TABLE 7.—Mortality rates for lung cancer and cancer of the respiratory tract for white females in the United States per 100,000 population for selected years, 1940 to 1976

Year	Lung and Bronchus	Respiratory System
1940	—	3.6
1945	—	4.6
1950	4.7	5.4
1955	5.1	5.7
1960	5.9	6.4
1965	8.0	8.6
1970	12.3	13.1
1975	17.8	18.8
1976	19.5	20.5

SOURCE: National Center for Health Statistics (150)

TABLE 8.—Percent of adult population who were current cigarette smokers in selected years in the United States

Year	Percent smokers	
	Females	Males
1964	31.5	52.9
1966	33.7	51.9
1970	30.5	42.2
1975	28.9	39.3
Percent reduction since 1964	2.6	13.6

SOURCE: National Clearinghouse for Smoking and Health (155)

reduction in the number of adult females who smoke cigarettes, whereas there has been a 13.6 percent reduction in the number of adult males smoking. Trends in the percentage of teenagers who are regular cigarette smokers are presented in Table 9. Cigarette smoking among girls has increased steadily, so that at the present time equal numbers of boys and girls are smoking cigarettes and many of the differences which existed in the past between male and female smokers have disappeared.

Epidemiological Studies

Three of the large prospective epidemiological studies contain information on lung cancer in women. Data from these studies are summarized in Table 10. A number of retrospective studies have examined the

TABLE 9.—Percent of teenagers who were current cigarette smokers in selected years in the United States

Year	Percent smokers Ages 12–18	
	Girls	Boys
1968	8.4	14.7
1970	11.9	18.5
1972	13.3	15.7
1974	15.3	15.8

SOURCE: National Clearinghouse for Smoking and Health (*155a*)

TABLE 10.—Lung cancer mortality ratios for women—prospective studies

Study	Population	Number of deaths	Mortality ratio	
			Female nonsmokers	Female smokers
A.C.S. 25-State Study(*65*)	562,671 Females	183	1.00	2.20
Swedish study(*32*)	27,732 Females	8	1.00	4.50
Japanese study(*78*)	142,857 Females	148	1.00	2.03

relationship of lung cancer to smoking habits in women (*46, 63, 64, 80a, 122, 128, 139, 160, 164, 167, 198, 222, 227, 232, 236, 242, 247*).

Dose-Response Relationships

Dose-response relationships between lung cancer and cigarette smoking have been described for females by the number of cigarettes smoked per day, the degree of inhalation, and the duration of smoking. These relationships from selected studies are presented in Tables 11 through 14. The mortality ratios are as high as 10.0 for females who have smoked more than 20 cigarettes per day and for females who have smoked for more than 30 years.

Patterns of Cigarette Use

Although death rates from lung cancer are increasing at an accelerated rate in females, it may be that the peak will be somewhat less than in males; this may be due to substantial differences in the way males

TABLE 11.—Lung cancer mortality ratios for females, by number of cigarettes smoked per day: A.C.S. 25–State Study

Cigarettes smoked per day	Mortality ratios
Nonsmoker	1.00
1-19	1.06
20+	4.76

SOURCE: Hammond, E.C. (65)

TABLE 12.—Lung cancer mortality ratios for females, by number of cigarettes smoked per day: Haenszel and Taeuber

Cigarettes smoked per day	Mortality ratios
Nonsmoker	1.00
Occasional	1.33
1-19	2.49
20+	10.80

SOURCE: Haenszel W. (64)

TABLE 13.—Lung cancer mortality ratios for females, by duration of smoking: Swedish Study

Duration of smoking in years	Mortality ratios
Nonsmokers	1.0
1-29 years	1.6
30+ years	9.6

SOURCE: Cederlof, R. (32)

TABLE 14.—Lung cancer mortality ratios for females, by degree of inhalation: A.C.S. 25–State Study

Degree of inhalation	Mortality ratios
Nonsmokers	1.00
None to slight	1.78
Moderate to deep	3.70

SOURCE: Hammond, E.C. (65)

and females smoke cigarettes. A recent survey (155) of cigarette smoking behavior shows that women do not smoke as far down on the cigarette where proportionally more nicotine and tar are inhaled. More than 91 percent of females use filter cigarettes, compared with 80 percent of males. Females report that they do not inhale cigarette smoke as deeply into their lungs as males do. Women also smoke fewer cigarettes per day and select brands of cigarettes with lower tar and nicotine yields, compared to men. In 1975, 76.7 percent of current female smokers smoked a pack or less per day, whereas this was true for only 63.6 percent of males (155). In the past, women began smoking later than men, but at the present time this is no longer true. The available evidence suggests that women who smoke cigarettes in the same amount and with equal depth of inhalation as men are likely to experience death rates similar to those found in men.

Twins

The best way to control genetic factors as a potentially complicating variable in studies of lung cancer and cigarette smoking is to conduct the investigation in a population of twins who are discordant as to smoking habits (one smokes, the other does not). Cederlof, et al. (33) published new data on smoking and lung cancer from the Swedish Twin Registries in 1977. Although the number of deaths from lung cancer among the monozygotic twins is quite low, the trend is clear. The authors state, "The well-documented evidence of a causal association between smoking and lung cancer found in other studies has been further supported."

Lung Cancer and the Use of Other Forms of Tobacco

Pipe and cigar smokers in the United States have experienced lung cancer mortality rates that are somewhat higher than those of nonsmokers but substantially lower than those of cigarette smokers (1). Most pipe and cigar smokers report that they do not inhale the smoke, and as a consequence the total exposure is relatively low. There is little evidence that lung cancer is associated with the use of chewing tobacco or snuff. These relationships are explored in detail in the Chapter on Other Forms of Tobacco Use (specifically in Tables 15, 16, 17 and 22 of that chapter).

Histology of Lung Cancer

There are several different histologic types of lung malignancies in humans. These include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, bronchiolo-alveolar, and mixed and undifferentiated carcinomas of the lung. The predominent type of carcinoma in males is squamous cell carcinoma, whereas the most common lung cancer in females is adenocarcinoma. Over the past

15 years there has been little change in the incidence of large-cell, bronchiolo-alveolar, and mixed and undifferentiated carcinomas. There has been an increase in adenocarcinoma and a decrease in squamous cell carcinomas.

In 1962, Kreyberg (111a) categorized epidermoid, small-cell, and large-cell carcinoma of the lung as Group I and adenocarcinoma and bronchiolo-alveolar carcinoma as Group II. He noted that the risk for smokers was substantially greater for Group I than for Group II tumors. This view has been supported by some investigators (40, 47, 221). Other investigators have disputed this classification (9, 14, 15, 100, 230, 254).

Weiss, et al. (230) followed the experience of 6,136 men over a 10-year period. They found that well-differentiated squamous cell carcinoma, small-cell carcinoma, and adenocarcinoma displayed a dose-response relationship to smoking, but poor-differentiated squamous cell carcinoma did not.

More recently, Auerbach, et al. (10) examined histologic types of lung cancer associated with smoking habits from autopsy data on 662 men who had had lung cancer. In this study all cell types seemed to be related to smoking to about the same degree.

Most recently, Vincent, et al. (221) reviewed the histopathology of lung cancer in patients seen over a 13-year period at the Roswell Park Memorial Institute. Their data indicated that adenocarcinoma is becoming progressively more prevalent, compared to other forms of lung cancer. They were unable to disassociate smoking as a causative factor in any of the presently defined pathological categories of lung cancer.

Cessation of Smoking

There is a decrease in the risk of developing lung cancer after cessation of smoking. This decrease in risk occurs over a period of several years. After 10 to 15 years, the risk of dying of lung cancer for ex-smokers has decreased to point where it is only slightly above the risk for nonsmokers. All of the major studies show this reduction in risk. The most recent data from the British Doctor's Study are presented here for illustration (Table 15). The mortality ratios for ex-smokers were higher in the first year after quitting than they were for continuing smokers. The explanation for this is that both healthy and sick individuals quit smoking. Higher mortality is experienced by those who quit because of illness. Lower mortality is experienced by those who quit while experiencing apparently good health. In the U.S. Veterans Study, a differentiation is made between ex-smokers who stopped smoking on the recommendation of a doctor and those who quit for other reasons. About 10 percent of the smokers quit because of doctors' orders and were presumably ill. This group had much higher death rates from lung cancer than those who stopped for other reasons.

5—24

TABLE 15.—Lung cancer mortality ratios in ex-cigarette smokers, by number of years stopped smoking

Years stopped smoking	Mortality ratio
Still Smoking	15.8
1–4	16.0
5–9	5.9
10–14	5.3
15+	2.0
Nonsmokers	1.0

SOURCE: Doll, R. (47a)

The magnitude of the residual risk which ex-smokers experience is determined by the cumulative exposure to cigarette smoke which the individual experienced before he quit smoking. The risk at any point in time would be determined by the maximum amount the individual smoked, the years since stopping smoking, the age when smoking began, degree of inhalation, and reasons for quitting smoking. The lung cancer mortality experience of ex-smokers is graphically presented in Figure 3. The risk of developing lung cancer increases with age, for both smokers and nonsmokers. The incidence in cigarette smokers is much higher than in nonsmokers. It can be seen that the lung cancer mortality of ex-smokers is initially similar to that of smokers, but, with the passage of time, the mortality risk moves progressively closer to that of nonsmokers. It is interesting to note that, except for the first 2 years after stopping smoking, there is a continued increase in the risk of developing lung cancer among ex-smokers, although it is less than that of those who continue to smoke. The slope of this line is less than that for nonsmokers, and so there is a convergence of these two curves.

Lung Cancer and Air Pollution

A number of studies have been conducted in which the relative influence of cigarette smoking, urban residence, and air pollution in the etiology of lung cancer is examined. Eight of the earlier studies were reviewed in the 1971 Report of the Surgeon General (212). More recent publications include: "Epidemiological review of lung cancer in man" by Higginson and Jensen (75) and a report of a task group, "Air Pollution and Cancer," edited by Cederlof, et al. (31). There have also been studies by Doll (43), Weiss (229), Carnow (30), and Kotin and Falk (109).

Lung cancer is consistently more common in urban than in rural areas. There is only a small urban-rural lung cancer gradient for nonsmokers. There is a much larger urban-rural gradient for smokers. Cigarette consumption is generally greater in urban areas, but it is
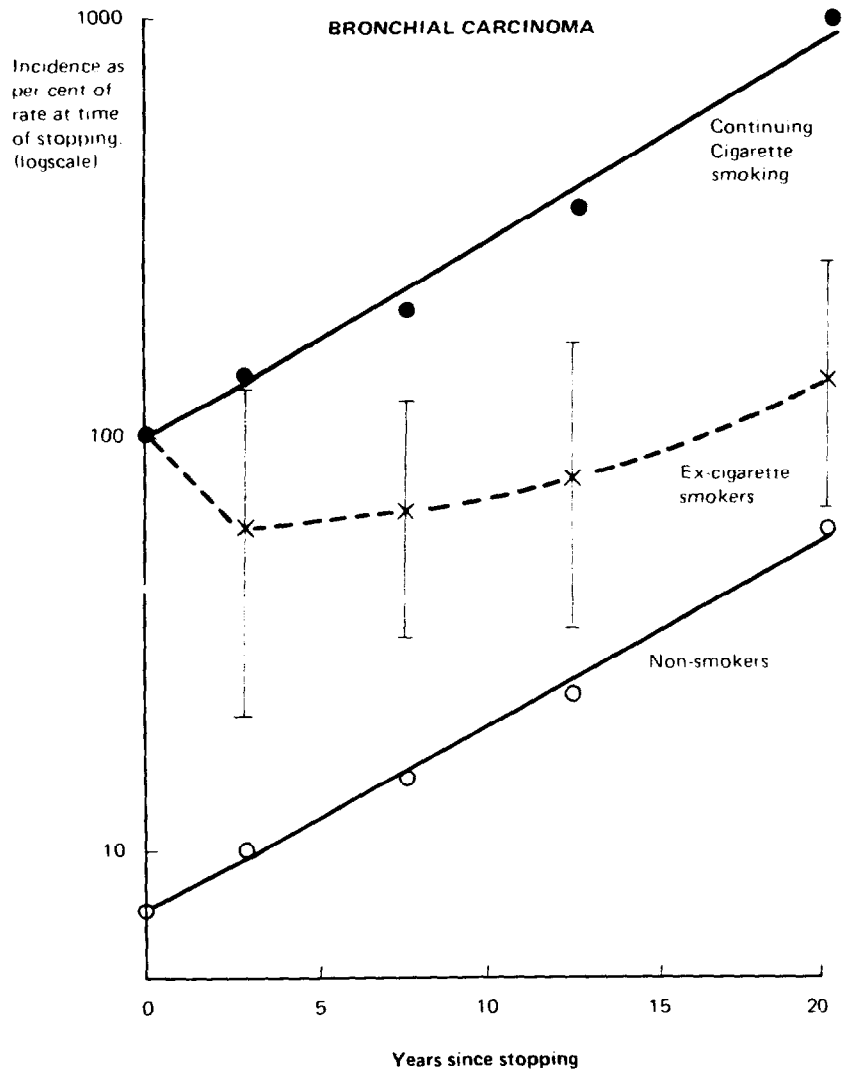
FIGURE 3.—Lung cancer mortality in continuing cigarette smokers and nonsmokers as a percentage of the rate among ex-cigarette smokers at the time they stopped smoking

SOURCE: UICC Technical Reports (*243*)

difficult to estimate how much of the excess urban mortality can be

accounted for by cigarette smoking alone. It is possible that there is an interaction between the carcinogens in cigarette smoke and other compounds in the ambient atmosphere.

Epidemiologic investigations thus far indicate that the most important cause of lung cancer is cigarette smoking and that urban factors such as air pollution have very little independent effect on the development of lung cancer. In the absence of cigarette smoking, the combined effects of all atmospheric agents do not increase the death rates for lung cancer more than a very few cases per 100,000 persons per year.

Lung Cancer and Occupational Factors

There are several occupations (described in Chapter 7) which are associated with the development of lung cancer and cancer at other sites (84). Estimates of the fraction of cancer deaths in the United States that can be attributed to occupational exposure have been made by several investigators. These estimates have been as low as 1 to 5 percent (45, 73, 74, 153, 241). Cole (37) has placed these estimates as high as 10 to 15 percent.

There are difficulties in estimating the proportion of cancers attributable to certain occupational exposures, tobacco, alcohol, or diet. Most of these estimates are based on the assumption that specific cancers are caused by specific agents. It is more likely that cancer is a disease of interactions. The precipitating cause and subsequent development of cancer is likely to be a process with multiple phases and multiple agents. Both internal and external factors interact at each of several stages before cancer becomes clinically apparent. The development of cancer, then, is influenced by two or more different external factors acting simultaneously or sequentially. This principle is illustrated by the synergistic effects of tobacco and alcohol. Cigarette smoking by itself is an important cause of oral cancer, whereas alcohol by itself is a relatively minor cause of oral cancer. Combined exposure to cigarette smoking and alcohol results in an increased risk of developing cancer of the oral cavity which is considerably higher than the risk experienced by cigarette smokers alone or drinkers alone.

The synergistic relationship between cigarette smoking and occupational exposure as it relates to the development of cancer is complicated. Most hazardous occupational exposures are to single agents or to a few at most. Cigarette smoking results in exposure to more than 2,000 chemical compounds, among which are carcinogens, tumor initiators, and promoters (see Chapter 14). It might be expected that cigarette smoking would have an adverse interaction with several occupational exposures, which it is important to try to identify. Insofar as possible, workers should be provided with a safe working environment, free from potentially harmful agents. It is equally true that workers can substantially reduce or eliminate the potential for

harmful occupational interactions by eliminating cigarette smoking from their lifestyle. This would probably eliminate the vast majority of the lung cancers which are occupationally related.

Short of giving up smoking entirely, it might be impossible for the worker to avoid many of the risks of developing cancer which may be related to his employment. Smoking at home but not on the job will not avoid this interaction, because the tars which are trapped in the airways will still be there when the individual goes to work.

Asbestos

In 1935, Lynch and Smith (*127*) in the United States and Gloyne (*61*) in in the United Kingdom reported an association between asbestos and lung cancer. In 1968, Selikoff, et al. (*188, 189*) first took into account the interaction between cigarette smoking and asbestos exposure in the development of lung cancer. They estimated that asbestos workers who smoked cigarettes had eight times the lung cancer risk of smokers without this occupational exposure. This was estimated to be 92 times the risk of nonsmokers who did not work with asbestos. This study has been continued and is supported by other investigations which consistently show a potent synergism between the carcinogens of tobacco smoke and asbestos (*19, 69*). There is evidence that exposure to asbestos carries some real risk to nonsmokers; however, this is of a low order of magnitude compared to the risks experienced by cigarette smokers (*135, 157*).

Uranium Mining

Lung cancer is an occupational risk associated with uranium mining. The causative agents in the atmosphere of mines are alpha particles resulting from the decay of short-lived radon daughters (*12, 48*). Several investigators (*7, 126, 173, 224, 225, 226*) have extensively studied underground uranium miners in the United States. The combined effect of tobacco smoke and radon daughter exposure results in high death rates from lung cancer among uranium miners. The risk for cigarette-smoking uranium miners is at least four times greater than for cigarette smokers who do not work in the mines.

Nickel

Epidemiological studies by Morgan (*146*) and Doll (*44*) and experimental studies by Hueper (*89*) and Sunderman, et al. (*200, 201, 202*) suggest that exposure to nickel or nickel carbonyl is a potent carcinogen for the respiratory tract in humans and animals. The interaction of cigarette smoking on the risk of respiratory cancer in nickel workers will probably never be adequately studied, since the Mond process for refining nickel is rarely used and conditions in nickel refining factories have improved.

5—28

Chloromethyl Ethers

Epidemiological and experimental studies (*59, 114*) have identified chloromethyl ethers as potent carcinogens for the human and animal respiratory tract. Investigations are in progress to more fully characterize these relationships, but the closing of the plants producing these substances makes it unlikely that the relative contribution of cigarette smoking to this type of occupational lung cancer will ever be known.

Animal Studies

Experimental animal models have been developed in which to study tobacco-induced carcinogenesis. Over the past 30 years, this field has acquired considerable sophistication and has enhanced our understanding of carcinogenesis in humans.

Experimental carcinogenesis has advanced to the point where it is now possible to reproduce in animals the major categories of respiratory tumors observed in humans and to link the induction of certain types of respiratory tumors to definite categories of exposure (*176*). By intratracheal administration of polynuclear hydrocarbons in rats and hamsters, bronchogenic squamous cell carcinoma is induced. Certain systemic carcinogens, particularly diethylnitrosamine in hamsters, give rise to adenomatous tumors of bronchial and bronchiolar-alveolar origin, as well as to papillary tumors in the trachea. Of the main types of respiratory tumors seen in human pathology, only one, the oat cell carcinoma, has not yet been found to be reproducible in experimental animals (*176*).

Skin Painting and Subcutaneous Injections

The earliest animal models for studying tobacco carcinogenesis involved the single or repeated painting of shaved or unshaved animal skin with solutions containing whole tobacco tar, various tobacco condensate subfractions, or single chemical compounds known to be present in tobacco smoke (*161*). Subcutaneous injections of various substances or fractions found in tobacco were also used as experimental models. Considerable criticism was directed towards these early studies, but they effectively demonstrated that a variety of carcinogenic compounds were found in tobacco smoke and that tobacco tar was a potent carcinogenic substance. Early experiments of these types have been reviewed by Wynder and Hoffmann (*245*).

Tracheobronchial Implantation and Instillation

More complex experiments have been performed using direct implantation, instillation, or fixation of suspected materials in the tracheobronchial tree of animals. Several authors have reviewed these studies (*115, 143, 175, 176, 245*).

5—29

Lung tumors which closely resemble lesions found in human cigarette smokers can be induced in hamsters by intratracheal instillation of benzo(a)pyrene (BaP). BaP induces a low incidence of bronchogenic tumors in hamsters when administered in saline; but when it is adsorbed into <1 μ ferric oxide carrier particles, its carcinogenicity is increased. When administered in the absence of BaP, ferric oxide particles alone do not induce tumors (176). The rate of elimination of BaP from the lung influences its tumorigenicity (71, 72). When BaP is administered alone or in simple mixtures with particles, 95 percent is eliminated within 24 hours. However, BaP adsorbed to particles is retained within the lung for several days (71, 72). Thus, the duration of the exposure to the carcinogen may be important to tumor induction by polycyclic aromatic hydrocarbons (PAH). These studies suggest that the particulate carrier increases the retention of PAH in the lung with a consequent increase in the exposure of respiratory tissue to the carcinogen.

In the hamster system, intratracheally-instilled BaP ferric oxide particles and subcutaneously-administered diethylnitrosamine (142, 143) were synergistic. Inhaled ferric oxide particles have also been found to enhance carcinogenicity of subcutaneously administered diethylnitrosamine (158) in the peripheral lung.

Inhalation Carcinogenesis

Various species, including mice, rats, hamsters, and dogs, have been exposed to cigarette smoke or to aerosols of its chemical constituents. Most of these substances have been administered to the experimental animal in a passive fashion. Active inhalation experiments more closely simulating human smoking behavior have been conducted by Rockey and Speer (169) and Auerbach, et al. (11, 66). In these experiments, animals were trained to inhale voluntarily through openings in the trachea.

Nitrosamines

A number of nitrosamines present in tobacco products or smoke have been found to produce respiratory tract tumors in animals. Various N-nitroso compounds of a nicotine metabolite, which are present in cured tobacco and chewing tobacco, can induce respiratory tract tumors in mice and hamsters (70, 77). Diethylnitrosamine, a volatile component of cigarette smoke, is a potent inducer of lung tumors in hamsters (141). Other nitrosamines present in tobacco products or smoke which have been shown to produce lung or tracheal tumors in animals include nitrosopiperidine (99) and N-nitrosodiethanolamine (81). This last compound is thought to be derived during curing from the maleic hydrazide triethanolamine salt which is sprayed on growing tobacco plants to reduce sucker formation.

Phagocytosis

Another factor which may be important is phagocytosis by macrophages. Some macrophages with engulfed particles remain in the lung for an extended period of time. A recent study by Palmer, et al. (*162*) showed that macrophages metabolized the potent carcinogen 7,12-dimethylbenz(*a*)anthracene (DMBA) and released the majority of the resultant derivatives into the surrounding medium. Unlike macrophages, cells from lung and tracheal tissues tended to retain the DMBA metabolites that they produced. This and related work by Harris, et al. (*69a*) showed that the human pulmonary macrophages under some conditions *in vitro* may permit the accumulation of metabolic products of carcinogens.

Conclusions

1. Cigarette smoking is the major cause of lung cancer in both men and women. This fact has been supported by prospective and retrospective epidemiological studies, clinical studies, autopsy studies, and experimental studies in animals. This conclusion is based on a weight of evidence which exceeds by several times the evidence available when this same conclusion was first reached in 1964.

2. The past 15 years have brought little significant progress in the earlier diagnosis or treatment of lung cancer. Taken as a whole, 30 percent of lung cancer patients live 1 year, and only 10 percent live 5 years after diagnosis. Fortunately, lung cancer is largely a preventable disease. Significant reductions in the number of deaths from lung cancer can be achieved if a significant portion of the smoking population can be persuaded to stop smoking and if a reduction can be brought about in the number of young people who take up smoking.

3. Lung cancer mortality is increasing in women and is increasing more rapidly than any other cause of death. If present trends continue, lung cancer will be the leading cause of cancer death among women in the next decade.

4. There are dose-response relationships for developing lung cancer with the number of cigarettes smoked per day, the duration of smoking, the age of starting to smoke, degree of inhalation, tar and nicotine content of cigarettes, and several other measures of dosage.

5. The long-term use (10 years or more) of filter cigarettes is associated with lower death rates from lung cancer than those experienced by persons who smoke an equal number of nonfilter cigarettes.

6. Ex-cigarette smokers experience decreasing lung cancer mortality rates, relative to continuing cigarette smokers. The risk of developing lung cancer for ex-smokers depends on the type of smoker he or she used to be. The risk is proportional to the number of cigarettes previously smoked per day, degree of inhalation, the age when smoking

was started, and duration of smoking. Whether the risk based on the previous smoking profile is high or low, there is a fairly rapid initial decline in risk following cessation of smoking which occurs over a 2- to 3- year period. It takes from 10 to 15 years, however, until the risk of developing lung cancer approaches the risk of nonsmokers.

7. Pipe and cigar smokers have lung cancer mortality rates which are higher than those of nonsmokers but which are considerable lower than those of cigarette smokers (see conclusions in the Chapter on Other Forms of Tobacco Use for further refinements and qualifications concerning pipe and cigar smoking).

8. Air pollution may be associated with the development of lung cancer; however, detailed epidemiological surveys indicate that the influence of air pollution on the development of lung cancer is small compared to the overriding effect of cigarette smoking. It is probable that there is a synergistic effect between cigarette smoking and air pollution in causing lung cancer. Air pollution does not appreciably influence lung cancer mortality rates in nonsmokers.

9. Certain occupational exposures, particularly uranium mining and working with asbestos, act synergistically with cigarette smoking, resulting in lung cancer mortality rates which exceed by several times the lung cancer mortality rates of unexposed cigarette smokers. Lung cancer mortality in these situations can be attributed to both cigarette smoking and the occupational exposure.

10. In the past few years, progress has been made in the development of animal models in which to study lung cancer. At the present time it is possible to reproduce in animals the major categories of respiratory tumors observed in man, using tobacco smoke, subfractions of tobacco tar, or specific compounds found in cigarette smoke.

Cancer of the Larynx

Approximately 1 percent of all deaths from cancer are from cancer of the larynx. It is estimated that in 1978 there were 3,350 deaths from cancer of the larynx, with 2,900 occurring in males and 450 occurring in females. The National Center for Health Statistics reported 3,351 deaths from cancer of the larynx in 1976. There were 2,808 deaths in males and 543 deaths in females (150). The most common histological lesion is squamous cell carcinoma. Approximately 70 percent are located in the glottis and 25 percent in the supraglottic region (132). Laryngeal cancer is predominantly a disease of males, although the incidence for females has increased somewhat over the past 20 years (181, 238). A typical patient with cancer of the larynx would be a 60-year-old male who was a heavy cigarette smoker and also a moderate-to-heavy alcohol drinker (132). The 5-year survival rate is improving and is presently at approximately 60 percent for all stages in both males and females.

TABLE 16.—Mortality ratios for cancer of the larynx—
prospectiive studies

Study	Population size	Number of deaths	Mortality ratio		Comments
			Nonsmokers	Smokers	
A.C.S. 9-State Study(68)	188,000 males	24	—	—	All larynx cancer deaths occurred in smokers
British doctors(47a)	34,000 males	38	1.00	13.00	Includes cancer of larynx and other upper respiratory sites.
U.S. veterans(90)	239,000 males	54	1.00	9.95	
A.C.S. 25-State Study(65)	440,000 males	57	1.00	6.09-males, 8.99-males,	ages 45–64 ages 65–79
California males in 9 occupations (228)	68,000 males	11	—	—	All larynx cancer deaths occurred in smokers
Japanese study(77a,80)	122,200 males	38	1.00	11.83	
	142,800 females	6	1.00	9.00	

Epidemiological Studies

Many epidemiological studies have investigated the relationship between smoking habits and cancer of the larynx. The major prospective studies are outlined in Table 16. In these studies, cigarette smokers had a mortality ratio which was 6 to 13 times greater than that of nonsmokers. In three of the prospective studies, mortality ratios could not be calculated because all of the deaths from cancer of the larynx occurred in cigarette smokers.

Recent retrospective studies confirm prior evidence of a strong positive association between cancer of the larynx and cigarette smoking (56, 238, 252, 253). Wynder, et al. (238) found that the large sex difference has diminished somewhat over the past 20 years. This is most likely due to the increase in female cigarette smokers in age groups for which laryngeal cancer rates are high. The relative risk for developing laryngeal cancer for male cigarette smokers was 15.8; for female cigarette smokers it was 9.0. There was also a strong dose-response relationship in the relative risk of laryngeal cancer with both

the number of cigarettes smoked per day and the duration of smoking. A distinct synergism with combined alcohol and tobacco use was also described, with a relative risk of 22.1 for the smoker of more than 35 cigarettes a day who was also a heavy drinker. This study also examined the relative risks experienced by long-term filter cigarette smokers. At every level of consumption, both males and females who smoked filter cigarettes had a lower risk than did nonfilter smokers. Among men, the reduction in risk ranged from 25 to 49 percent for cancer of the larynx, and a substantial lowering of risk was also found for women. For ex-smokers, the risk of developing laryngeal cancer diminished gradually with time in a curve that paralleled that for cancer of the lung. The most rapid reduction in risk occurred during the first 5 years after cessation of smoking. After approximately 10 years, the risk approached that of nonsmokers. Several of these relationships are demonstrated in Figures 4 through 7.

Williams and Horm (233), using data from the Third National Cancer Survey, reported a strong dose-response relationship for the number of cigarettes smoked per day and the risk of developing cancer of the larynx. The relative risks for males, controlling for age and race, were 2.9 for level-one smokers, 3.3 for level-two smokers, and 17.7 for level-three smokers (the levels for cigarette-smoke exposure were established by using both the amount and the duration of cigarette use). Considering tobacco use at each level of alcohol consumption, the risk of developing cancer of the larynx increased as tobacco exposure increased. There was a positive association for the intake of alcoholic beverages and the development of cancer of the larynx. In previous reports of the U.S. Public Health Service (212, 217), most of the older retrospective epidemiological studies have been reviewed (22, 56, 172, 174, 184, 185, 193, 196, 203, 205, 218, 237, 246, 250).

Asbestos

Several authors have found an association between asbestos exposure and cigarette smoking with development of laryngeal carcinoma (28, 121, 148, 190, 197).

Animal Studies

The Syrian golden hamster has been found to be a suitable species for the investigation of cancer of the larynx. The distribution of malignant lesions in the upper airway of the hamster is not due to an unusual susceptibility of the larynx for tumor induction but rather reflects the distribution of smoke aerosol precipitation within the upper respiratory tract. The most recent experimental studies are those of Bernfeld, et al. (18), Dontenwill, et al. (49, 50), Homburger (86), and Karbe and Koster (93). Cigarette smoke inhalation has not been found to induce laryngeal tumors in other rodents. Such tumors have been induced,
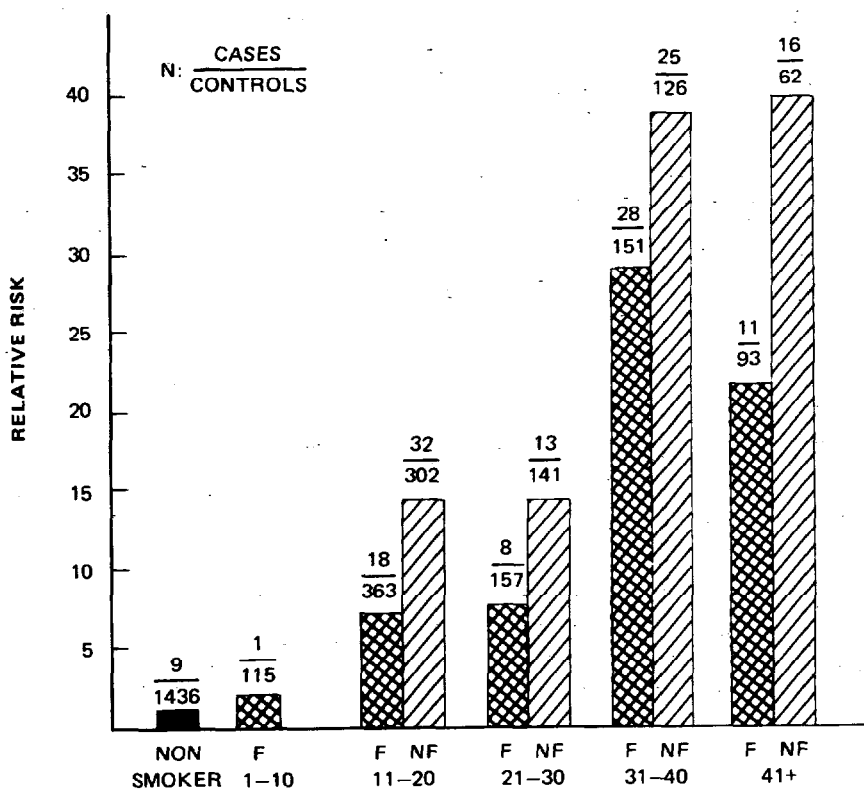
FIGURE 4.—Relative risk of developing larynx cancer for males, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes
SOURCE: Wynder, E.L. (*253*)

however, by the direct application of carcinogens known to be present in cigarette smoke. This is accomplished by the intratracheal instillation of benzo(a)pyrene in combination with particulate dusts into hamster lungs. In this animal model, laryngeal tumors, as well as tumors in other parts of the respiratory tract, are induced (*143, 176, 177*).
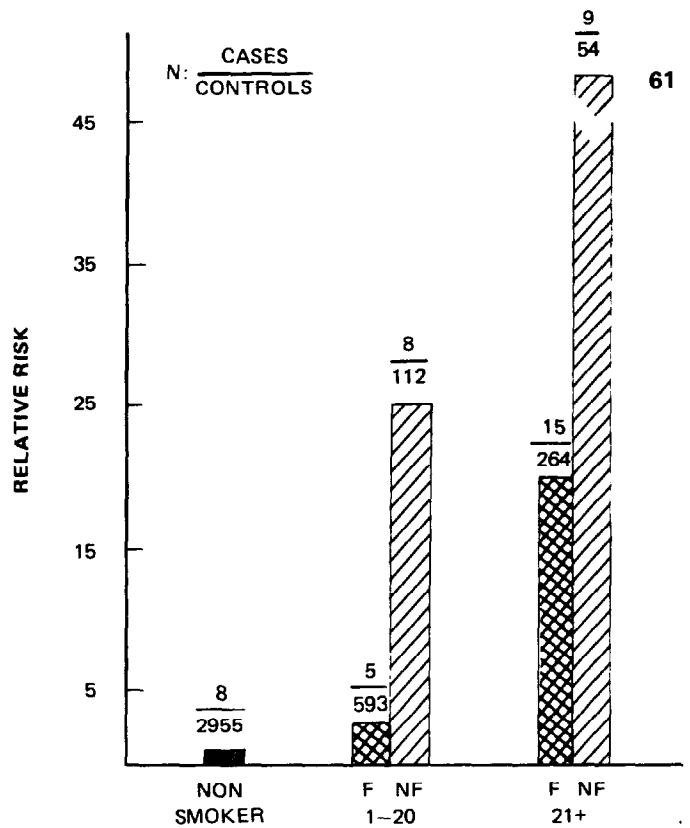
FIGURE 5.—Relative risk of developing larynx cancer for females, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes
SOURCE: Wynder, E.L. (*255*)

Conclusions

1. Epidemiological, experimental, and autopsy studies indicate that cigarette smoking is a significant causative factor in the development of cancer of the larynx.

2. The risk of developing cancer of the larynx in pipe and cigar smokers is similar to that for cigarette smokers.
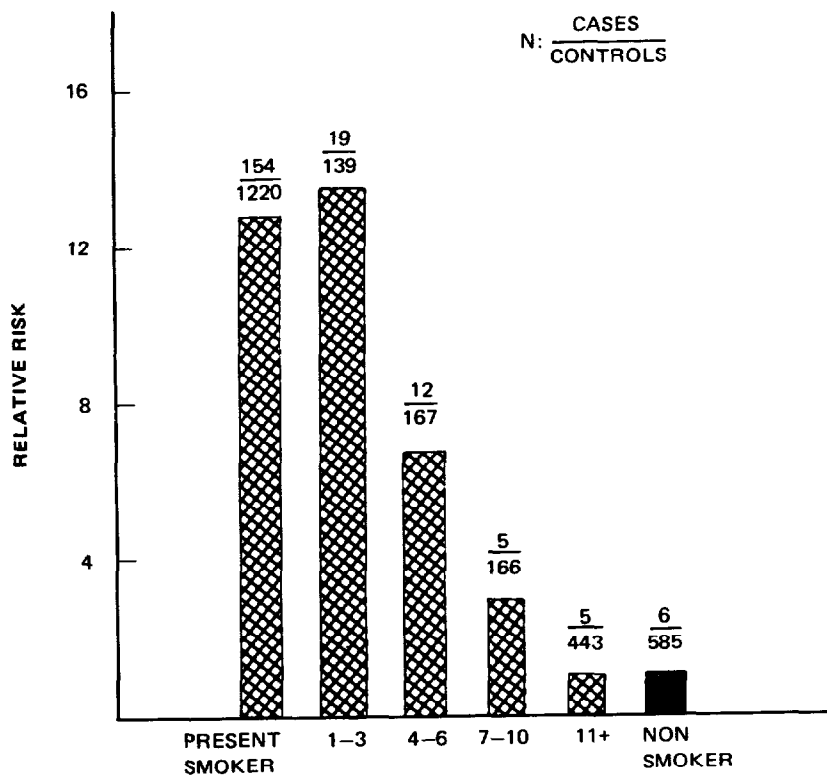
5—36

FIGURE 6.—Relative risk of developing larynx cancer for male ex-smokers, by years of smoking cessation
SOURCE: Wynder, E.L. (*253*)

3. There are positive dose-response relationships for the development of laryngeal cancer with the number of cigarettes smoked per day and the duration of cigarette smoking.

4. There is a synergistic effect with the use of cigarettes and alcohol. The risk of developing cancer of the larynx is much greater for heavy smokers who also drink heavily, compared with individuals who only have exposure to either substance.
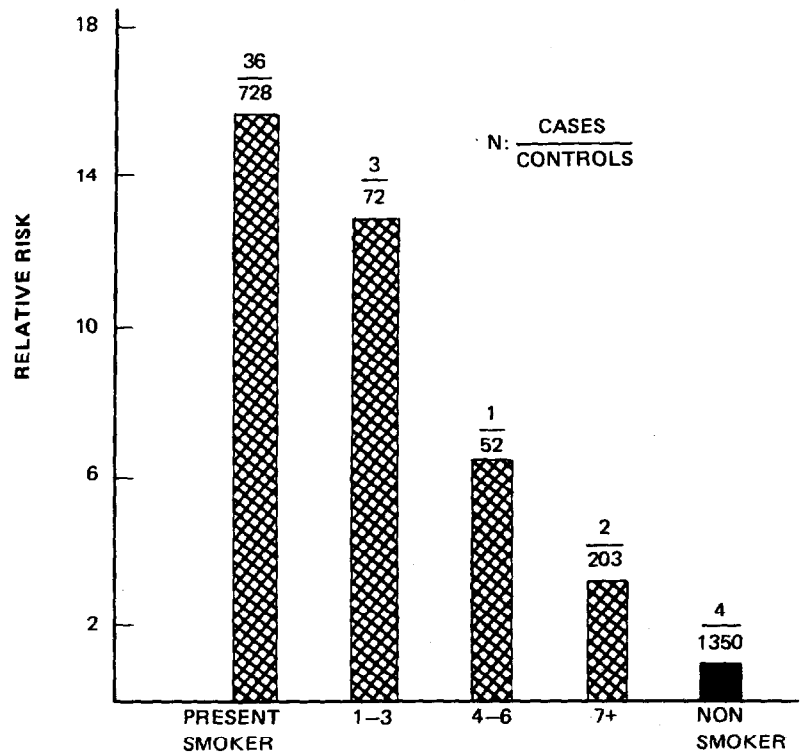
FIGURE 7.—Relative risk of developing larynx cancer for female ex-smokers, by years of smoking cessation
SOURCE: Wynder, E.L. (253)

5. There is a substantial decrease in the risk of developing cancer of the larynx with the long-term use of filter cigarettes (10 years or more), compared to the use of nonfilter cigarettes.

6. There is a gradual reduction in the risk of developing laryngeal cancer after cessation of smoking. After approximately 10 years, the risk of developing cancer of the larynx is similar to that of nonsmokers.

7. It has been reported that exposure to both asbestos and cigarette smoking synergistically increases the likelihood of an individual developing cancer of the larnyx.

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8. Animal models have been found in which inhalation of cigarette smoke induces cancer of the larynx.

Oral Cancer

Cancers included in the oral cancer category are those malignant tumors of the lip, tongue, floor of the mouth, hard and soft palate, the gums, buccal mucosa, and oropharynx. The National Center for Health Statistics reported that in 1976 there were 8,114 deaths from cancer of the oral cavity, buccal surfaces, and pharynx. There were 5,731 deaths among males and 2,383 deaths among females (*150*). It is estimated that, in 1978, 24,400 new cases were diagnosed with a total of 8,400 deaths (*4*). The incidence in males is three times that in females. For the floor of the mouth, tongue, and pharynx, 5-year survival rates vary from 25 to 45 percent. A variety of histological types of malignant neoplasms can affect these tissues, but squamous cell carcinoma is the most common type, accounting for 90 percent of cancer of the oral cavity.

Epidemiological Studies

The use of tobacco in various forms has been associated with the development of cancer of the oral cavity and pharynx. Studies of cancer of the oral cavity are international. Many investigations have been carried out in Asian nations, as well as in the West. Data from the major prospective epidemiological studies show increased mortality ratios for these cancers among cigarette smokers, as well as among pipe and cigar smokers, compared to nonsmokers. There is some variation in mortality ratios, ranging from about 3.0 to 10.0. The results of these investigations are presented in Table 17.

There are a large number of retrospective studies which have examined the relationship of cigarette smoking to the development of cancer of the oral cavity (*26, 57, 94, 95, 116, 117, 119, 133, 134, 138, 139, 144, 145, 163, 170, 174, 178, 193, 220, 223, 239, 246*). These studies almost uniformly show a significant relationship between the various forms of tobacco use and cancer of the oral cavity and pharynx. One large survey recently conducted in India was reported by Bhargava, Smith, Malaowalla, and associates (*21, 130, 192*). The prevalence of oral cancer was determined in 57,518 industrial workers in Gujarat, India. A 2-year follow-up survey was conducted, and the incidence of oral cancer was determined. There was a strong association with tobacco use in various forms. In the Third National Cancer Survey (*233*), Williams and Horm reported a significant correlation between cancer of the gum and mouth and the use of pipes, cigars, cigarettes, and unsmoked tobacco.

In many of the studies dose-reponse relationships were examined. Increasing relative risks with increasing tobacco use were noted.

TABLE 17.—Mortality ratios for cancer of the oral cavity—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
A.C.S. 9-State Study(68)	188,000 males	55	1.00	18.00	Only 3 deaths among nonsmokers
British doctors(47a)	34,000 males	38	1.00	13.00	Includes lip, tongue, mouth, pharynx, larynx, and trachea
U.S. veterans(90)	239,000 males	61	1.00	4.09	
A.C.S. 25-State Study(65)	440,000 males	95	1.00	9.90	Ages 45–64
California males in 9 occupations (228)	68,000 males	19	1.00	2.76	
Japanese study(77a,80)	122,200 males 142,800 females	43 11	1.00 1.00	2.88 males 1.22 females	
Swedish study(32)	55,000 Swedish males and females	15	Mortality ratios not published		5 deaths in non-smoking males. 10 deaths in smoking males.

Other Forms of Tobacco

All forms of tobacco use expose the oral cavity to compounds found in raw tobacco or tobacco smoke. In most of the prospective and retrospective studies where other forms of tobacco use were accounted for, significant correlations were found between the use of tobacco and the development of oral cancer. These relationships are of the same general magnitude or slightly greater than those found with cigarette smoking. These relationships are examined in detail in the Chapter on Other Forms of Tobacco Use.

Other Risk Factors

Other than tobacco use, alcohol consumption and possibly poor dentition appear to be risk factors for the development of oral and pharyngeal cancers. The most recent investigations of the interaction

between alcohol and tobacco in the development of oral cancer are the studies of Rothman and Keller (*170*), Feldman, et al. (*58*), Graham, et al. (*62*), Browne, et al. (*28*), and the Third National Cancer Survey (*233*). In the latter survey, cancer of the oral cavity was associated significantly with both cigarettes and alcohol. The relative strength of each exposure after controlling for the other was evaluated by multiple regression analysis. For cancer of the pharynx, the standardized regression slope (based on standard deviation units) in males, after controlling for age, race, education, and cigarettes or alcohol, was 0.104 for alcohol and 0.084 for cigarettes. For cancer of the oral cavity and gums, the values were: alcohol 0.081 and cigarettes 0.018. For cancer of the lip and tongue, the values were: alcohol 0.057 and cigarettes 0.043. Hence, in this survey, oral cancer in males was somewhat more related to drinking than to smoking.

Rothman and Keller (*170*) also reported a strong synergy between the two exposures. They attributed 76 percent of oral cancer in males to the interaction of tobacco and alcohol. Feldman, et al. (*58*) found that nonsmoking alcohol users had only a slightly increased risk for head and neck cancer, whereas smokers who did not use alcohol still had two to four times the risk of abstainers from alcohol and tobacco. The risk for the heavy drinker who smokes, however, was from 6 to 15 times greater than for the individual who did not use tobacco or alcohol. In the study of Graham, et al. (*62*), the relative risk for heavy smoking alone was only 1.54; for heavy drinking alone it was 1.70. Heavy smoking and heavy drinking resulted in a relative risk of 2.49. When this was combined with inadequate dentition, the risk rose to 7.68. Browne, et al. (*28*) reported that alcohol and tobacco use was particularly prevalent among patients with oral squamous cell carcinoma.

Leukoplakia

Leukoplakia of the oral mucosa represents an abnormal thickening and keratinization of the oral mucosa. Leukoplakia is generally recognized as a precursor of malignancy in the oral cavity and is associated with tobacco use in various forms. The largest survey of leukoplakia in a Western population has been conducted by Banoczy and associates (*13, 168, 199*). Leukoplakia is quite common in India where tobacco and betel-nut chewing occurs and where bidis are smoked. The prevalence and incidence of leukoplakia has been reviewed in several large studies (*21, 130, 137, 192*).

Animal Studies

An ideal animal model in which to study oral carcinogenesis has not been found. Cigarette smoke and cigarette-smoke condensates generally fail to produce malignancies when applied to the oral cavity of mice, rabbits, or hamsters. Mechanical factors, such as secretion of saliva,

interfere with the retention of carcinogenic agents. The only positive results with carcinogens have been obtained with benza(a)pyrene, 20-methyl-cholanthrene, and 9,10-dimetyl-1,2 benzanthracene applied to the cheek pouch of hamsters. The cheek pouch, however, lacks the salivary gland, and its structure and function differ from those of the oral mucosa. These studies have been reviewed in previous reports of the U.S. Public Health Service (212, 217).

Conclusions

1. 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.

2. 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.

3. 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.

Cancer of the Esophagus

The National Center for Health Statistics reported that there were 7,224 deaths from cancer of the esophagus in 1976. There were 5,343 deaths in males and 1,881 deaths in females (150). It has been estimated that these figures rose to 7,100 deaths from cancer of the esophagus in 1978 (4). In addition, esophageal cancer incidence and mortality in the United States are substantially higher for blacks than for whites (39). Epidermoid carcinoma is the most common cancer of the esophagus (3). The prognosis is extremely poor with a 5-year survival rate of only 3 percent; the median survival time is less than 6 months after diagnosis (152).

Epidemiological Studies

Data from the major prospective epidemiological studies demonstrate a significant relationship between smoking and esophageal cancer. The mortality ratios for male cigarette smokers range from 1.82 to 8.75. These relationships are shown in Table 18. In several of these studies a positive dose-response relationship for the number of cigarettes smoked per day is shown. Available evidence indicates a similar relationship for men and women.

A number of retrospective studies have been published concerning smoking and esophageal cancer. Risk ratios for smokers in these studies range from 1.3 to 11.1, compared to nonsmoking controls (24, 105, 133, 174, 178, 186, 194, 204, 235, 246).

TABLE 18.—Mortality ratios for cancer of the esophagus— prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
A.C.S. 9-State Study(68)	188,000 males	1 nonsmoker 33 smokers	1.00	—	Esophagus and other respiratory sites
British doctors (47a)	34,000 males	65	1.00	8.75	Esophagus and other respiratory sites
U.S. veterans(90)	293,000	111	1.00	6.17	
A.C.S. 25-State Study(65)	440,000 males	46	1.00	4.17	
California males in 9 occupations (228)	86,000	32	1.00	1.82	
Japanese Study(77a)	122,200 males	215	1.00	2.35	
Swedish Study(32)	55,000 Swedish males and females	1 nonsmoker 12 smokers	1.00	—	

Other Forms of Tobacco Use

In most of the prospective and retrospective epidemiological investigations, the association of esophagus cancer with the use of tobacco in other forms was examined. These relationships are discussed in some detail in the Chapter on Other Forms of Tobacco Use. The mortality ratios for cancer of the esophagus are approximately equal in users of cigars, pipes, and cigarettes.

Other Risk Factors

Numerous investigations have been made into the synergistic relationships between the use of tobacco in various forms, alcohol consumption, and the development of cancer of the esophagus (78, 92, 105, 182, 183, 204, 208, 233, 235, 249). Some investigators report that tobacco is a more important carcinogen than alcohol in the development of cancer of the esophagus, but others report that the reverse is true. Most of these studies support a synergism with the combined use of tobacco and alcohol, resulting in higher rates of cancer of the esophagus compared to those resulting from the use of either substance alone. The mechanism of the association is not known. Alcohol may act as a

solvent for carcinogenic hydrocarbons in tobacco smoke or alter microsomal enzymes in the mucosal cells of the esophagus (*234*). This hypothesis has received support from experimental observations by Kuratsune, et al. (*113*). The picture is complicated by the fact that alcoholism may be accompanied by severe nutritional deficiencies which may also predispose an individual to certain diseases.

Autopsy Studies

Histologic changes in the esophagus in relationship to smoking of tobacco in various forms were investigated by Auerbach, et al. (*11*). A total of 12,598 sections were made from esophageal tissue obtained from 1,268 subjects. It was found that tobacco smoking in any form resulted in the formation of atypical nuclei, disintegrating nuclei, hyperplasia, and hyperactive esophageal glands. Each of these parameters was significantly more abnormal in smokers than in nonsmokers; however, these changes were more frequently seen and more severe in cigarette smokers (*11*).

Animal Studies

There is experimental evidence that benzo(*a*)pyrene is able to penetrate the cell membranes of the esophageal epithelium, producing papillomas and squamous cell carcinomas. This process can be accelerated and better penetration achieved if the carcinogen is dissolved in an aqueous ethanol solution. This effect was reported by Kuratsune, Horie, and Kohchi (*88, 113*). Nitrosamine-induced esophageal cancer in experimental animals has also been reported by a number of investigators (*34, 52, 53, 54, 179*). These observations are significant because a variety of nitrosamine compounds have been identified in cigarette smoke.

Schmaehl (*179*) administered methyl-phenyl-nitrosamine orally or subcutaneously to Sprague-Dawley rats. Carcinomas of the esophagus were found in 46 to 87 percent of the animals. Simultaneous application of 25 percent ethyl alcohol did not affect the tumor incidence.

Mirvish (*140*) has reported that ^{3}H-thymidine incorporation in rat esophageal epithelium can be inhibited in the presence of nitrosamine *in vivo* and *in vitro*, lending further support to the role of these compounds in esophageal carcinogenic mechanisms.

Conclusions

1. Epidemiological studies demonstrate that cigarette smoking is a significant causal factor in the development of cancer of the esophagus. The risk of developing esophageal cancer increases with the amount smoked.