permanent airflow obstruction in cigarette smokers. In the 1984 Surgeon General's Report, chronic obstructive lung disease (COLD) referred to chronic mucus hypersecretion, airways abnormalities, and emphysema. In this Report, the term COPD is used for the permanent airflow obstruction that develops in cigarette smokers. Thirty years ago, the most widely advanced hypothesis on the etiology of COPD linked progressive lung damage to recurrent respiratory infection and atmospheric pollution (Stuart-Harris 1954). However, epidemiologic investigations, largely carried out in the United Kingdom, quickly indicated the predominant role of cigarette smoking in causing COPD (Stuart-Harris 1968a,b).

By 1964, the evidence was sufficiently compelling to support the conclusion by the Advisory Committee to the Surgeon General that "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis and emphysema" (US PHS 1964). The Report stopped short of classifying the relationship between cigarette smoking and emphysema as causal, however. The Report also noted the increased prevalence of respiratory symptoms and the reduction of lung function in smokers. The epidemiologic data cited in support of these conclusions were drawn from seven prospective studies of mortality in relation to cigarette smoking and about a dozen surveys of respiratory morbidity; only one prospective study on lung function had been reported at that time.

In the 25 years that have elapsed since the release of the 1964 Surgeon General's Report, the findings of numerous laboratory, clinical, and epidemiologic studies have continued to reaffirm the predominant role of cigarette smoking in causing COPD and have extended understanding of the pathogenesis, pathophysiology, and natural history of this disorder. As the evidence has accumulated, the conclusions of the Surgeon General's Reports on cigarette smoking and COPD have been strengthened. The 1967 Surgeon General's Report labeled cigarette smoking as the most important of the causes of COPD (US PHS 1968). In the 1971 and 1979 Reports, the conclusions of the 1964 and 1967 Reports were strengthened (US DHEW 1979). Increased morbidity and mortality from chronic bronchitis and emphysema were documented in cigarette smokers compared with nonsmokers. Additionally, autopsy evidence confirmed that the lungs of smokers were widely damaged, and the evolving protease-antiprotease hypothesis provided a framework for understanding mechanisms through which cigarette smoke causes emphysema.

The 1984 Surgeon General's Report focused on COLD (US DHHS 1984). The overall conclusion of the Report was: "Cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive lung disease morbidity and mortality

far outweighs all other factors.” In contrast to the sparse evidence in the 1964 Report, the 1984 Report reviewed numerous cross-sectional and longitudinal studies of morbidity and mortality. The longitudinal studies described the evolution of the cigarette-related decline in lung function that leads to impairment sufficient to result in a clinical diagnosis of COPD.

This Section provides an overview of the evidence on COPD that has accumulated since the 1964 Report in the areas of pathogenesis, pathophysiology, and natural history of COPD and the role of cigarette smoking.

Pathogenesis

The 1964 Report described the deposition of cigarette-smoke particles and gases in the lungs and the effects of cigarette smoke on lung defenses but did not address the mechanisms by which cigarette smoking causes COPD (US PHS 1964). Much of the subsequent investigation of the mechanism of lung injury by cigarette smoke was sparked by the observation that homozygous deficiency of alpha₁-antitrypsin, the major protease inhibitor, is associated with familial panlobular emphysema (Laurell and Eriksson 1963; Eriksson 1964). This observation led to the hypothesis, generally referred to as the protease–antiprotease hypothesis, that the development of emphysema results from an imbalance between proteolytic enzymes and their inhibitors (Janoff 1985; Niewoehner 1988). Cigarette smoking is postulated to produce unchecked proteolytic activity by increasing proteolytic enzyme activity in the lung while decreasing antiprotease activity.

Experimental and clinical observations have been consistent with the protease–antiprotease hypothesis (US DHHS 1984). Observations that smokers, compared with nonsmokers, have an increased number of neutrophils in peripheral blood (Yeung and Buncio 1984), in bronchoalveolar lavage fluid, and in lung biopsy specimens (Hunninghake and Crystal 1983) provide indirect evidence for an increased elastase burden in smokers’ lungs, since neutrophils are the primary source of elastase (Janoff 1985). Furthermore, elastase levels are elevated in bronchial lavage fluid immediately after smoking cigarettes (Fera et al. 1986). Cigarette smoking has also been shown to decrease the levels and activity of antiproteases, an effect attributed to oxidants in cigarette smoke and the pulmonary macrophages of smokers (Janoff 1985; US DHHS 1984). Animal models confirm that unchecked proteolytic activity can cause emphysema (US DHHS 1984).

The lungs of patients with COPD generally display both emphysema and abnormalities of the small airways. Mechanisms by which cigarette smoke damages small airways have not been so extensively investigated as the factors determining the development of emphysema.

Pathophysiology

The lungs of smokers with COPD generally have both thickening and narrowing of airways and emphysema, although the extent of these two processes is variable (US DHHS 1984). Both the airways changes and emphysema produce airflow obstruction.

The 1964 Report noted that smokers' lungs displayed airways changes and emphysema; however, the pathophysiological correlates of these changes were not explored.

Subsequent investigations, correlating structural changes with function, have described the relationship between smoking-caused changes in lung structure and airflow obstruction. Emphysema and small-airway injury contribute to the physiological impairment found in COPD; in individuals with symptomatic airflow obstruction, either type of injury may be predominant, but both are probably important (US DHHS 1984). While the 1964 Report described effects of cigarette smoking on the airways, the importance of the small airways as a site of airflow obstruction was not recognized until the late 1960s (Hogg, Macklem, Thurlbeck 1968). More recent investigations have confirmed that measures of small-airway injury are correlated with the degree of airflow obstruction (US DHHS 1984; Hale et al. 1984; Nagai, West, Thurlbeck 1985). Autopsy studies have shown that changes in the small airways develop in the lungs of young smokers and antedate the development of symptomatic airflow obstruction (Niewoehner, Kleinerman, Rice 1974).

The importance of emphysema in producing chronic airflow obstruction has also been amply documented since the 1964 Report. Emphysema reduces the driving pressure for expiratory flow and contributes to increased airways resistance by reducing tethering of small airways. In patients with symptomatic airflow obstruction, the extent of anatomic emphysema is correlated with the severity of airflow obstruction, as are small-airway abnormalities (US DHHS 1984; Hale et al. 1984; Nagai, West, Thurlbeck 1985). Thus, the smoking-caused lung changes in the airways and parenchyma have both been unequivocally linked to airflow obstruction.

Natural History of COPD and the Role of Cigarette Smoking

Nearly all the epidemiologic evidence reviewed in the 1964 Report was cross-sectional in nature. These data established that cigarette smoking increased respiratory symptoms and reduced the level of ventilatory function, but they did not provide insight into the temporal evolution of COPD. Subsequent cross-sectional studies have provided more complete quantitative descriptions of the effects of cigarette smoking on lung function, and new longitudinal studies have partially described the evolution of lung function changes in smokers and the factors determining the rate of change over time.

The numerous cross-sectional studies published since the 1964 Surgeon General's Report have shown that cigarette smoking is a strong determinant of the level of ventilatory function, which is most often assessed by the measurement of the 1-sec forced expiratory volume (FEV₁). The level of FEV₁ declines as the amount of smoking increases (US DHHS 1984). Multiple regression techniques have been applied to data from several different populations to describe the quantitative relationship between the amount smoked and loss of ventilatory function. These analyses indicate that ventilatory function declines in a linear fashion with cumulative consumption of cigarettes, usually expressed as pack-years (Burrows et al. 1977; Dockery et al. 1988). For example, based on analysis of data from 8,191 men and women from six U.S. cities, Dockery and others (1988) reported that male smokers of average height lose 7.4 mL of FEV₁

on average for each pack-year and that women lose 4.4 mL per pack-year. Although the decline in mean level of FEV₁ appears small, the distributions of lung function level in smokers and in nonsmokers are different; the distribution for smokers is skewed toward lower levels so that a much greater proportion of smokers than nonsmokers have levels below the usual limit of normal (Figure 11) (US DHHS 1984; Burrows et al. 1977; Dockery et al. 1988).

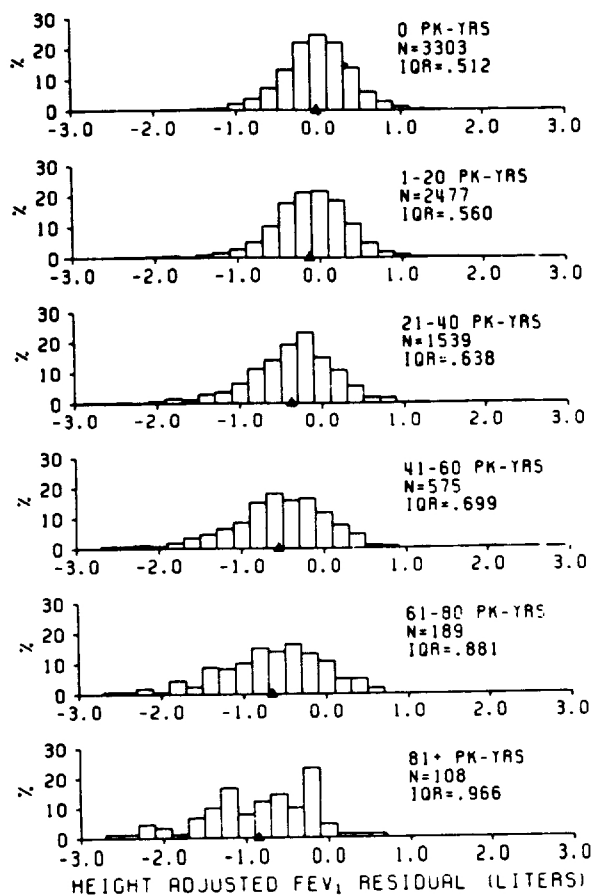


FIGURE 11.—Percent distribution of predicted values of forced expiratory volume in 1-sec (FEV₁) in subjects with varying pack-years of smoking.

NOTE: Triangle indicates mean. IQR is interquartile range.
 SOURCE: Dockery et al. (1988).

The longitudinal studies published since the 1964 Report have partially described the natural history of lung function changes in COPD (Fletcher et al. 1976; US DHHS 1984). Ventilatory function, as measured by FEV₁, for example, increases during

childhood and reaches a peak level during early adulthood (Figure 12). From the peak level, ventilatory function declines with increasing age. In cigarette smokers who develop symptomatic airflow obstruction, a similar loss of function takes place, but at a more rapid rate than in nonsmokers and in smokers who do not develop disease. A physician is likely to diagnose COPD when continued excessive loss of ventilatory function results in sufficient impairment to cause dyspnea and limitation of activity.

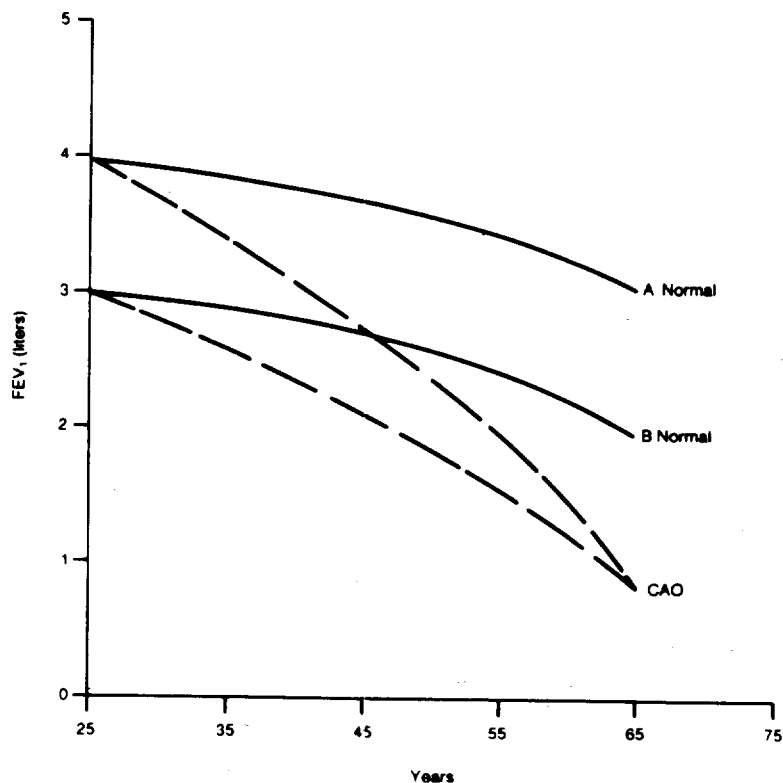


FIGURE 12.—Decline of FEV₁ at normal rate (solid line) and at an accelerated rate (dashed line)

NOTE: A, person who has attained a "normal" maximal FEV₁ during lung growth and development; B, person whose maximal FEV₁ has been reduced by childhood respiratory infection. CAO, chronic airflow obstruction.

SOURCE: Samet et al. (1983).

The factors influencing rate of lung function decline in cigarette smokers have not yet been fully characterized. The rate of decline tends to increase with the amount smoked, and former smokers generally revert to the rate of loss of nonsmokers. In fact, the excessive decline observed in some smokers may represent a common physiological consequence of different pathophysiological mechanisms. Habib and coworkers (1987) carefully characterized 13 subjects from a longitudinal study in Tucson with a mean annual decline in FEV₁ greater than 60 mL per year. Clinically, these subjects were not unique and none had alpha₁-antitrypsin deficiency. Physiological assessment

suggested that some were developing emphysema, whereas others appeared to have disease of the large and/or small airways.

The studies of longitudinal change in lung function have spanned only segments of the full natural history of COPD, and many questions remain unanswered. It is unclear, for example, whether the excessive decline takes place at a constant rate in continuous smokers, as suggested by much of the epidemiologic evidence, or whether the excessive decline occurs intermittently after some triggering event. The factors determining the susceptibility of individuals to cigarette smoking are also unclear. Current hypotheses emphasize determinants of protease–antiprotease imbalance, level of non-specific airways reactivity, and severe respiratory illness during early childhood.

Since the release of the 1964 Surgeon General's Report, abundant evidence has indicated the overwhelming importance of cigarette smoking in causing COPD; in fact, COPD would be an uncommon condition in the United States without cigarette smoking. Unfortunately, death rates due to COPD have paralleled those for lung cancer and have increased progressively over the last 25 years (National Center for Health Statistics 1986). The trends are consistent with cohort changes in smoking; in this regard, while age-specific rates for males have been increasing at older ages, a recent decline in COPD mortality has been observed at younger ages (US DHHS 1984). While important scientific questions remain unanswered concerning the pathogenesis of COPD, the available evidence provides sufficient rationale for preventing COPD through smoking prevention and cessation.

Pregnancy and Infant Health

Several endpoints have been studied to evaluate the adverse effects of smoking on pregnancy, including (1) infant birthweight; (2) fetal and infant mortality; (3) congenital malformations; (4) fertility; and (5) long-term effects on the child.

The 1964 Report indicated an association between smoking and low-birthweight babies (US PHS 1964), but it did not consider the evidence sufficient to establish a causal relationship.

The 1969 Report (US PHS 1969) confirmed the association between maternal smoking and low-birthweight babies, an increased incidence of prematurity, spontaneous abortions, stillbirths, and neonatal deaths. The 1971 Report (US DHEW 1971) concluded that maternal smoking during pregnancy exerts a retarding influence on fetal growth. The 1973 Report (US DHEW 1973) noted that cigarette smoking is a probable cause of increased late fetal mortality and infant mortality. The 1977–78 Report (US DHEW 1978) noted a dose–response relationship between smoking and abruptio placentae, placenta previa, bleeding during pregnancy, and prolonged premature rupture of membranes, as well as the association of smoking during pregnancy with impaired physical and intellectual development of the offspring. The 1979 Report (US DHEW 1979) linked smoking with sudden infant death syndrome. The 1980 Report (US DHHS 1980) noted that up to 14 percent of preterm deliveries in the United States may be attributed to maternal smoking. It also surveyed studies of men and women suggesting that cigarette smoking may impair fertility.

In 1985, the Center for Health Promotion and Education of the Centers for Disease Control, Atlanta, GA, defined the fetal tobacco syndrome as follows. (1) The mother smoked 5 or more cigarettes a day throughout the pregnancy. (2) The mother had no evidence of hypertension during pregnancy, specifically no preeclampsia and documentation of normal blood pressure at least once after the first trimester. (3) The newborn has symmetrical growth retardation at term, 37 weeks, defined as birthweight less than 2,500 g, and a ponderal index (weight in grams divided by length) greater than 2.32. (4) There is no obvious cause of intrauterine growth retardation, that is, congenital malformation or infection (Nieburg et al. 1985).

Infant Birthweight

A clear dose-response relationship exists between the number of cigarettes smoked during pregnancy and the birthweight deficit (US DHHS 1980; Committee to Study the Prevention of Low Birthweight 1985). Compared with nonsmokers, light and heavy smokers have a 54- and 130-percent increase, respectively, in the prevalence of newborns weighing less than 2,500 g. A review of five studies including 113,000 births in the United States, Canada, and Wales found that from 21 to 39 percent of the incidence of low birthweight was attributed to maternal cigarette smoking (Committee to Study the Prevention of Low Birthweight 1985). Also, cigarette smoking seems to be a more significant determinant of birthweight than the mother's prepregnancy height, weight, parity, payment status, or history of previous pregnancy outcome, or the infant's sex. The reduction in birthweight associated with maternal tobacco use seems to be a direct effect of smoking on fetal growth.

Mothers who smoke also have increased rates of premature delivery. The newborns are also smaller at every gestational age. The infants display symmetrical fetal growth retardation with deficits in measurements of crown-heel length, chest and head circumferences, and birthweight.

A recent study in Boston (Lieberman et al. 1985) attempted to evaluate the reasons for differences in rates of prematurity between blacks and whites. Of the 1,365 black women, 34.7 percent were cigarette smokers compared with only 23.4 percent of the white women. Cigarette smoking and low hematocrit levels were two of the most important risk factors accounting for the differences in prematurity rates between blacks and whites.

Finally, a number of careful studies have found that the effect of cigarette smoking on birthweight is not mediated through decreased maternal appetite or weight gain (US DHHS 1980).

The most widely accepted hypothesis relating maternal smoking and the effects on the fetus and newborn is intrauterine hypoxia (Rush and Cassano 1983). The hypoxia could occur as a result of factors associated with smoking, such as increased levels of carbon monoxide (CO) in the blood, reduction of blood flow, or inhibition of respiratory enzymes. There is strong experimental evidence that maternal smoking causes fetal hypoxia.

Several studies have demonstrated that smoking cessation prior to or during pregnancy can partly reverse the reduction in the child's birthweight (Rush and Cassano 1983; Hebel, Fox, Sexton 1988). In a large study using the 1970 British Birth Cohort (Lieberman et al. 1987), an inverse relationship between measures of social class and the prevalence of smoking was demonstrated that was similar to that seen in the United States. In all social class groups, babies of the nonsmokers weighed more than those whose mothers had smoked during pregnancy, and the women who had stopped smoking either before or during pregnancy had babies with higher birthweights than women who continued to smoke throughout pregnancy.

Fetal and Perinatal Mortality

Kleinman and colleagues (1988) from the National Center for Health Statistics used Missouri birth records from 1979–83 (Table 4) to study the relationship between cigarette smoking in mothers and infant mortality. Among the 134,429 primiparas, the infant mortality rates (adjusted for age, parity, education, and marital status) were (per 1,000 subjects) 15.1 for white nonsmokers, 18.8 for whites who smoked less than 1 pack of cigarettes per day, and 23.3 for whites who smoked more than 1 pack of cigarettes per day. For black nonsmoking women, the infant mortality rate (per 1,000 women) was 26.0; for blacks who smoked less than 1 pack per day, 32.4; and for blacks who smoked greater than 1 pack per day, 39.9. Mortality was increased during the fetal, neonatal, and postneonatal periods. It was estimated that if all pregnant women stopped smoking, the number of fetal and infant deaths would be reduced by approximately 10 percent. In the United States this would result in about 4,000 fewer infant deaths each year. A study conducted by the Office on Smoking and Health attributed approximately 2,500 infant deaths to maternal smoking in 1984 (CDC 1987).

Stein and associates (1981) have studied the causes of spontaneous abortion in three New York City hospitals. They compared women with spontaneous abortion to controls (women who carried their pregnancy to 28 weeks or more). Within the spontaneous abortion groups, they then compared those with evidence of chromosomal abnormalities and those with apparently normal chromosomes. The odds of a spontaneous abortion increased by 46 percent for the first 10 cigarettes smoked per day and by 61 percent for the first 20 cigarettes smoked. Smoking was not associated with the spontaneous abortion of chromosomally abnormal conceptions, but only with those in which the chromosomes were normal. These results were not confounded by such factors as maternal age or race.

Congenital Malformations

Evidence that exposure to tobacco and cigarette smoking could be related to congenital malformations is less clear. About 3 percent of all live births have major congenital malformations (Behrman and Vaughn 1987). Maternal smoking has not been demonstrated to be a major risk factor for the induction of congenital malformations, although elevated risks have been reported in some studies. Kelsey and coworkers (1978) reported an increased risk of 1.6 for congenital malformations among the

TABLE 4.—Infant mortality rates and odds ratios (95% confidence intervals), by maternal race, among 134,429 primiparas, based on multiple logistic regression, Missouri, 1979–83

	Crude rates (per 1,000)		Adjusted rates (per 1,000)		Adjusted odds ratios	
	Whites	Blacks	Whites	Blacks	Whites	Blacks
Marital status						
Married	14.5	25.4	15.9	29.5	1.00	1.00
Unmarried	24.0	28.6	21.0	27.2	1.33 (1.18–1.50)	0.92 (0.73–1.16)
Education (years)						
<12	22.9	33.2	19.8	34.1		1.36 (1.16–1.59)
12	15.2	25.9	16.7	28.8		1.14 (1.02–1.28)
>12	12.8	21.5	14.6	25.3		1.00
Age (years)						
<18	24.0	33.7	18.8	32.2		1.24 (1.06–1.45)
18–19	18.2	26.0	16.3	27.9		1.08 (0.95–1.22)
20–24	14.2	23.4	15.2	26.0		1.00
25–29	13.2	27.1	16.1	27.6		1.06 (0.94–1.20)
30–34	16.1	19.9	18.6	31.9		1.23 (1.01–1.50)
≥35	25.4	69.3	31.1	52.9		2.09 (1.49–2.93)
Smoking						
0	13.9	25.3	15.1	26.0		1.00
<1 pack/day	19.1	33.7	18.8	32.4		1.25 (1.13–1.39)
≥1 pack/day	24.3	41.5	23.3	39.9		1.56 (1.37–1.77)

SOURCE: Kleinman et al. (1988).

offspring of women smoking more than 1 pack of cigarettes per day compared with women reporting no smoking during pregnancy. Similarly, Himmelberger, Brown, and Cohen (1978) reported a 2.3-fold higher risk of congenital abnormalities for smoking mothers than for nonsmokers.

One study has also reported an increased frequency of congenital malformations based on the smoking habits of the father (Schardein 1985). The trends with paternal smoking were independent of maternal smoking level, maternal and paternal age, and social class.

The relatively low incidence of congenital malformations, the different types of malformations, and the various possible biological mechanisms have made the study of the relationship between environmental factors and congenital malformations extremely difficult. New techniques to monitor pregnancy outcomes may enhance our understanding of the interrelationship between cigarette smoking, other environmental factors, and congenital malformations.

Fertility

A recent study has substantiated previous reports that suggested that women who smoke may have reduced fertility (Baird and Wilcox 1985). Data on smoking history and number of noncontraceptive cycles until conception were collected from 678 pregnant women. Of nonsmokers, 38 percent conceived in their first cycle compared with 28 percent of smokers. Smokers were 3.4 times more likely than nonsmokers to have taken greater than 1 year to conceive. After adjustment for other risk factors, it was estimated that the fertility of smokers was 72 percent of that of nonsmokers. Heavy smokers experienced lower fertility than light smokers. Fertility was not affected by the husbands' smoking.

The effects of cigarette smoking on sperm quality in men (Ablin 1986) were also evaluated in relation to density, motility, and morphological abnormalities in 238 age-related smokers and 135 nonsmokers. Spermatozoa from smokers possessed significantly decreased density and motility compared with those from nonsmokers. Morphological abnormalities of the sperm were also noted more frequently among smokers than among nonsmokers (Ablin 1986).

Long-Term Effects on the Child

Relatively few studies have evaluated the long-term consequences of smoking during pregnancy on the child. One of the larger recent studies looked at neurological handicaps among children up to 14 years of age whose mothers had smoked during pregnancy and among control children born in northern Finland in 1966 (Rantakallio and Koiranen 1987). Seventy-eight children of smokers and 62 controls had mental retardation (IQs less than 85), cerebral palsy, or epilepsy. The incidence of mental retardation alone was 15.9/1,000 among the children of the mothers who smoked and 13.9 among the controls. For any combination of mental retardation, cerebral palsy, and epilepsy, the rates were 42.8/1,000 for children of smoking mothers and 34/1,000 for the controls, a relative risk of 1.27 with confidence limits of 0.90 to 1.79.