

TABLE 23.—Relative risk of cancer of the larynx for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

| Author (Reference) | Number | Relative Risk Ratio and Percentage of Cases and Controls by Type of Smoking | | | | | |
|------------------------|--------|---|------------|-----------|----------------------|----------------|-------|
| | | Non-smoker | Cigar only | Pipe only | Total pipe and cigar | Cigarette only | Mixed |
| Schrek et al. (244): | | Relative risk | 1.0 | 0 | 1.1 | 2.3 | |
| Cases | 73 | Percent cases | 14 | 0 | 7 | 80 | |
| Controls | 522 | Percent controls | 24 | 10 | 11 | 59 | |
| Sadowsky et al. (230): | | Relative risk | 1.0 | 2.2 | 2.3 | 3.7 | 4.1 |
| Cases | 273 | Percent cases | 4 | 2 | 5 | 60 | 29 |
| Controls | 615 | Percent controls | 13 | 3 | 7 | 53 | 23 |
| Wynder et al. (309): | | Relative risk | 1.0 | 15.5 | 27.7 | 11.1 | 24.6 |
| Cases | 209 | Percent cases | .5 | 8 | 5 | 1 | 86 |
| Controls | 209 | Percent controls | 11 | 10 | 4 | 2 | 74 |
| Wynder et al. (317): | | Relative risk | 1.0 | 9.7 | 4.5 | 6.3 | 6.3 |
| Cases | 60 | Percent cases | 5 | 17 | 15 | 47 | 17 |
| Controls | 271 | Percent controls | 24 | 9 | 16 | 36 | 13 |
| Wynder et al. (324): | | Relative risk | 1.0 | 14.5 | 16.0 | 22.0 | 16.0 |
| Cases | 142 | Percent cases | 1 | 20 | 1 | 62 | 16 |
| Controls | 220 | Percent controls | 16 | 22 | 1 | 45 | 16 |
| Pernu (209): | | Relative risk | 1.0 | | 4.5 | 8.7 | 3.2 |
| Cases | 546 | Percent cases | 7 | | 4 | 78 | 4 |
| Controls | 713 | Percent controls | 39 | | 5 | 50 | 7 |
| Staszewski (252): | | Relative risk | 1.0 | | 5.9 | 50.2 | |
| Cases | 207 | Percent cases | .5 | | 2 | 88 | |
| Controls | 912 | Percent controls | 17 | | 11 | 61 | |
| Svoboda (261): | | Relative risk | 1.0 | | 2.6 | 10.0 | |
| Cases | 205 | Percent cases | 3 | | 3 | 95 | |
| Controls | 320 | Percent controls | 22 | | 7 | 71 | |
| Stell (254): | | Relative risk | 1.0 | | 1.3 | 2.4 | |
| Cases | 190 | Percent cases | 11 | | 8 | 79 | |
| Controls | 190 | Percent controls | 17 | | 10 | 50 | |

CASES=239
 CONTROLS=4725

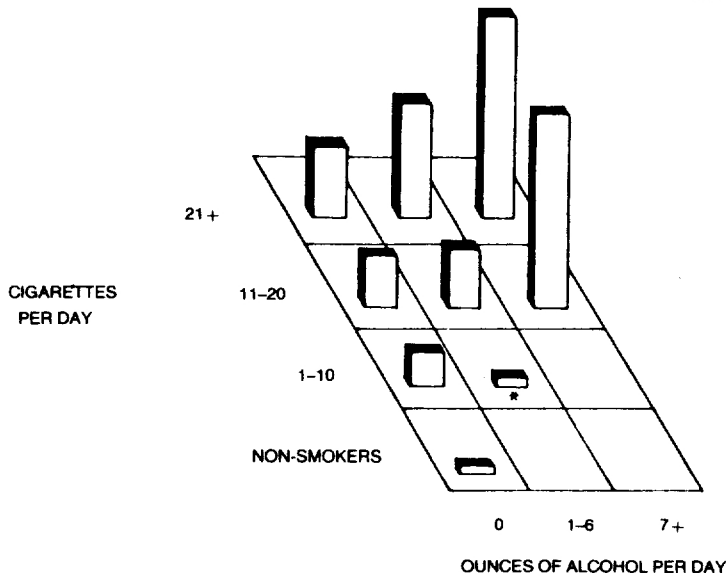


FIGURE 25.—Relative risks of larynx cancer by daily consumption of alcohol and cigarettes for males

* Not significant.
 SOURCE: McCoy et al. (179).

respiratory tract. Several recent experiments have been performed (23, 24, 72, 73, 125, 126, 133).

Cigarette smoke inhalation has not been found to induce laryngeal tumors in other rodents. Such tumors have been induced, however, by 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 particulates into hamster lungs. In this animal model, laryngeal tumors, as well as tumors in other parts of the respiratory tract, are induced (184, 231, 232). One study has recently reported a synergy of alcohol and benzo[a]pyrene injection (257).

Conclusion

1. Cigarette smoking is the major cause of laryngeal cancer in the United States. Cigar and pipe smokers experience a risk for laryngeal cancer similar to that of a cigarette smoker.
2. The risk of developing laryngeal cancer increases with increased exposure as measured by the number of cigarettes smoked daily as well as other dose measurements. Heavy

smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers.

3. Cessation of smoking reduces the risk of laryngeal cancer mortality compared to that of the continuing smoker. The longer a former smoker is off cigarettes the lower the risk.
4. Smokers who use filtered lower tar cigarettes have lower laryngeal cancer risks than those who use unfiltered higher tar cigarettes.
5. The use of alcohol in combination with cigarette smoking appears to act synergistically to greatly increase the risk for cancer of the larynx.

Oral Cancer

Introduction

Cancers of the oral cavity include malignant tumors of the lip, tongue, salivary gland, floor of the mouth, mesopharynx, and hypopharynx. It is estimated that in 1982 there will be 26,800 new cases and 9,150 deaths due to these tumors (2). Males are affected more commonly than females (by about threefold). Several authors (29, 175) have reported geographic differences in mortality. In the southeast, females living in urban and rural areas have mortality rates that exceed those of northern females by 30 and 90 percent respectively.

Cancer of the Buccal Cavity and Pharynx, Excluding Lip²

From 1950 to 1967, the age-adjusted rate remained stable at 2.8 per 100,000. The increase in the age-adjusted death rate from 2.8 to 2.9 per 100,000 between 1967 and 1968 resulted in part from changes in coding procedures in the International Classification of Diseases. From 1968 to 1977, the age-adjusted rate rose from 2.9 to 3.1. Total deaths from cancer of these sites increased from 1,461 in 1950 to 8,291 in 1977.

While the age-adjusted death rate of white males fell slightly over the study period (Figure 26), rates of white females and of males and females of races other than white increased. The largest increases occurred among other than white males, whose mortality rates rose from 4.1 to 7.7 per 100,000 between 1950 and 1977. The white male to female mortality ratio fell gradually over the study period, from 4.09 to 2.93. In contrast, the mortality sex ratio (male/female) in the other than white population increased from 2.56 to 3.85. The mortality ratio of other than white males to white males increased from 0.91 to 1.75, while the mortality ratio of other than white females to white females decreased slightly, from 1.45 to 1.33.

² Cancer of the lip is causally associated with smoking, particularly pipe smoking. However, because this cancer site represents so few deaths in the United States, only 163 in 1977, it is excluded from this review.

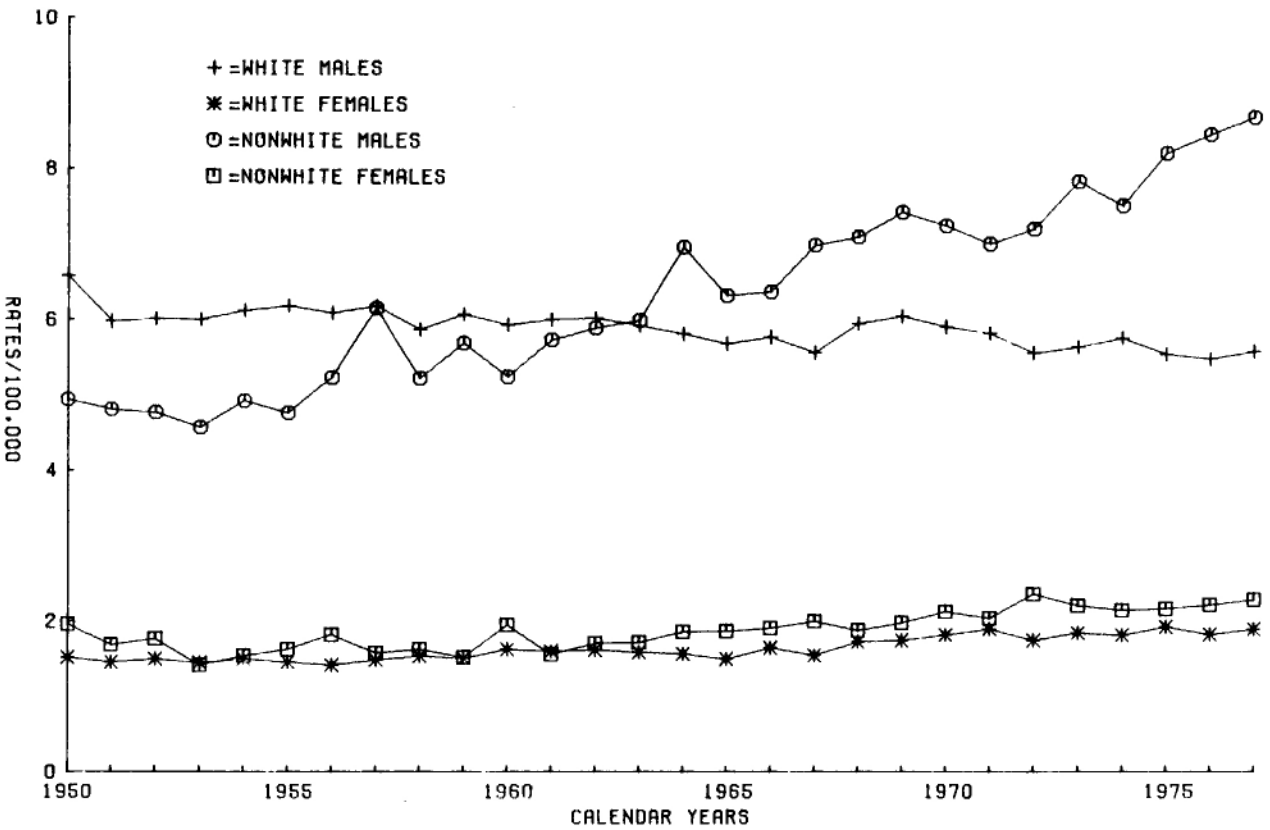


FIGURE 26.—Age-adjusted* mortality rates for cancer of the buccal cavity plus oral pharynx, by race and sex, United States, 1950-1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.
 SOURCE: National Cancer Institute (1967).

The death rates of white males 35 to 54 years of age and of those at least 75 years old were lower in 1977 than in 1960 (Figure 27), but rates were higher among white males between 55 and 74 years of age, as well as among white females in the same age range. In contrast, among other than white males in every 10-year age group from 35 through 84, as well as among females between 35 and 64, death rates were higher in 1977 than in 1960; the average increase in mortality in these age groups was 60 percent (Figure 28).

When age-specific death rates are plotted by calendar year and age (Figures 29 and 30), a three-dimensional graph is produced, which can be examined from 1950 to 1977, or from the reverse perspective.

Squamous cell cancer is the most common histological type of oral cancer and comprises about 90 percent of these tumors. The 5-year survival for cancer of the floor of the mouth, tongue, and pharynx ranges from 25 to 45 percent.

Numerous epidemiological and experimental studies have established a close association between smoking and oral cancer. Alcohol has an incompletely understood but important synergistic role with tobacco in increasing disease incidence and mortality.

Causal Significance of the Association

Consistency of the Association

More than 25 retrospective studies have examined the relationship between smoking and the development of cancer of the oral cavity (269, 276).

These studies have been done in many countries, in different areas, and have involved diverse study methods. Almost uniformly, they show an association between cigarettes and other forms of tobacco use and cancer of the oral cavity and pharynx. The TNCS study (299) and the Hawaiian Study of Five Ethnic Groups (113) reported similar findings.

Six of the major prospective studies examined the relationship between smoking and oral cancer. These data, presented in Table 24, show a close association between smoking and oral cancer.

Strength of the Association

The relative risks for oral cancer among smokers were substantially greater compared with nonsmokers in the retrospective studies. Similarly, in the prospective studies, the mortality ratios for cancer of the oral cavity among smokers ranged from 1.22 among Japanese females to over 13 in the U.S. Veterans and British Physicians studies (Table 24).

A dose-response relationship was noted in many of the retrospective and prospective studies (Table 25) (64, 98, 120, 131, 276). The American Cancer Society 25-State Study (155) reported a reduction

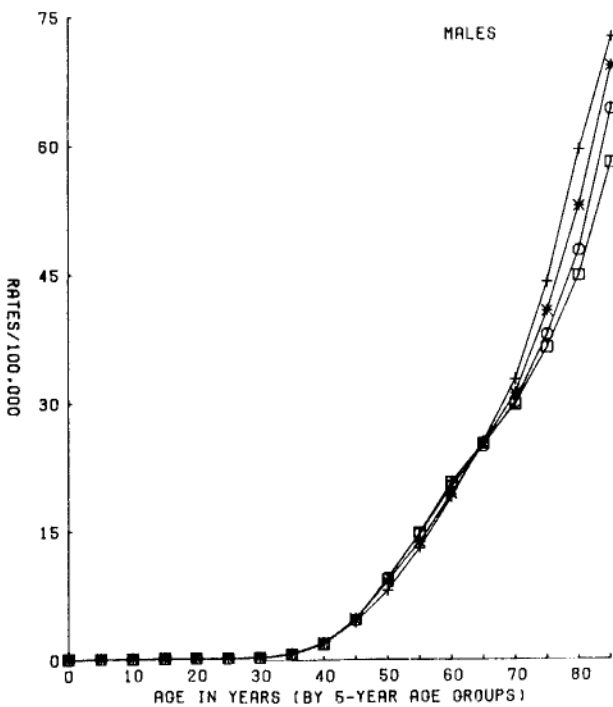
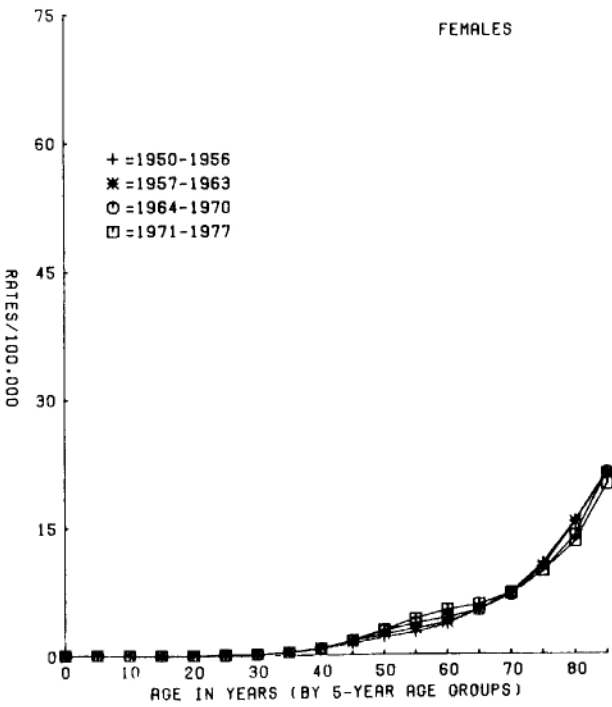


FIGURE 27.—Age-specific mortality rates for whites in the United States for cancer of the buccal cavity plus oral pharynx
 SOURCE: National Cancer Institute (1981)

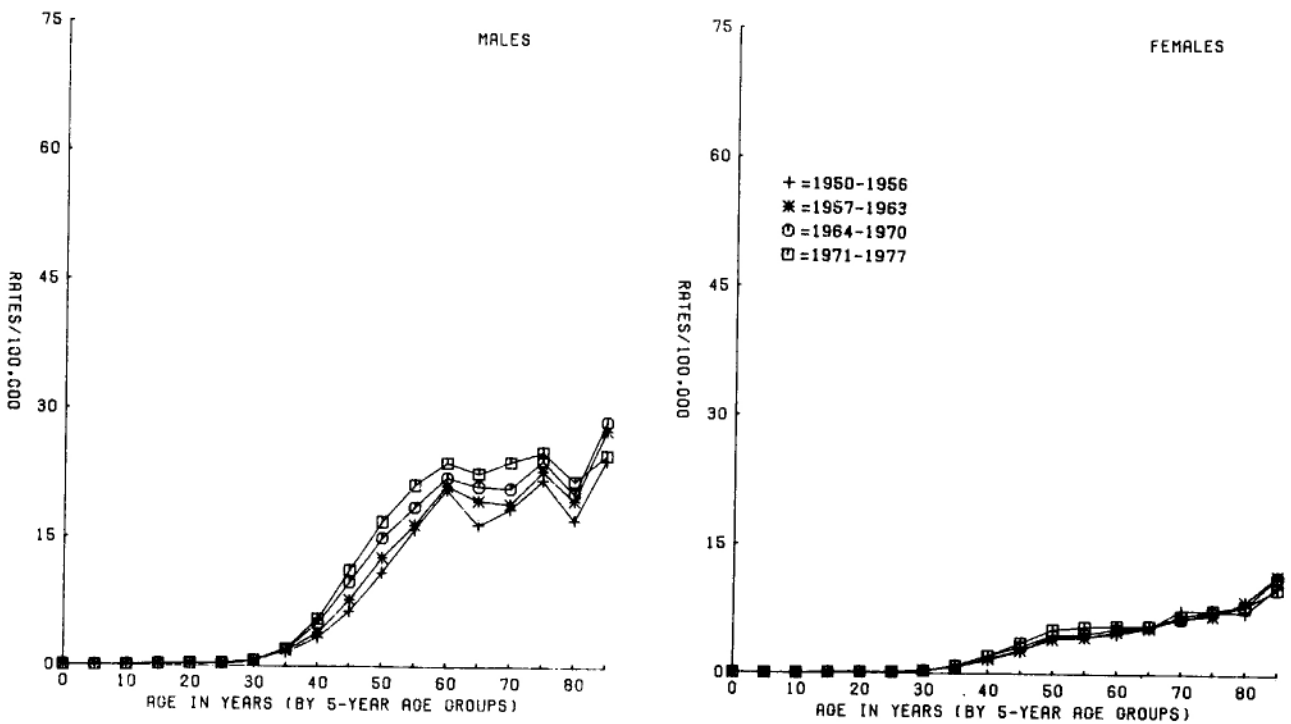


FIGURE 28.—Age-specific mortality rates for nonwhites in the United States for cancer of the buccal cavity plus oral pharynx
 SOURCE: National Cancer Institute (1981).

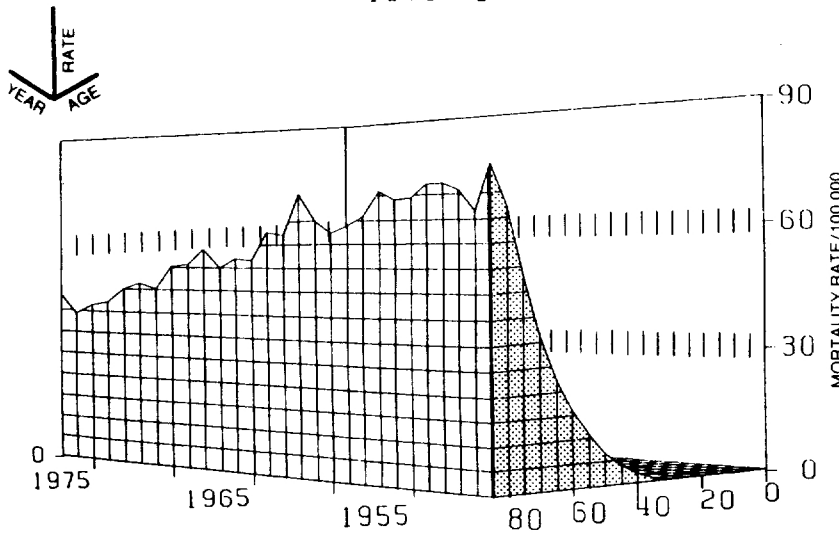
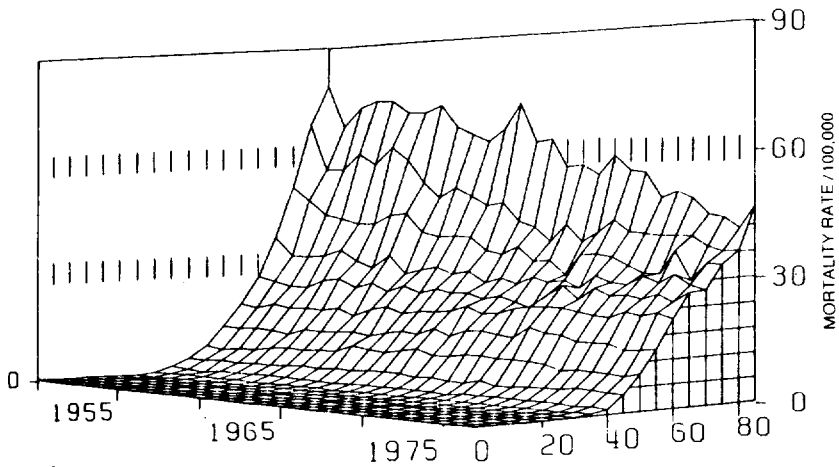


FIGURE 29.—Age-specific mortality rates by 5-year age groups for cancer of the buccal cavity and pharynx for white males, United States, 1950-1977

SOURCE: National Cancer Institute (198).

in risk for cancer of the buccal cavity and pharynx among smokers of lower tar and nicotine cigarettes, but the reduction was not statistically significant. Wynder and Hoffmann (316) reported similar findings in a retrospective study of smokers of filter cigarettes versus smokers of nonfilter cigarettes.

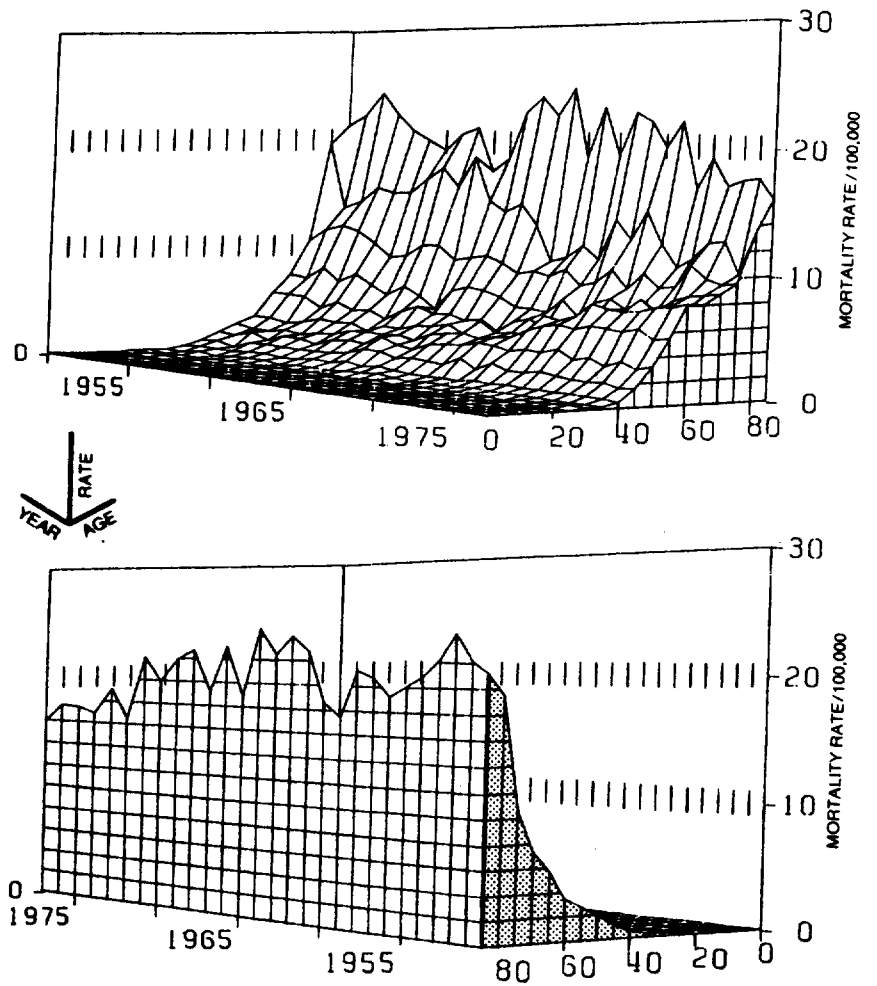


FIGURE 30.—Age-specific mortality rates by 5-year age groups for cancer of the buccal cavity and pharynx for white females, United States, 1950-1977

SOURCE: National Cancer Institute (198).

Specificity of the Association

The prospective studies have reported mortality data for a large number of diseases. Specificity, which is related to the magnitude of the association between smoking and oral cancer, is evidenced by the differences in the mortality ratios (smokers versus nonsmokers) of oral cancer and other cancers (Appendix Tables A and B). These

TABLE 24.—Mortality ratios for cancer of the oral cavity—prospective studies

| Study | Population size | Number of deaths | | Cigarette smokers | Comments |
|-----------------------------------|--------------------------|------------------|--------------------------------|-------------------|---|
| | | Nonsmokers | | | |
| ACS 9-State Study | 188,000 males | 55 | 1.00 | 5.06 | Only 3 deaths among nonsmokers |
| British Physicians | 34,000 males | 38 | 1.00 | 13.00 | Includes lip, tongue, mouth, pharynx, larynx, and trachea |
| U.S. Veterans | 290,000 | 61 | 1.00 | 4.22 | Buccal cavity Pharynx |
| | | | 1.00 | 14.05 | |
| ACS 25-State Study | 358,000 males | 167 | 1.00 | 6.52 | Buccal cavity and pharynx |
| | 483,000 females | 65 | 1.00 | 3.25 | |
| California males in 9 occupations | 68,000 males | 19 | 1.00 | 2.76 | |
| Japanese Study | 122,200 males | 43 | 1.00 | 2.88 males | Data for mouth only |
| | 142,800 females | 11 | 1.00 | 1.22 females | |
| Swedish Study | 55,000 males and females | 15 | Mortality ratios not published | | 5 deaths in nonsmoking males; 10 deaths in smoking males |

differences are even greater when comparisons are made with the mortality ratios of heavy smokers.

Temporal Relationship of the Association

Evidence for a temporal relationship of this association is provided by the prospective studies in which populations of apparently disease-free smokers and nonsmokers were followed over time for oral cancer mortality. In addition, the finding of premalignant oral mucosal changes in greater proportions of smokers than nonsmokers provides evidence for the temporality of the association (see below).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship between smoking and oral cancer mortality in both retrospective and prospective studies lends support to the causal nature of the association.

TABLE 25.—Oral cancer mortality ratios by amount smoked—prospective studies

| Study | Population | Amount Smoked per Day | | | | Comments |
|-----------------------------------|---------------|-----------------------|--------|---------|------|---------------------------------------|
| | | Males | | Females | | |
| British Physicians | 40,000 | NS | 1.00 | NS | 1.00 | Male data by grams of tobacco per day |
| | | 1-14 | 5.00 | 1-14 | — | |
| | | 15-24 | 7.00 | 15-24 | 4.00 | |
| | | 25 + | 33.00 | 25 + | 6.50 | |
| U.S. Veterans | 290,000 | NS | 1.00 | | | *Based on fewer than 20 deaths. |
| | | 1-9 | 2.92* | | | |
| | | 10-20 | 2.87 | | | |
| | | 21-39 | 6.15 | | | |
| | | 40 + | 12.40* | | | |
| Japanese in 29 Health Districts | 265,000 | NS | 1.00 | | | Hypopharynx only |
| | | 1-19 | 1.20 | | | |
| | | 20-29 | 5.50 | | | |
| | | 30 + | 9.10 | | | |
| ACS 9-State Study | 188,000 males | NS | 1.00 | | | Includes larynx and esophagus |
| | | 1-9 | 7.00 | | | |
| | | 10-20 | 6.00 | | | |
| | | 20 + | 7.67 | | | |
| California males in 9 occupations | 68,000 males | NS | 1.00 | | | |
| | | < 1/2 pack | 3.69 | | | |
| | | 1 pack | 1.17 | | | |
| | | 1 1/2 pack | 5.52 | | | |

NOTE: NS: Nonsmoker.

Correlation of Sex Differences in Oral Cancer With Different Smoking Habits

Oral cancer is predominantly a disease of males, but the difference between male and female rates of disease is narrowing. This finding is consistent with the differences in the smoking trends of males and females noted above. As with laryngeal and esophageal cancer, there is a strong association between oral cancer and alcohol consumption. This must be considered as contributing to the excess ratio of male to female oral cancer mortality (see below).

Correlation of Oral Cancer Mortality Rates Among Populations With Different Tobacco Consumption

In populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the incidence and mortality rates of cancer of the gum, mouth, tongue, and pharynx are substantially reduced (79, 165, 166, 211, 294).

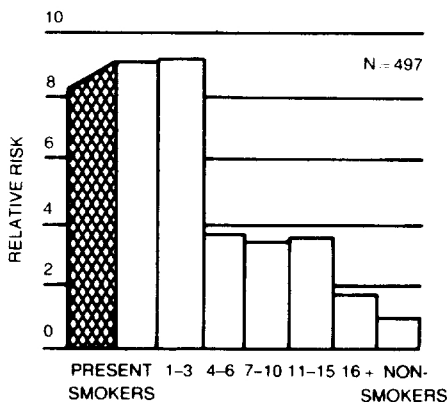


FIGURE 31.—Relative risk of male ex-smokers for cancer of the oral cavity by years since quitting smoking

SOURCE: Wynder and Stellman (326).

Oral Cancer Mortality and Cessation of Smoking

In the U.S. Veterans Study (224), ex-smokers had approximately 40 percent of the risk for oral cancers of current smokers. Data from the American Health Foundation study found that the risk of cancer of the oral cavity among former smokers declined with the number of years off cigarettes when compared to the risk of continuing smokers. After 16 or more years of cessation, the risk of oral cancer approaches that of nonsmokers (Figure 31). This is consistent with the causal nature of the association.

Smoking and Histological Changes in the Oral Mucosa

Leukoplakia is an abnormal thickening and keratinization of oral mucosa and is recognized as a precursor of malignancy of the oral cavity (124). A few studies have established a relationship between smoking in various forms and leukoplakia (269).

Oral Cancer and Non-Cigarette Tobacco Use

The oral cavity and pharynx are the sites most consistently exposed to tobacco smoke. A summary of the data from the prospective epidemiological studies is presented in Table 26. They demonstrate that cigar and pipe smokers experience a significant risk of developing cancer of the oral cavity compared with nonsmokers. This risk is approximately equal for all smokers whether an individual uses a pipe, cigar, or cigarette.

Several authors have reported a relationship between chewing tobacco and/or snuff dipping (the placement and retention of fine

TABLE 26.—Mortality ratios for oral cancer in cigar and pipe smokers. A summary of prospective epidemiological studies

| Study | Smoking Type | | | | | |
|---------------------------------|--------------|------------|-----------|----------------------|------------------|-------|
| | Non-Smoker | Cigar Only | Pipe Only | Total Pipe and Cigar | Cigarette Only | Mixed |
| ACS 9-State Study ¹ | 1.00 | 5.00 | 3.50 | — | 5.06 | — |
| British Physicians ² | 1.00 | — | — | ³ 9.00 | 13.00 | 11.00 |
| ACS 25-State Study | 1.00 | — | — | 4.94 | M 6.52 F 3.75 | — |
| U.S. Veterans Study | | | | | | |
| Oral ⁴ | 1.00 | 4.11 | 3.12 | 4.20 | 4.22 | 3.79 |
| Pharynx | 1.00 | — | 1.98 | 7.76 | 14.05 | 7.75 |

¹ Combines data for oral, larynx, and esophagus.

² Figures for all non-lung respiratory cancers.

³ Mortality ratios for ages 45 to 64 only as presented.

⁴ Excludes pharynx.

ground or powdered tobacco in the oral vestibule between the gums and cheek) and oral cancer (36, 186, 207, 234, 299, 301, 310). A recent report found a fourfold increase in risk for oral cancer among female snuff dippers compared to nontobacco users (301). The excess risk for cancers of the cheek and gum was nearly fiftyfold among long-term users. The authors estimated 87 percent of these tumors were related to snuff use. In the Third National Cancer Survey, Williams and Horm (299) noted an excess relative risk for cancers of the gum and mouth in male and female users of chewing tobacco or snuff. However, this risk was only statistically significant for males.

A few epidemiological investigations have demonstrated an association between the combined use of alcohol and pipe or cigar smoking and the development of oral cancer (135, 172, 173, 310). Heavy pipe and/or cigar smoking and heavy drinking are associated with higher rates of oral cancer than are seen with either habit alone.

Synergistic Role of Alcohol and Cigarettes for Oral Cancer

Oral cancer occurs more commonly in heavier users of alcohol (37, 88, 136, 227, 283, 301, 310). A recent study (179) noted an interaction (Figure 32) for oral cavity cancer in white males who use both alcohol and cigarettes. Nonsmokers who consumed 7 ounces or more of alcohol per day had a relative risk of 2.5. Those cigarette smokers who consumed 7 ounces or more of alcohol per day had a relative risk of 5.1 if they smoked one-half a pack or less daily, 20.5 if they smoked 11 to 20 cigarettes per day, and 24.0 if they smoked more than one pack of cigarettes per day. A distinct synergy (a multiplicative effect) of alcohol and cigarette smoking has been described elsewhere (271). The mechanism by which these two factors interact is unclear.

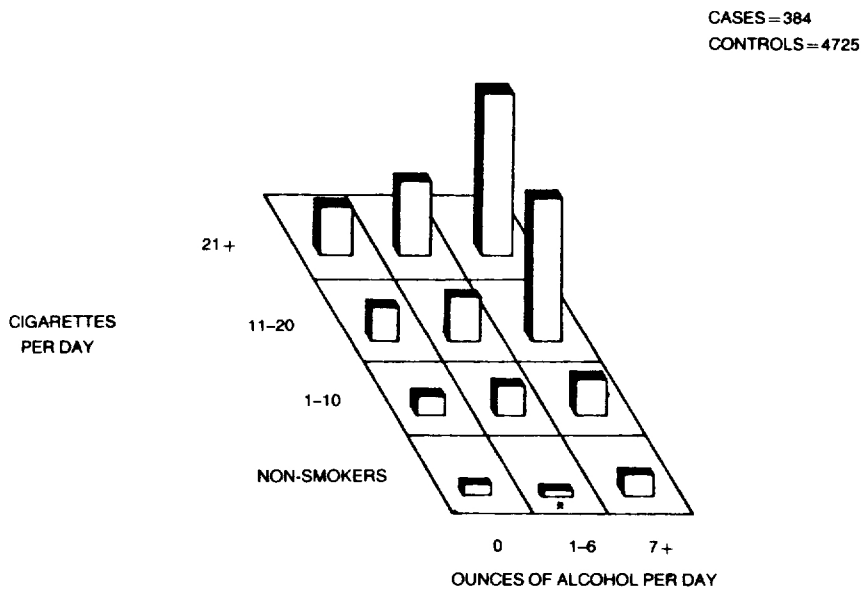


FIGURE 32.—Relative risks of oral cavity cancer by daily consumption of alcohol and cigarettes for males

* Not significant.

SOURCE: McCoy et al. (179).

Experimental Studies

A useful animal model for the experimental study of 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. However, positive results have been obtained with benzo[a]pyrene, 20-methyl-cholanthrene, 9,10-dimethyl-1,2 ben-zanthracene, and other tobacco smoke carcinogens when applied to the cheek pouch of hamsters. The cheek pouch, however, lacks salivary glands, 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 (272, 276).

Conclusion

1. Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker.

2. Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking.
3. Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers.
4. Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum.

Carcinoma of the Esophagus

Introduction

Carcinoma of the esophagus is a rapidly fatal neoplasm; there is a median survival of less than 6 months following diagnosis and a 5-year survival rate of 3 percent.

The number of deaths caused by esophageal cancer rose from 3,866 in 1950 to 7,283 in 1977. The age-adjusted death rate increased from 2.3 to 2.6 over this period (Figure 33).

In the United States in 1977, 3,924 white males and 1,520 white females died from esophageal cancer; in the other than white population, 1,404 males and 435 females died from this disease. While these figures represent only a slight increase in age-adjusted mortality in the white population, they do reflect nearly a twofold increase in the other than white population from 1950 to 1977.

The ratio of the age-adjusted death rate of the other than white population to that of the white population increased over the study period. In 1977, the death rate from this cause among other than white males between the ages of 35 and 44 years was eight times that among white males of the same age. The death rate of other than white females in this age group was 13 times the corresponding rate of white females. Mortality ratios by race (white/other-than-white) decreased with age in both males and females.

Among whites, the mortality sex ratio (male/female) declined slightly between 1968 and 1977. In the other than white group, there was also a greater relative increase in the age-adjusted death rate of females than in those of males.

Among white males and females, age-specific death rates from cancer of the esophagus (Figure 34) increased in each succeeding 10-year age group to the end of the lifespan. In other than white males, mortality peaked between ages 65 and 74 (Figure 35). The pattern was irregular in other than white females, varying with age group and time span over the 1950-1977 period.

A three-dimensional graph of age-specific death rates for white males and females for cancer of the esophagus over the period 1950-1977 is shown in Figures 36 and 37.

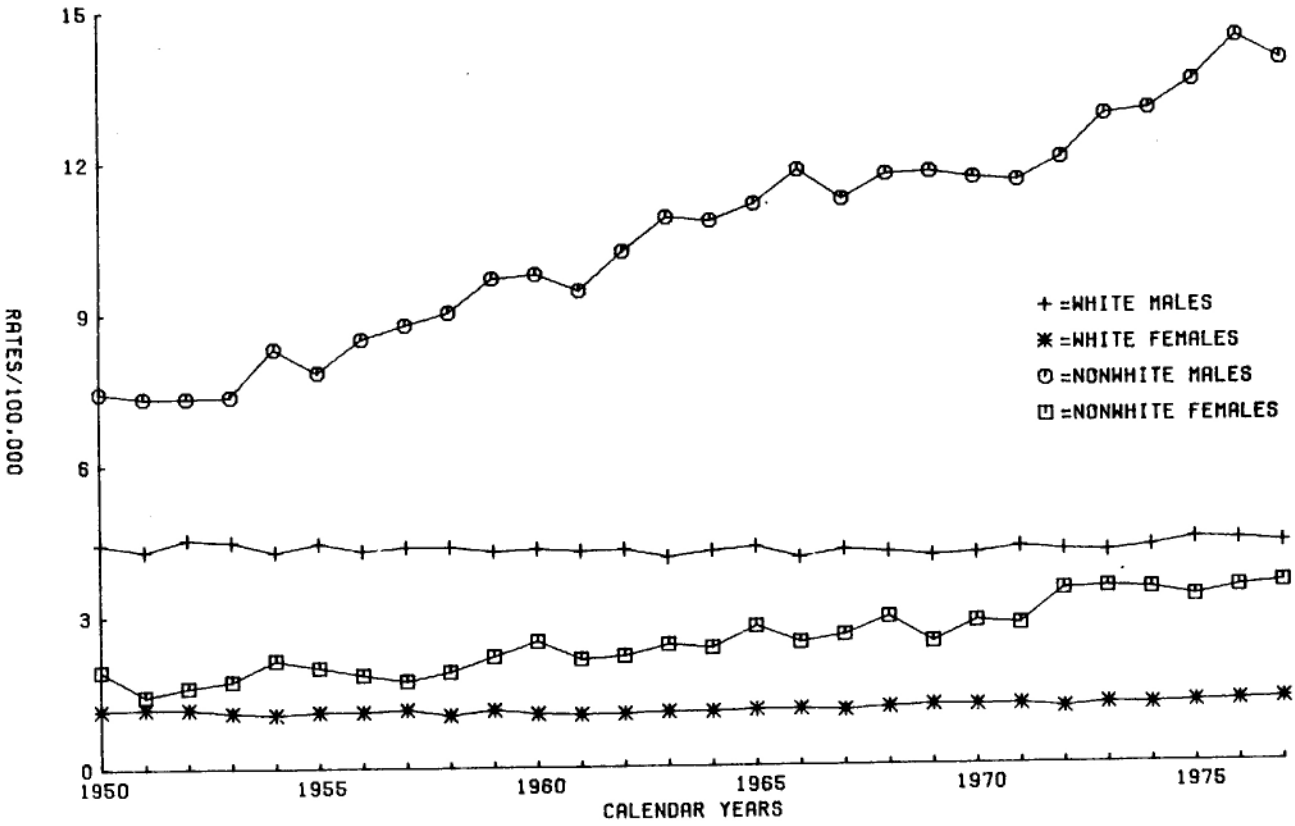


FIGURE 33.—Age-adjusted* mortality rates for cancer of the esophagus, by race and sex, United States, 1950-1977

* This graph is age-adjusted to the U.S. population as enumerated in 1970; all rates cited within the text of the Report, however, are adjusted to the population as enumerated in 1940.
 SOURCE: National Cancer Institute (1981).

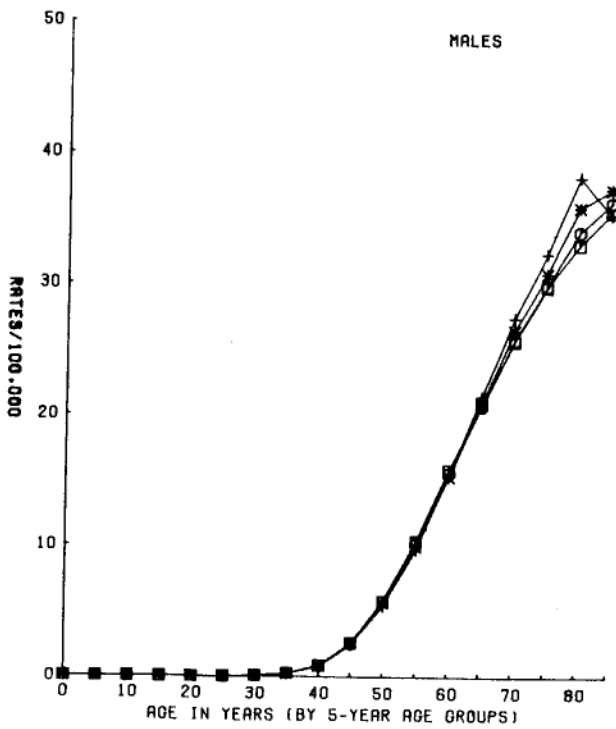
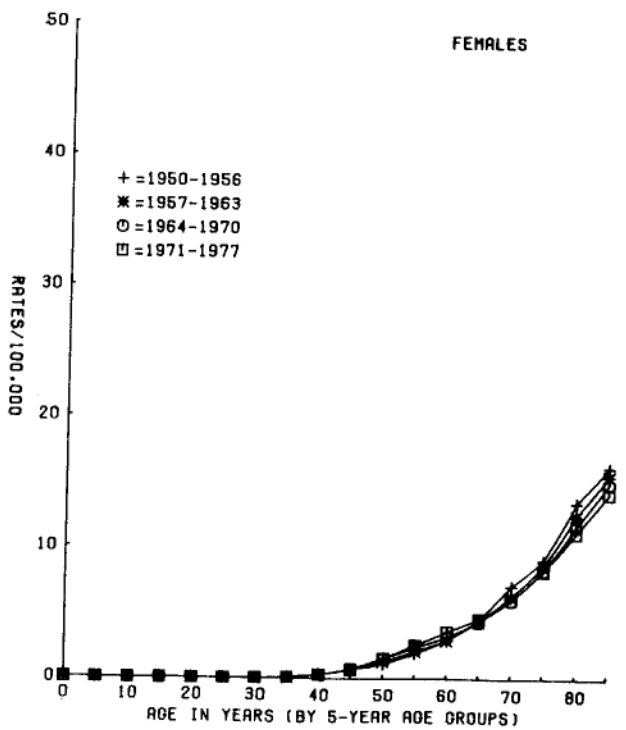


FIGURE 34.—Age-specific mortality rates for whites in the United States for cancer of the esophagus
 SOURCE: National Cancer Institute (1981).

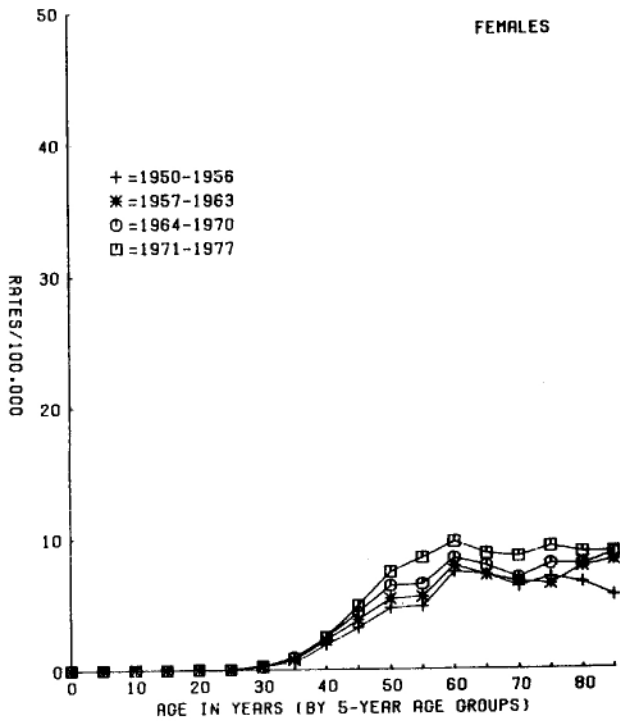
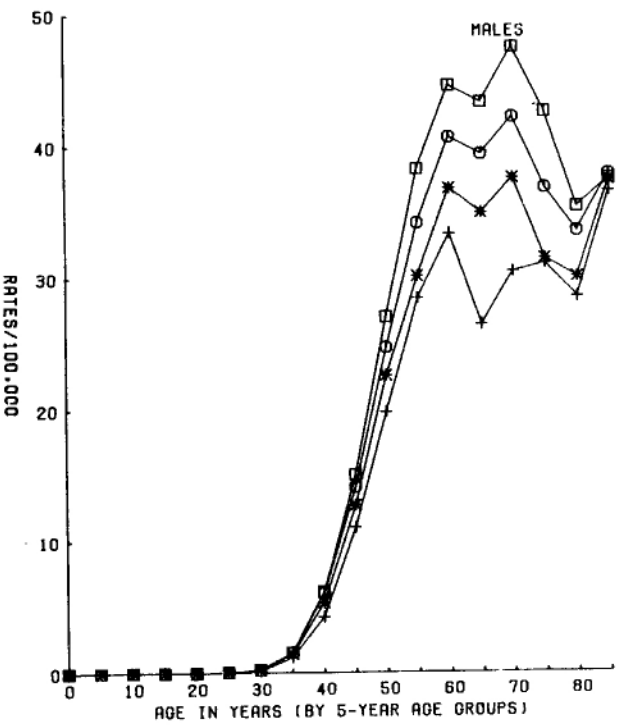


FIGURE 35.—Age-specific mortality rates for nonwhites in the United States for cancer of the esophagus

SOURCE: National Cancer Institute (198).

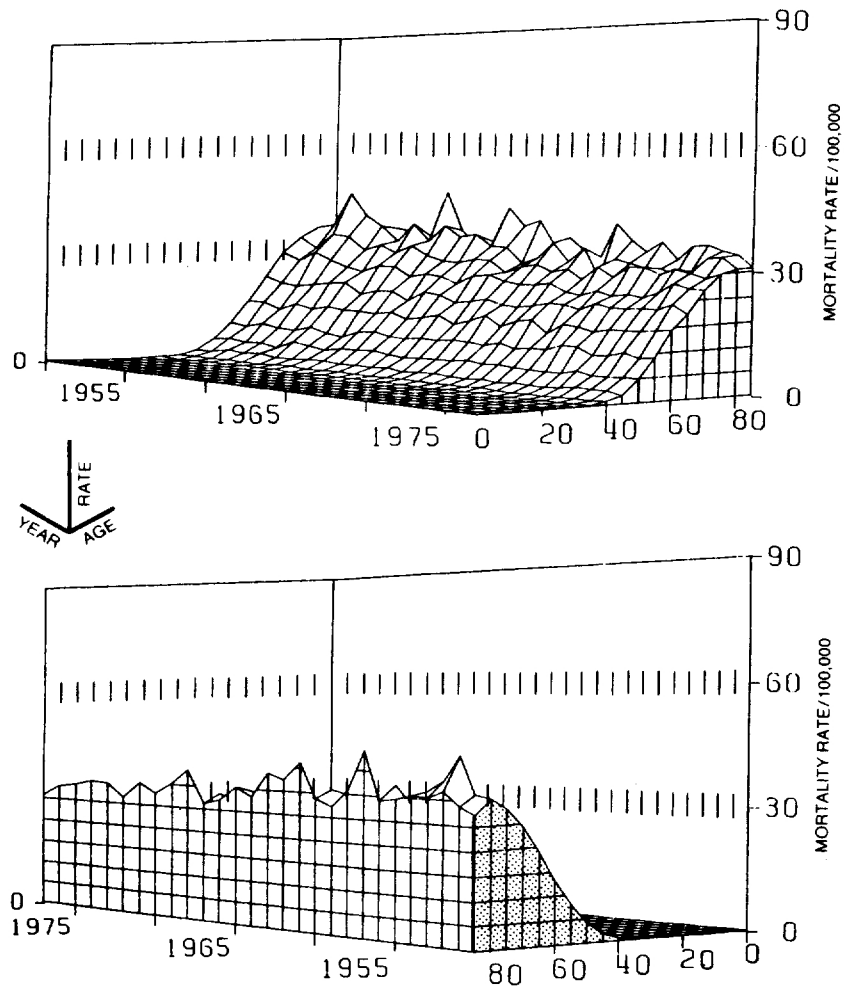


FIGURE 36.—Age-specific mortality rates by 5-year age groups for cancer of the esophagus for white males, United States, 1950-1977
 SOURCE: National Cancer Institute (198).

It is estimated that in 1982 in the United States there will be 8,900 new cases and 8,300 deaths from this disease (2).

A number of epidemiological and experimental studies have established an association between smoking and esophageal cancer.

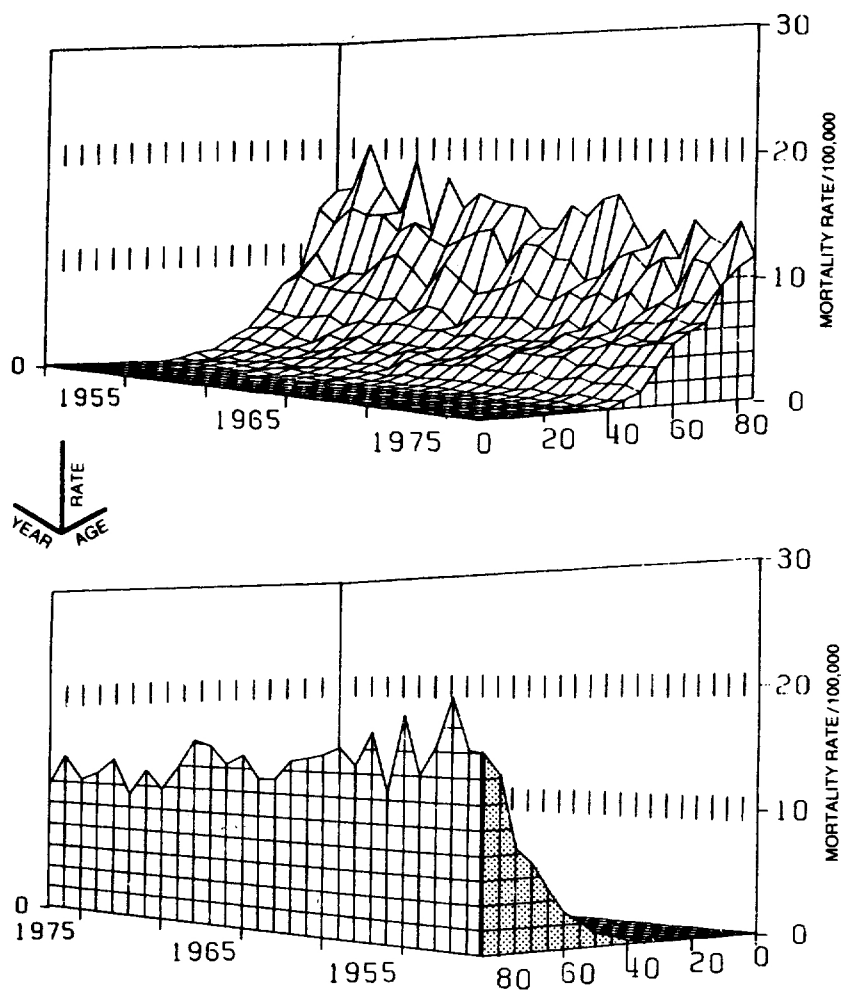


FIGURE 37.—Age-specific mortality rates by 5-year age groups for cancer of the esophagus for white females, United States, 1950-1977

SOURCE: National Cancer Institute (198).

Causal Significance of the Association

Consistency of the Association

At least 10 retrospective studies have examined the relationship between smoking and esophageal cancer (276). Regardless of methodology, risk ratios were consistently increased. Data from the major prospective studies (Table 27) also demonstrate consistently increased mortality ratios for male smokers as compared with non-

TABLE 27.—Mortality ratios for cancer of the esophagus—prospective studies

| Study | Population size | Number of deaths | Nonsmokers | Cigarette smokers | Comments |
|-----------------------------------|----------------------------------|---------------------------|--------------|-------------------|---------------------------------------|
| ACS 9-State Study | 188,000 | 1 nonsmoker 33 smokers | 1.00 | 5.06 | Esophagus and other respiratory sites |
| British Physicians | 34,000 males | 65 | 1.00 | 4.70 | Esophagus and other respiratory sites |
| U.S. Veterans | 290,000 | 119 | 1.00 | 6.43 | |
| ACS 25-State Study | 398,000 males 483,000 females | 116 48 | 1.00 1.00 | 3.96 4.89 | |
| California males in 9 occupations | 68,000 males | 32 | 1.00 | 1.82 | |
| Japanese Study | 122,200 males | 215 | 1.00 | 2.35 | |
| Swedish Study | 55,000 males and females | 1 nonsmoker 12 smokers | 1.00 | — | |

smokers. The ACS 25-State Study showed similar results for female smokers and cancer of the esophagus.

Strength of the Association

Mortality ratios in the retrospective studies ranged from 1.3 to 11.1 among heavy smokers; mortality ratios in the prospective studies ranged from 1.8 to 6.4. In four of the large prospective studies, a dose-response relationship was demonstrated (Table 28). A reduced risk for esophageal cancer among female but not male smokers of lower tar and nicotine cigarettes has also been reported (155).

Specificity of the Association

Specificity of the association between smoking and esophageal cancer is evidenced by substantial differences in the mortality ratios (smokers versus nonsmokers) for esophageal cancer compared to other smoking-related cancers (Appendix Tables A and B).

Temporal Relationship of the Association

The temporal relationship of this association is supported by the prospective studies in which populations of initially disease-free subjects were followed for the development of esophageal carcinoma. In addition, there are histological data suggesting that smoking

TABLE 28.—Mortality ratios for cancer of the esophagus by amount smoked—prospective studies

| Study | Population Size | Cigarettes/Day | Ratio | Comments |
|-----------------------------------|-----------------|----------------|-------|--------------------------------|
| British Physicians | 34,000 males | Nonsmoker | 1.00 | Grams of tobacco per day |
| | | 1-14 | 4.00 | |
| | | 15-24 | 4.33 | |
| | | 25 + | 10.00 | |
| U.S. Veterans | 290,000 | Nonsmoker | 1.00 | *Based on fewer than 20 deaths |
| | | 1-9 | 3.06* | |
| | | 10-20 | 4.34 | |
| | | 21-39 | 12.42 | |
| Japanese in 29 Health Districts | 122,200 males | Nonsmoker | 1.00 | |
| | | 1-19 | 2.20 | |
| | | 20-29 | 2.80 | |
| | | 30 + | 3.20 | |
| California males in 9 occupations | 68,000 | Nonsmoker | 1.00 | |
| | | about ½ pk | 1.27 | |
| | | about 1 pk | 1.69 | |
| | | about 1½ pk | 1.82 | |

antedates premalignant and malignant transformation of esophageal epithelium (13, 16).

Coherence of the Association

Dose-Response Relationship

There is a dose-response relationship between smoking and esophageal cancer mortality in retrospective and prospective studies (276).

Esophageal Cancer Mortality and Cessation of Smoking

Several of the prospective studies noted reduced risks for cancer of the esophagus after quitting smoking. The U.S. Veterans Study found that the mortality ratio for ex-smokers decreased to 2.41 compared to 6.43 for continuing smokers. For the British Physicians Study, the corresponding ratios were 1.66 and 5.33, respectively. Thus, ex-smokers had only about one-third the risk for esophageal cancer of current smokers.

Figure 38 presents data from the American Health Foundation study for esophageal cancer mortality risk by the number of years off cigarettes. After quitting smoking for 4 years or more, former smoker rates were not substantially above those of nonsmokers.

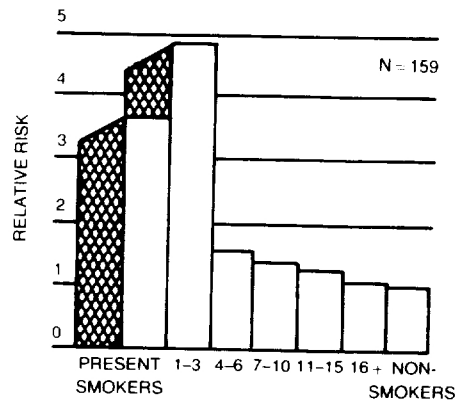


FIGURE 38.—Relative risk of male ex-smokers for cancer of the esophagus by years since quitting smoking

SOURCE: Wynder and Stellman (326).

Correlation of Sex Differences in Esophageal Cancer With Different Smoking Habits

Esophageal cancer is predominantly a disease of males. The sex differences observed for esophageal cancer mortality are compatible with the sex differences in smoking patterns. As with oral and laryngeal cancer, esophageal cancer has also been related to excessive alcohol consumption. This must be considered as contributing to the excess ratios of male to female esophageal cancer mortality (see page 101).

Correlation of Esophageal Cancer Mortality Among Populations With Different Tobacco Consumption

In populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the mortality rates from esophageal cancer are substantially reduced (79, 165, 166, 211, 294).

TABLE 29.—Mortality ratios for cancer of the esophagus in cigar and pipe smokers—a summary of prospective epidemiological studies

| Study | Smoking type | | | | | |
|--------------------------------|--------------|------------|-----------|----------------------|--|-------|
| | Non-smoker | Cigar only | Pipe only | Total pipe and cigar | Cigarette only | Mixed |
| ACS 9-State Study ¹ | 1.00 | 5.00 | 3.50 | — | 5.06 | — |
| British Physicians | 1.00 | — | — | 3.70 | 4.70 | 9.0 |
| ACS 25-State Study | 1.00 | — | — | 3.97 | males 3.96 ² females 4.89 ² | — |
| U.S. Veterans | 1.00 | 5.33 | 1.99 | 4.05 | 6.43 | — |

¹ Combines data for oral, larynx, and esophagus.

² Mortality ratio for ages 45 to 64.

Smoking and Histologic Changes in the Esophagus

Examination of 12,598 histologic sections of esophageal autopsy tissue from 1,268 men showed histologic findings which were similar to the abnormalities generally accepted as being premalignant in respiratory tract epithelium (16). Only 2.5 percent of the slides from current smokers exhibited no atypical cells, compared with 93.5 percent of slides from nonsmokers. The finding of 60 percent or more atypical cells was rare in the tissue of nonsmokers (0.3 percent), but much more common in tissue of smokers (17.7 percent).

Esophageal Cancer and Non-Cigarette Tobacco Use

The esophagus is not directly exposed to inhaled tobacco smoke, but tobacco smoke constituents condense on the mucous membranes of the mouth and pharynx and are swallowed, thus contacting esophageal cells. The esophagus also receives mucous cleared from the lungs by the ciliary mechanism or by coughing which is also swallowed. Variations in the inhalation of the smoke of different tobacco products may not appreciably alter the degree of exposure of the esophagus. This possibility is suggested by the prospective and retrospective epidemiological studies which demonstrate similar mortality rates for cancer of the esophagus in smokers of cigars, pipes, and cigarettes. These data are presented in Table 29.

Several retrospective investigations have examined the association between smoking in various forms and cancer of the esophagus (Table 30). These studies suggest that cigar, pipe, and cigarette smokers develop cancer of the esophagus at rates substantially higher than do nonsmokers and that little difference exists between these rates observed in smokers of pipes, cigars, or cigarettes. Histologic changes in the esophagus have been related to smoking of

cigarettes and other forms of tobacco (16). Several retrospective studies conducted in the United States and other countries have examined the synergistic role of tobacco use and heavy alcohol intake and the risk of mortality from cancer of the esophagus. At least four of these investigations contain data on pipe and cigar smoking (33, 172, 173, 307). It appears that smoking in any form in combination with heavy drinking results in especially high rates of cancer of the esophagus.

TABLE 30.—Relative risk of cancer of the esophagus for men, comparing cigar, pipe, and cigarette smokers with nonsmokers. A summary of retrospective studies

| Author, reference | Number | | Relative risk ratio and percentage of cases and controls by type of smoking | | | | | |
|-------------------------------------|--------|------------------|---|------------|-----------|----------------------|----------------|-------|
| | | | Non-smoker only | Cigar only | Pipe only | Total pipe and cigar | Cigarette only | Mixed |
| Sadowaky (296): | | | | | | | | |
| Cases..... | 104 | Relative risk | 1.0 | 4.8 | 3.8 | 5.1 | 3.8 | 3.3 |
| Controls..... | 615 | Percent cases | 4 | 5 | 8 | 6 | 60 | 18 |
| | | Percent controls | 13 | 3 | 7 | 4 | 53 | 19 |
| Wynder (317): | | | | | | | | |
| Cases..... | 39 | Relative risk | 1.0 | 3.1 | 2.1 | | 2.6 | .4 |
| Controls..... | 115 | Percent cases | 13 | 15 | 18 | | 51 | 3 |
| | | Percent controls | 24 | 9 | 16 | | 36 | 13 |
| Pernu (300): | | | | | | | | |
| Cases..... | 202 | Relative risk | 1.0 | | 3.0 | | 2.7 | 5.9 |
| Controls..... | 713 | Percent cases | 17 | | 7 | | 59 | 18 |
| | | Percent controls | 39 | | 5 | | 50 | 7 |
| Schwartz (247): | | | | | | | | |
| Cases..... | 249 | Relative risk | 1.0 | | 2.6 | | 11.7 | 8.6 |
| Controls..... | 249 | Percent cases | 2 | | 2 | | 98 | 7 |
| | | Percent controls | 18 | | 7 | | 67 | 7 |
| Wynder and Bross (307): | | | | | | | | |
| Cases..... | 150 | Relative risk | 1.0 | 3.6 | 9.0 | 6.0 | 2.8 | 3.7 |
| Controls..... | 150 | Percent cases | 5 | 19 | 9 | 4 | 51 | 11 |
| | | Percent controls | 15 | 16 | 3 | 2 | 55 | 9 |
| Bradshaw and Schonland (23): | | | | | | | | |
| Cases..... | 117 | Relative risk | 1.0 | | 4.8 | | 2.3 | |
| Controls..... | 366 | Percent cases | 15 | | 41 | | 63 | |
| | | Percent controls | 32 | | 18 | | 58 | |
| Martinez (172): | | | | | | | | |
| Cases..... | 120 | Relative risk | 1.0 | 2.0 | | | 1.5 | 2.2 |
| Controls..... | 360 | Percent cases | 8 | 9 | | | 31 | 43 |
| | | Percent controls | 14 | 8 | | | 34 | 34 |
| Martinez¹ (173): | | | | | | | | |
| Cases..... | 346 | Relative risk | 1.0 | 2.0 | 2.8 | | 1.7 | 2.5 |
| Controls..... | 346 | Percent cases | 21 | 10 | 15 | | 34 | 34 |
| | | Percent controls | 22 | 9 | 1 | | 36 | 25 |

¹This study combines data for oral cancer and cancer of the esophagus.