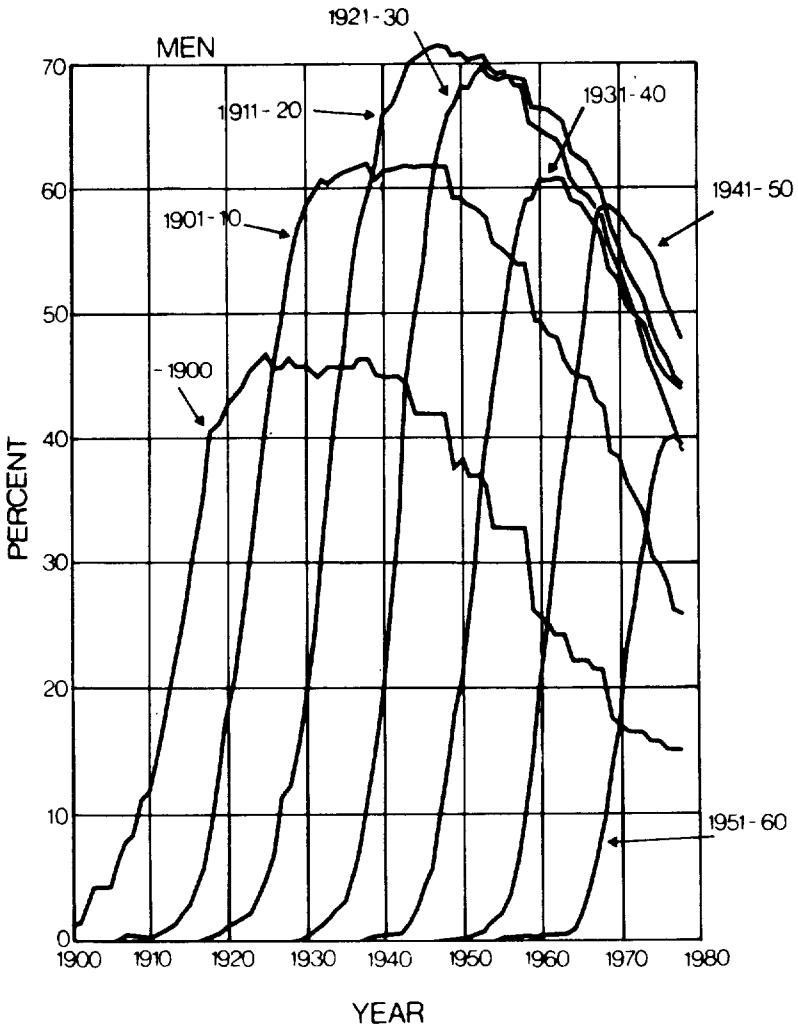

FIGURE 12.—Changes in the prevalence of cigarette smoking among successive birth cohorts of men, 1900–1978

NOTE: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics.

SOURCE: U.S. Department of Health, Education, and Welfare (*200*).

A third concern about the coherence of smoking behavior and lung cancer mortality has been that overall lung cancer mortality continues to rise at a time when the prevalence of cigarette smoking continues to decline, and the consumption of lower tar and nicotine cigarettes is increasing. Part of this apparent discrepancy can be accounted for by the relatively slow decline in the excess risk of

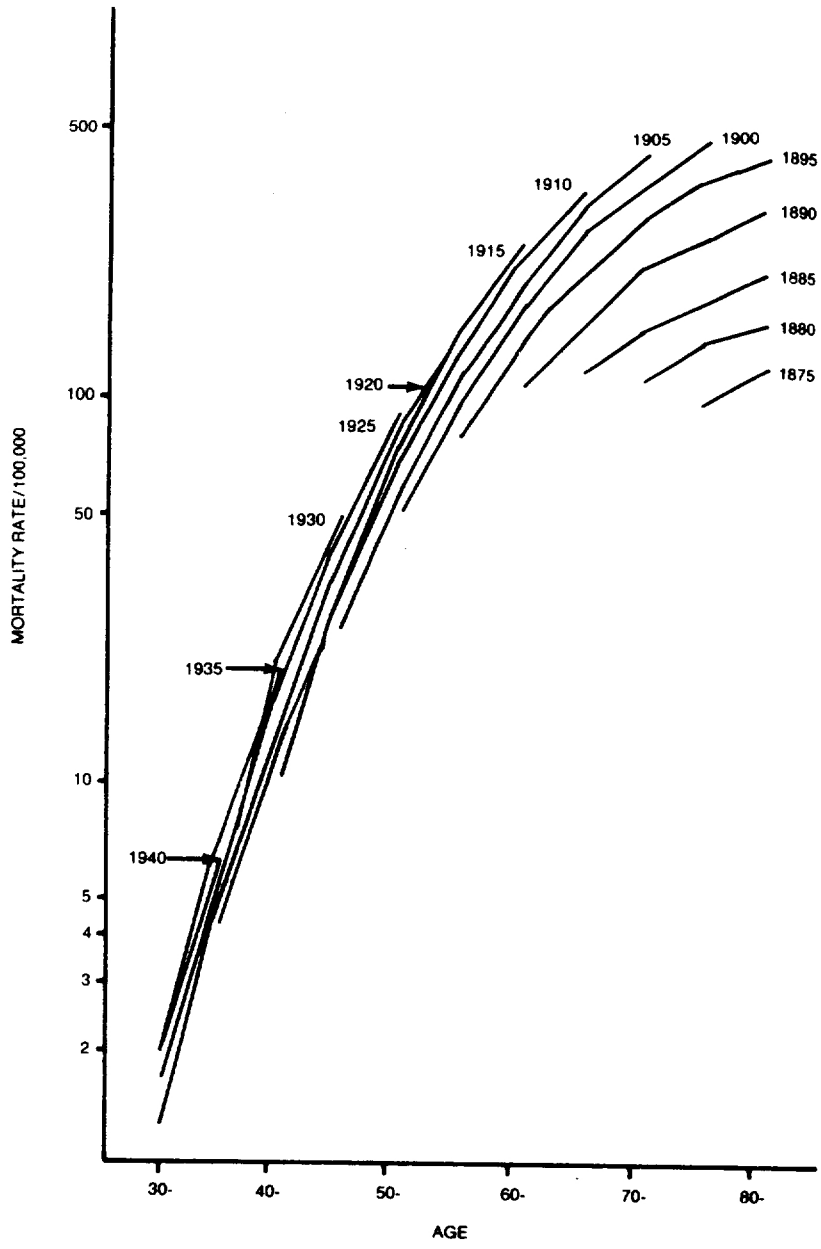

FIGURE 13.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death for males, United States, 1950–1975

SOURCE: Derived from data available in National Cancer Institute (*198*).

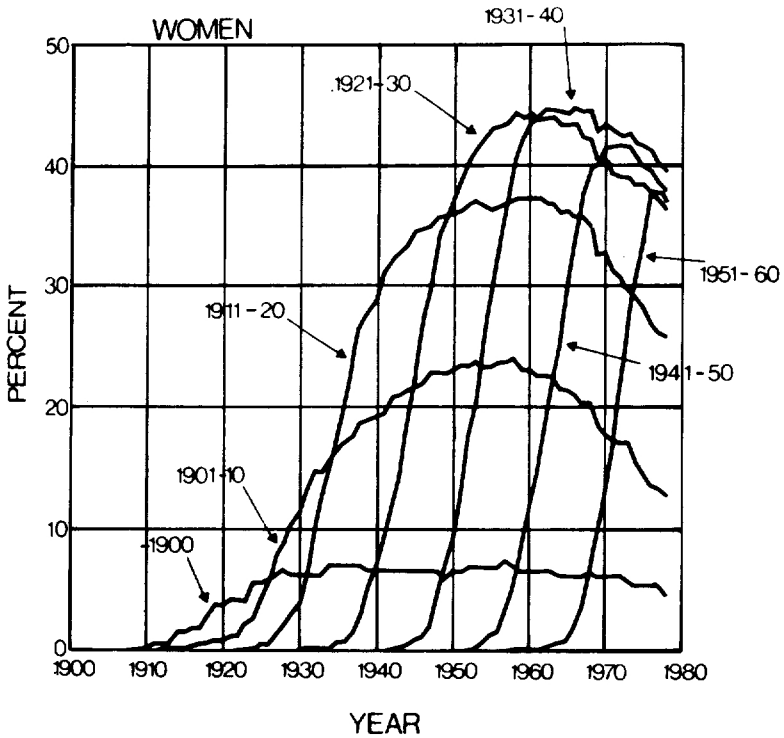

FIGURE 14.—Changes in the prevalence of cigarette smoking among successive birth cohorts of women, 1900–1978

NOTE: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics.
SOURCE: U.S. Department of Health, Education, and Welfare (*200*).

developing lung cancer once someone actually stops smoking, compared to persons who continue to smoke cigarettes. However, in the youngest male birth cohorts (birth years 1931–1940 and 1941–1950), there is a substantially lower peak prevalence of smoking which should result in a lower lung cancer mortality experience. From the smoking prevalence data and Figure 12, one would expect to see this declining mortality experience in those birth cohorts born after 1930, and the data in Figure 13 for 1935 and 1940 birth cohorts suggest that a decline in mortality experience is occurring. This trend can be visualized easily in Figure 16, which plots the age-specific lung cancer mortality rates for 5-year age groups over time, and reveals that the male rates for the youngest age groups do appear to be declining. No such trend can be seen in the female mortality experience, and this, too, is consistent with the smoking prevalence data presented in Figure 14.

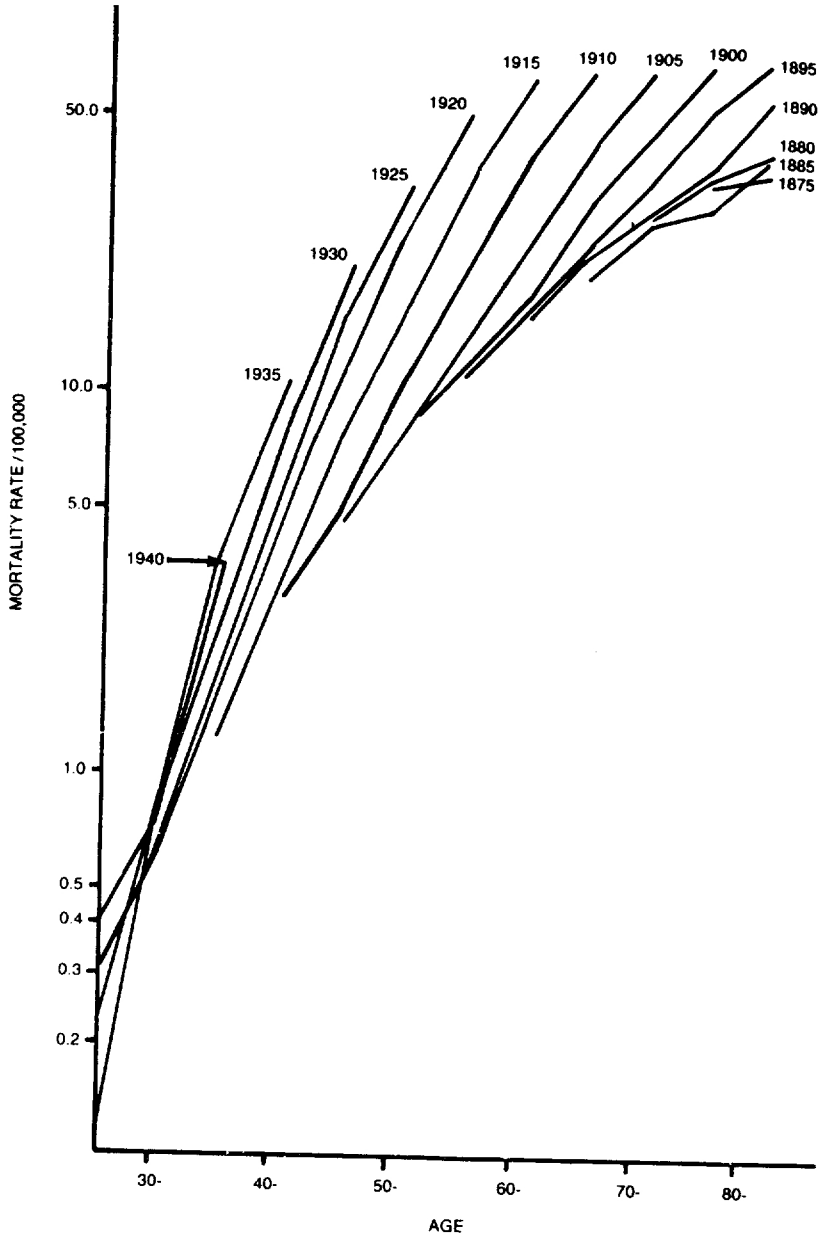

FIGURE 15.—Age-specific mortality rates for cancer of the bronchus and lung, by birth cohort and age at death for females, United States, 1950–1975

SOURCE: Derived from data available in National Cancer Institute (*198*).

TABLE 13.—Lung cancer mortality ratios for male and female smokers at 6- and 12-year followup, ACS 25-State Study

Sex	Mortality ratios		
	Non-smokers	6-year followup	12-year followup
Males	1.00	9.20	8.53
Females	1.00	2.20	3.58

When the prevalence of cigarette smoking by birth cohort is compared with the mortality experience by birth cohort, the relationship between cigarette smoking behavior and lung cancer mortality experience is extremely coherent.

This is also supported when lung cancer mortality ratios are examined at various periods of followup in the prospective studies. In the ACS 25-State Study, a different pattern of lung cancer mortality emerges for males compared to females. In contrast to lung cancer mortality ratios among male smokers, which remained almost constant during the 6-year followup interval, ratios for female smokers increased (Table 13). A similar trend is observed among male U.S. Veterans as noted above for males in the ACS 25-State Study. Figure 17 presents lung cancer mortality ratios by amount smoked for male veterans at $8^1/_2$ years compared to 16 years' followup. No differences between the two periods are evident and the pattern is constant at each level of exposure.

Lung Cancer Mortality and Premalignant Changes in Bronchial Epithelium

Since smoking is significantly associated with lung cancer, smokers could be expected to develop premalignant changes in bronchial epithelium more commonly than nonsmokers prior to the development of frank cancer. In the late 1950s, one scientist (*9, 14, 15*) examined the tracheobronchial tree of 402 males at post mortem in a controlled blinded study and found that several kinds of changes were much more common in the tracheobronchial tree of smokers as compared with nonsmokers (Table 14). The frequency and intensity of these epithelial changes (loss of cilia, basal cell hyperplasia, presence of atypia) correlated with the number of cigarettes smoked. The most severe lesions, aside from invasive cancer, were not seen among males who did not smoke regularly and were found only rarely among light smokers. They were present, however, in 4.3 percent of sections from males who smoked one to two packs a day,

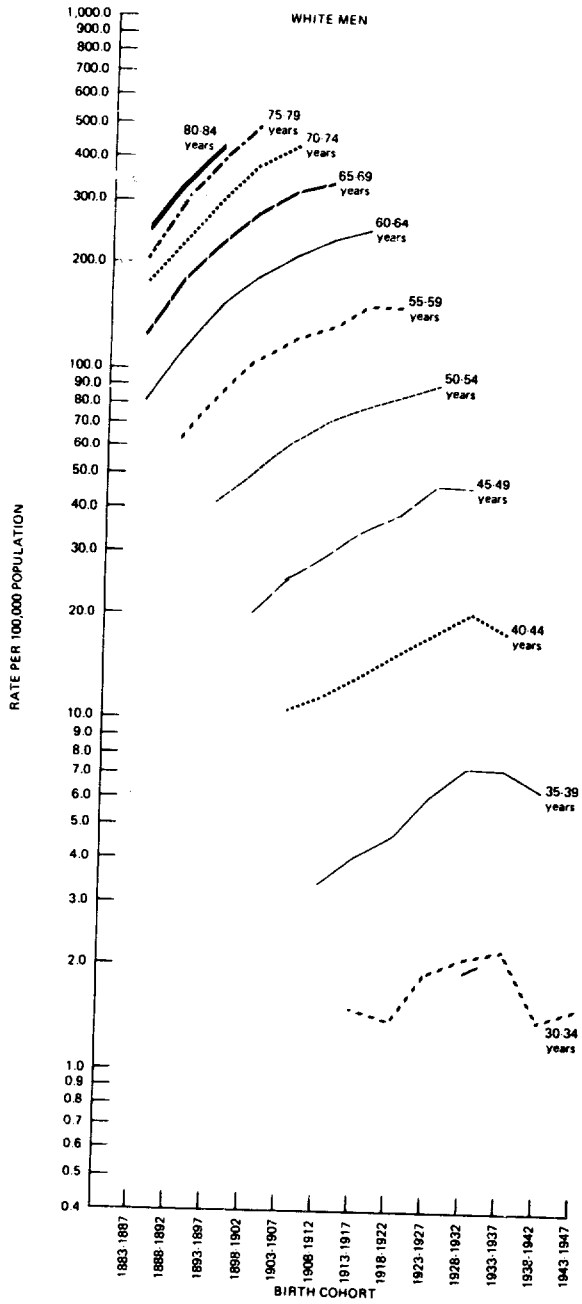

FIGURE 16.—Mortality rates for malignant neoplasm of the trachea, bronchus, and lung, for white men and white women, by birth cohort and age at death, United States, 5-year intervals during 1947–1977

SOURCE: National Center for Health Statistics (*200*).

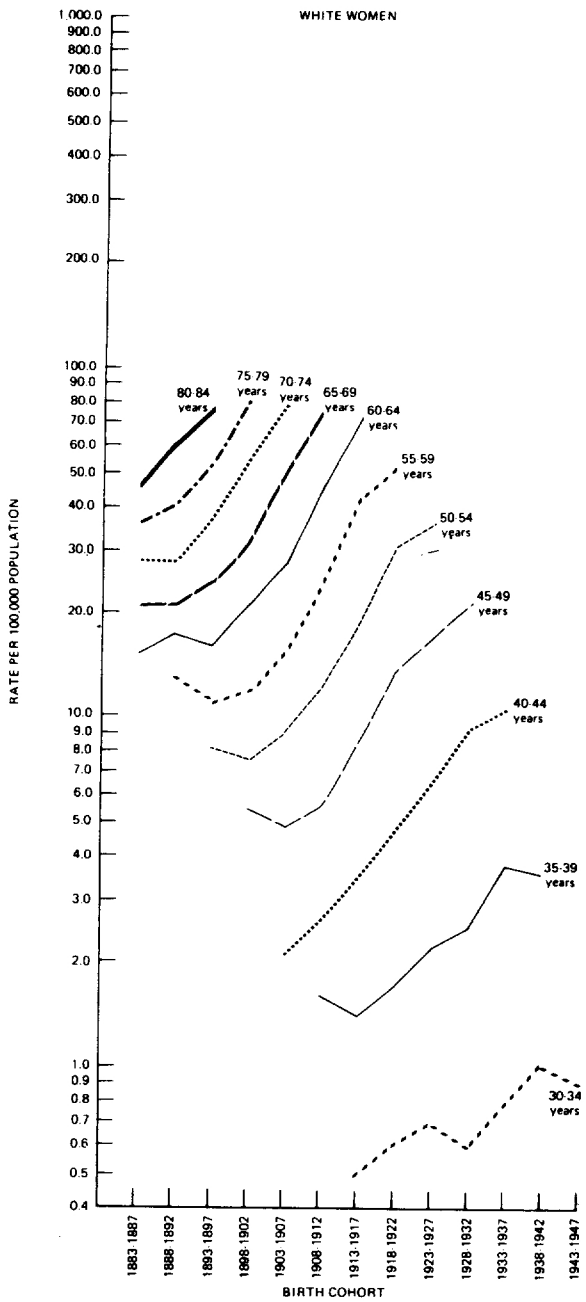

FIGURE 16, continued.—Mortality rates for malignant neoplasm of the trachea, bronchus, and lung, for white men and white women, by birth cohort and age at death, United States, 5-year intervals during 1947–1977

SOURCE: National Center for Health Statistics (*200*).

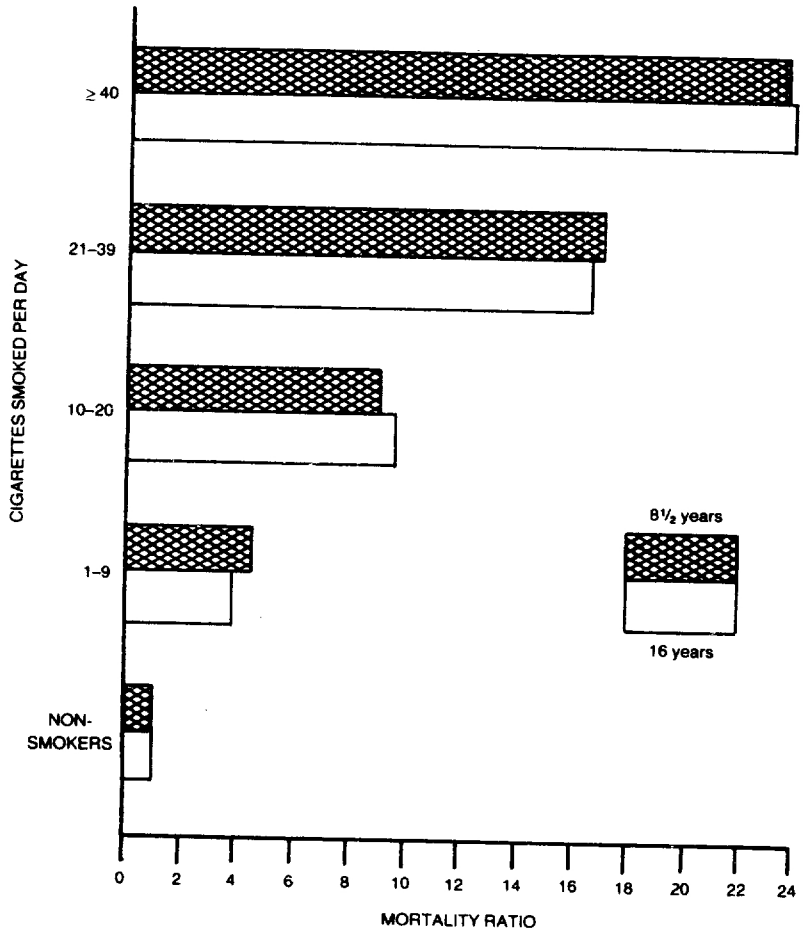

FIGURE 17.—Lung cancer mortality ratios for male smokers by amount smoked, 8½- and 16-year followup, U.S. Veterans Study

in 11.4 percent of sections from males who smoked two or more packs a day, and in 14.3 percent of sections from smokers who died of lung cancer. Studies by the same authors and others (*7, 10, 28, 39, 51, 89, 96, 144, 206, 217, 233, 268, 298, 319*) have confirmed this relationship between smoking and premalignant changes in bronchial epithelium in males and females, with and without lung cancer.

More recent investigations (*12*), which examined the histologic changes in the bronchial epithelium of male cigarette smokers who had died from causes other than lung cancer, found that changes occurred far less frequently in nonsmokers than in cigarette smokers. Changes in smokers correlated with the amount smoked. When comparing the degree of histologic changes of men who died in

TABLE 14.—Percent of slides with selected lesions,[a] by smoking status and presence of lung cancer

Group	Number cases	Number slides	Percent of slides with cilia absent and averaging 4 or more cell rows in depth			
			No cells atypical	Some cells atypical	All cells atypical[b]	Total
Cases without lung cancer						
Never smoked regularly	65	3,324	1.0	0.03	—	1.1
Ex-cigarette smokers	72	3,436	3.5	0.4	0.2	4.1
Cigarettes—½ pk. a day	36	1,824	0.2	4.2	0.3	4.7
Cigarettes—½—1 pk. a day	59	3,016	—	7.1	0.8	7.9
Cigarettes—1-2 pks. a day	143	7,062	—	12.6	4.3	16.9
Cigarettes—2+ pks. a day	36	1,787	—	26.2	11.4	37.5
Lung cancer cases[c]	63	2,784	—	12.5	14.3	26.8

[a] In some sections, two or more lesions were found. In such instances, all of the lesions were counted and are included in both individual columns and in the total column of the table. Lesions found at the edge of an ulcer were excluded.

[b] These lesions may be called carcinoma in-situ.

[c] Of the 63 who died of lung cancer, 55 regularly smoked cigarettes up to the time of diagnosis, 5 regularly smoked cigarettes but stopped before diagnosis, 1 smoked cigars, 1 smoked pipe and cigars, 1 was an occasional cigar smoker.

SOURCE: Auerbach (*9, 14, 15*).

the period 1955–1960 with those who died in 1970–1977, these investigators found the latter exhibited less advanced histologic changes. The authors attributed this finding to the reduced tar and nicotine yield of cigarettes smoked by this group when compared to the average tar and nicotine yield of those smoked by the earlier group (Table 15).

Several investigators have examined the relationship between smoking and cytological changes in respiratory epithelial cells shed into sputum in groups of smokers and nonsmokers. These studies (*171, 193, 220, 262*) have generally found increased proportions of sputum specimens showing atypical cells among smokers as compared with nonsmokers, and these changes have progressed toward cancer with increasing duration of the smoking habit. In addition, these changes have reverted toward normal in individuals who stopped smoking. These data support the causal nature of the association between smoking and lung cancer.

Experimental Studies

Over the past 30 years, a number of experimental models have been developed to study tobacco-induced carcinogenesis. These data are explored in detail in the Part of this Report on the mechanisms of carcinogenesis.

Lung Cancer and Non-Cigarette Tobacco Use

The relationship between lung cancer and other forms of tobacco was comprehensively reviewed in reports by the U.S. Public Health

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TABLE 15.—Percentage of sections with each of several categories of histologic change, classified according to smoking habit*

Histologic change	Adjusted % Never Smoked Regularly		Adjusted % Smoked 1–19 Cigarettes/ Day		Adjusted % Smoked 20–39 Cigarettes/ Day		Adjusted % Smoked 40+ Cigarettes/ Day	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Basal-cell hyperplasia:								
Total	3.8	5.8	87.8	63.1	93.2	76.2	98.8	86.3
6+ rows	0	0.1	2.1	0.4	5.7	0.5	13.0	0.8
10%+ cells with atypical nuclei	0.1	0.5	87.6	62.4	93.2	75.0	98.8	86.3
30%+ cells with atypical nuclei	0.1	0.4	77.2	53.9	92.6	72.5	98.8	85.1
50%+ cells with atypical nuclei	0	0.1	56.7	9.6	84.1	26.3	98.6	56.1
70%+ cells with atypical nuclei	0	0	0.1	0	12.2	0.1	66.6	<0.1
Lesion with cilia absent:								
Total	5.3	4.2	13.8	8.8	22.5	10.5	30.3	11.7
10%+ cells with atypical nuclei	0	<0.1	13.8	8.5	22.3	9.8	30.3	11.7
30%+ cells with atypical nuclei	0	<0.1	12.9	7.6	22.3	9.3	30.3	11.7
50%+ cells with atypical nuclei	0	0	10.0	2.2	21.9	6.0	30.3	9.3
70%+ cells with atypical nuclei	0	0	2.6	0.1	14.6	0.8	28.6	2.2
100% cells with atypical nuclei	0	0	2.6	0.1	13.2	0.8	22.5	2.2
No. of sections	2,580	2,628	2,208	3,026	2,881	3,471	1,413	2,217
No. of subjects	57	53	51	61	68	73	35	47

* Percentages adjusted for age to the distribution of age at death of all subjects in the study. An *A* denotes subjects who died in 1955–1960, a *B* denotes subjects who died in 1970–1977.
SOURCE: Auerbach et al. (*12*).

Service in 1973 and 1979 (*269, 278*). A brief summary follows. In contrast with cigarette smokers, most pipe and cigar smokers reported they did not inhale the smoke, and as a consequence, the total exposure of the lung to tobacco smoke was relatively lower. There was little evidence that lung cancer is associated with the use of chewing tobacco or "snuff." Several prospective epidemiological studies have demonstrated higher lung cancer mortality ratios for pipe and cigar smokers than for nonsmokers, but the risk of developing lung cancer for pipe and cigar smokers is less than for cigarette smokers. Table 16 presents a summary of these prospective studies. Two studies (*64, 131*) have reported (Table 17) that lung cancer mortality ratios for pipe and cigar smokers exhibited a dose-

TABLE 16.—Mortality ratios for lung cancer in male current smokers. A summary of prospective studies

Study	Smoking type					
	Non-smoker	Cigar only	Pipe only	Total pipe and cigar	Cigarette only	Mixed
ACS 25-State Study	1.00	1.02	3.00	—	10.00	7.63
British Physicians	1.00	—	—	5.80	14.00	8.20
Canadian Veterans	1.00	2.94	4.35	—	14.20	—
U.S. Veterans	1.00	1.66	2.14	1.67	11.28	—

TABLE 17.—Lung cancer mortality ratios for cigar and pipe smokers by amount smoked

Smoking type	Mortality ratio	Number of deaths
Nonsmoker	1.00	78
Cigar smokers:		
< 5 cigars per day	1.14	12
5 to 8 cigars per day	2.64	11
> 8 cigars per day	2.07	2
Pipe smokers:		
< 5 pipefuls per day	.77	2
5 to 19 pipefuls per day	2.20	12
> 19 pipefuls per day	2.47	3
Cigar and pipe:		
8 or less cigars, 19 or less pipefuls	1.62	18
> 8 cigars, > 19 pipefuls	2.19	2

SOURCE: Kahn (*131*).

response relationship; however, the relationship is not as strong as that noted for cigarette smoking.

A few retrospective studies contain adequate numbers of smokers to allow an examination of dose-response relationships between pipe and cigar smoking and lung cancer (*1, 161, 215, 230*). An increased risk for developing lung cancer correlated with the increased use of pipes and cigars as measured by amount smoked and depth of inhalation.

Several investigators have examined histological changes in lungs of cigar and pipe smokers. One study (*15*) examined 36,340 histologic sections for various epithelial lesions obtained from 1,522 white adults. The numbers and types of pathological findings in the bronchial epithelium of pipe and cigar smokers were compared with those found in nonsmokers and cigarette smokers. Pipe and cigar smokers had abnormalities that were intermediate between those of nonsmokers and cigarette smokers, although cigar smokers had pathological changes that in some categories approached the changes seen in cigarette smokers. Others have reported similar findings (*144, 233*).

Several experimental investigations have been conducted to examine the relative tumorigenic activity of tobacco smoke condensates obtained from cigarettes, cigars, and pipes. Most of these studies were standardized in an attempt to make the results of the cigar and pipe experiments more directly comparable with cigarette data, and most used the shaved skin of mice for the application of tar. Tar from cigars, pipes, and cigarettes was usually applied on an equal weight basis so that qualitative differences in the tars could be determined. In several experiments, the nicotine was extracted from the pipe and cigar condensates in an attempt to reduce the acute toxic effects that resulted from the high concentration of nicotine frequently found in these products (*50, 53, 127, 138, 221, 328*). These experimental data suggest that cigar and pipe tobacco condensates have a carcinogenic activity that is comparable to cigarette condensates. This is supported by human epidemiologic data for those sites exposed equally to the smoke of cigars, pipes, and cigarettes. The alkaline smoke derived from pipes and cigars is generally not inhaled, and as a result there appears to be a lesser exposure of the lungs and possibly other organs to pipe and cigar smoke than that which occurs due to cigarette smoking.

Further, evidence from countries where smokers tend to inhale cigar smoke to a greater degree than smokers do in the United States (*1*) indicates that rates of lung cancer become elevated to levels approaching those of cigarette smokers.

Conclusion

1. Cigarette smoking is the major cause of lung cancer in the United States.
2. Lung cancer mortality increases with increasing dosage of smoke exposure (as measured by the number of cigarettes smoked daily, the duration of smoking, and inhalation patterns) and is inversely related to age of initiation. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than nonsmokers.

3. Cigar and pipe smoking are also causal factors for lung cancer. However, the majority of lung cancer mortality in the United States is due to cigarette smoking.
4. Cessation of smoking reduces the risk of lung cancer mortality compared to that of the continuing smoker. Former smokers who have quit 15 or more years have lung cancer mortality rates only slightly above those for nonsmokers (about two times greater). The residual risk of developing lung cancer is directly proportional to overall life-time exposure to cigarette smoke.
5. Filtered lower tar cigarette smokers have a lower lung cancer risk compared to nonfiltered, higher tar cigarette smokers. However, the risk for these smokers is still substantially elevated above the risk of nonsmokers.
6. Since the early 1950s, lung cancer has been the leading cause of cancer death among males in the United States. Among females, the lung cancer death rate is accelerating and will likely surpass that of breast cancer in the 1980s.
7. The economic impact of lung cancer to the nation is considerable. It is estimated that in 1975, lung cancer cost $3.8 billion in lost earnings, $379.5 million in short-term hospital costs, and $78 million in physician fees.
8. Lung cancer is largely a preventable disease. It is estimated that 85 percent of lung cancer mortality could have been avoided if individuals never took up smoking. Furthermore, substantial reductions in the number of deaths from lung cancer could be achieved if a major portion of the smoking population (particularly young persons) could be persuaded not to smoke.

Cancer of the Larynx

Introduction

Cancer of the larynx was responsible for about 1 percent of cancer deaths in the United States in 1977. It is estimated that in 1982 there will be 10,900 new cases and 3,700 deaths due to this disease (2). Males are affected more commonly than females, but the ratio of new cases and deaths in males and females (now about 6:1) has been narrowing over the last 20 years (*240, 312*). In 1950, 1,852 people died of cancer of the larynx. By 1977, this figure had nearly doubled, rising to 3,390. The age-adjusted death rate increased slightly, from 1.1 to 1.2 per 100,000 (Figure 18).

There is a considerable difference in this increased death rate when examined by sex and race. Among other than white males, the age-adjusted rate climbed from 1.6 to 3.5 per 100,000 between 1950 and 1977. By contrast, age-adjusted rates of white males rose less, from 2.0 to 2.1. As is seen with lung cancer, mortality rates of females were lower than those of males throughout the study period. Between 1950 and 1977, the age-adjusted mortality rate for white

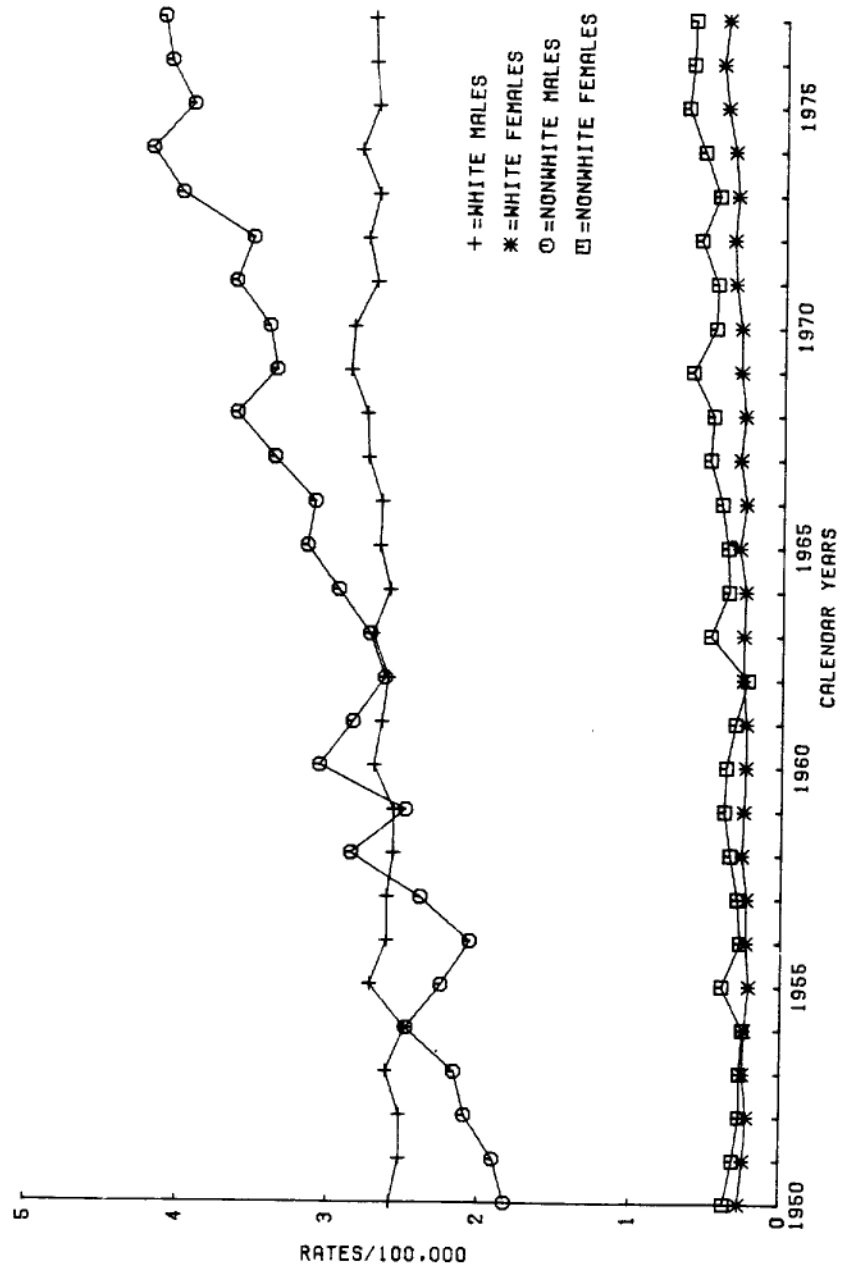

FIGURE 18.—Age-adjusted* mortality rates for cancer of the larynx, by race and sex, United States, 1950–1977

* 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 (*198*).

females increased from 0.2 to 0.3 per 100,000, while that of other than white females increased from 0.3 to 0.6 per 100,000.

Generally, there was a pattern of increasing mortality after middle age (Figures 19 and 20). Among white males 55 years of age or older, mortality rates from cancer of the larynx were higher in 1977 than in 1950. Among other than white males, this pattern was evident for those 35 years of age or older. Both white and other females 45 to 74 years of age had higher mortality rates in 1977 than in 1950.

Squamous cell carcinoma is the most common cell type among laryngeal cancers. Approximately 70 percent of the cases involve the glottis and 25 percent involve the supraglottic region.

In contrast to lung cancer, the 5-year survival for cancer of the larynx is at present about 60 percent (*2*), and has been improving over the past 15 years. As a result, the trend over time in death rates from cancer of the larynx is not an accurate reflection of the incidence of this disease.

Over the last 30 years, numerous epidemiological, pathological, and experimental investigations have established a strong association between smoking and cancer of the larynx. One group of scientists (*296*) conducted a retrospective study of 3,924 patients attending a cancer clinic in Alberta, Canada. The authors estimated that 84 percent of laryngeal cancer among men could be attributed to smoking.

Causal Significance of the Association

Consistency of the Association

More than 25 retrospective studies have examined the relationship between smoking and laryngeal cancer. These studies have employed diverse methodology and have been performed in different time periods and in different countries. Regardless of the study design, these studies have found a positive association between smoking and cancer of the larynx. Relative risk ratios for 12 studies up to 1968 (Table 18) were consistently above 2.0. Subsequent studies show similar findings (*30, 35, 44, 52, 113, 114, 134, 142, 202, 254, 296, 299, 316, 327*). The TNCS study (*299*) and the Hawaiian Study of Five Ethnic Groups (*113*) have also reported a positive association. Data from studies of populations with low proportions of smokers (e.g., Mormons (*165, 166, 294*) and Seventh Day Adventists (*211*)) show low laryngeal cancer rates. Six of the major prospective studies have examined the relationship between smoking and laryngeal cancer (Table 19); as in the retrospective studies, a large positive association was consistently noted.

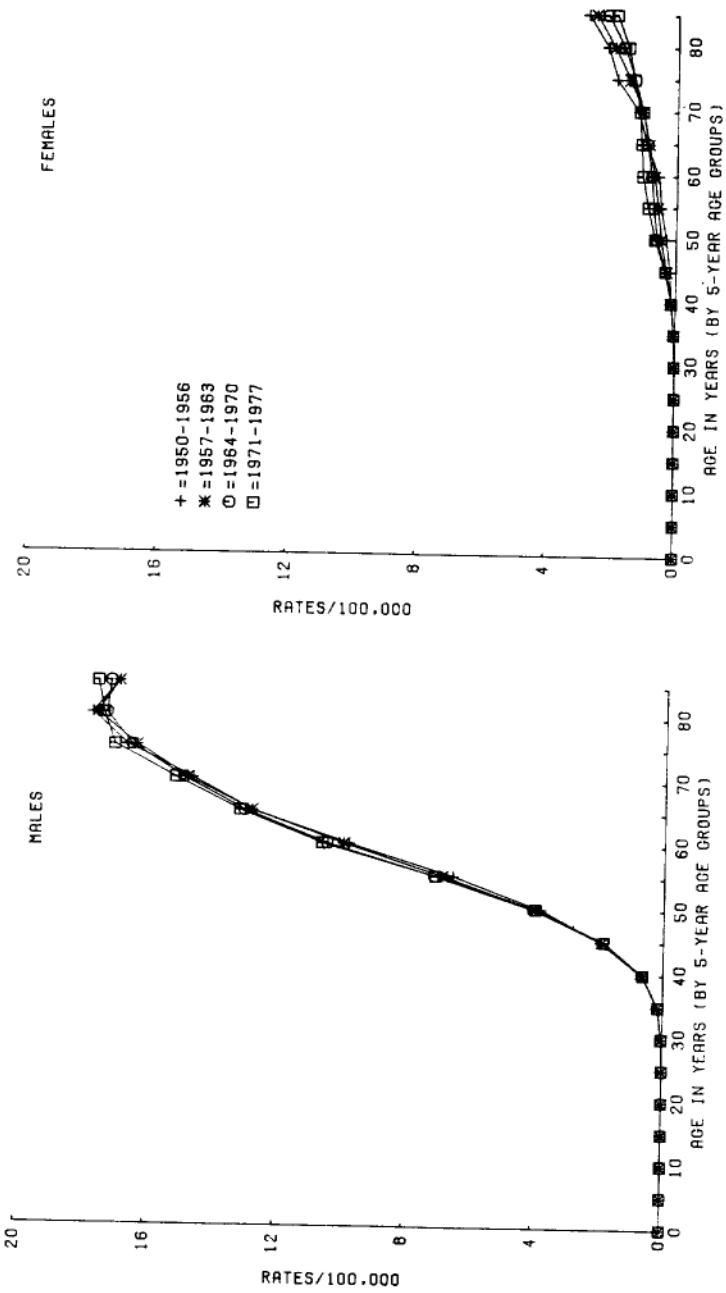

FIGURE 19.—Age-specific mortality rates for whites in the United States for cancer of the larynx

SOURCE: National Cancer Institute (*198*).

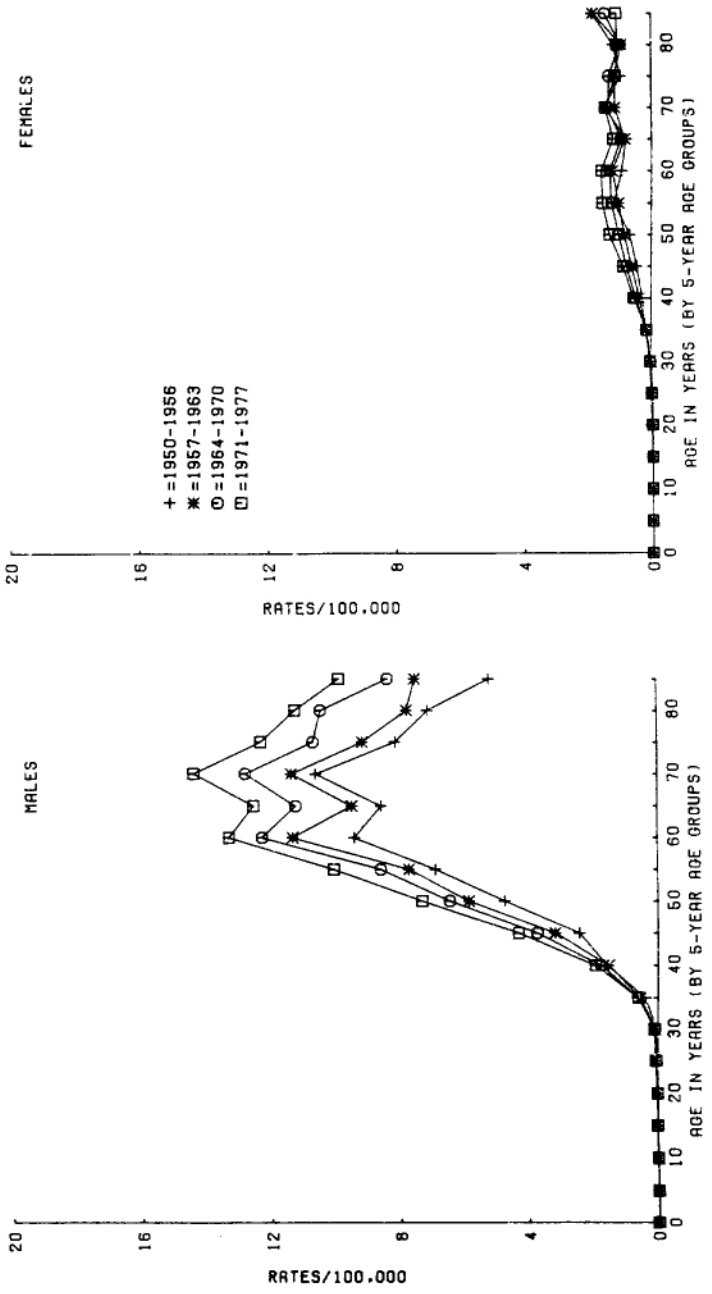

FIGURE 20.—Age-specific mortality rates for nonwhites in the United States for cancer of the larynx

SOURCE: National Cancer Institute (*198*).

TABLE 18.—Summary of results of retrospective studies of tobacco use and cancer of the larynx

Investigator, (reference)	Relative risk ratio[a] all smokers to nonsmokers
Schrek et al., U.S.A. (*244*)	2.0
Valko, Czechoslovakia (*282*)	3.5
Sadowsky et al., U.S.A. (*230*)	3.7
Blümlein, Germany (*31*)	27.5
Wynder et al., U.S.A. (*309*)	23.6
Wynder et al., India (*309*)	3.1
Schwartz et al., France (*246*)	4.6
Wynder et al., Sweden (*317*)	6.0
Wynder et al., Cuba (*324*)	(18.9)[b] (males only)
Dutta-Choudhuri et al., India (*77*)	4.3
Stazewski, Poland (*252*)	(40.0) (males only)
Svoboda, Czechoslovakia (*261*)	8.3

[a] Computed according to the method of J. Cornfield (*49*).
[b] Figures in parentheses represent ratios based on less than five case nonsmokers.

TABLE 19.—Mortality ratios for cancer of the larynx—prospective studies

Study	Population size	Number of deaths	Nonsmokers	Cigarette smokers	Comments
ACS 9-State Study	188,000 males	24	—	—	All larynx cancer deaths occurred in smokers
British Physicians	34,000 males	38	1.00	13.00	Includes cancer of larynx and other upper respiratory sites
U.S. Veterans	290,000 males	116	1.00	11.49	
ACS 25-State Study	358,000 males	67	1.00	6.52	Includes buccal, pharyngeal, and laryngeal cancers
	483,000 females	11	1.00	3.25	
California males in 9 occupations	68,000 males	11	—	>2.90	All larynx cancer deaths occurred in smokers[a]
Japanese Study	122,000 males	38	1.00	13.59	
	142,800 females	6	1.00	6.52	

[a] Ratio derived by comparing smokers of half a pack with all other smokers

TABLE 20.—Relative risk of laryngeal cancer for males and females by amount smoked per day*

Number of Cigarettes Per Day	Number	Relative Risk	Confidence Limits
	Males (N = 243)		
1-10	16	4.4	1.6 ~ 12.6
11-20	87	13.5	5.3 ~ 33.1
21-40	99	17.3	6.8 ~ 44.2
41+	41	34.4	12.3 ~ 96.1
	Females (N = 48)		
1-20	19	4.4	
21+	29	28.2	

* Risk relative to 1.0 for nonsmokers.
SOURCE: Wynder and Hoffmann (*316*).

Strength of the Association

In the retrospective studies, the relative risk of laryngeal cancer (Table 18) ranged from 2.0 in a study of 73 U.S. veterans (*244*) to 40.0 in a Polish study of 207 males admitted to a chronic disease hospital (*252*). Two other studies (*30, 316*) found substantial increases in relative risk among smokers as compared with nonsmokers. Several studies have reported a strong dose-response relationship between the number of cigarettes smoked per day and laryngeal cancer mortality (*299, 316*). The mortality ratios for male and female cigarette smokers from one of these studies (*316*) are summarized by daily consumption in Table 20.

One study (*327*) examined the impact of long-term filter cigarette usage on laryngeal cancer risk. After adjustment for duration of smoking, inhalation, and butt length, the relative risk for developing laryngeal cancer was decreased in male and female users of filter cigarettes compared to users of unfiltered cigarettes, although this risk was still substantially greater than that for nonsmokers (Figures 21 and 22). The American Cancer Society 25-State Study data (*155*) also showed a reduced risk of laryngeal cancer among smokers of lower tar and nicotine cigarettes, but this reduction was not statistically significant.

In the prospective studies, the mortality ratios for smokers ranged from over 3 among U.S. females to 13 or greater among Japanese males and British male physicians (Table 19). In two of the prospective studies, mortality ratios could not be accurately calculated because all the deaths occurred in smokers. Several of these prospective studies have confirmed the strong dose-response relationship reported in the retrospective studies (Table 21).

Specificity of the Association

The prospective studies have measured mortality data for a large number of diseases. The specificity of the association is evidenced by

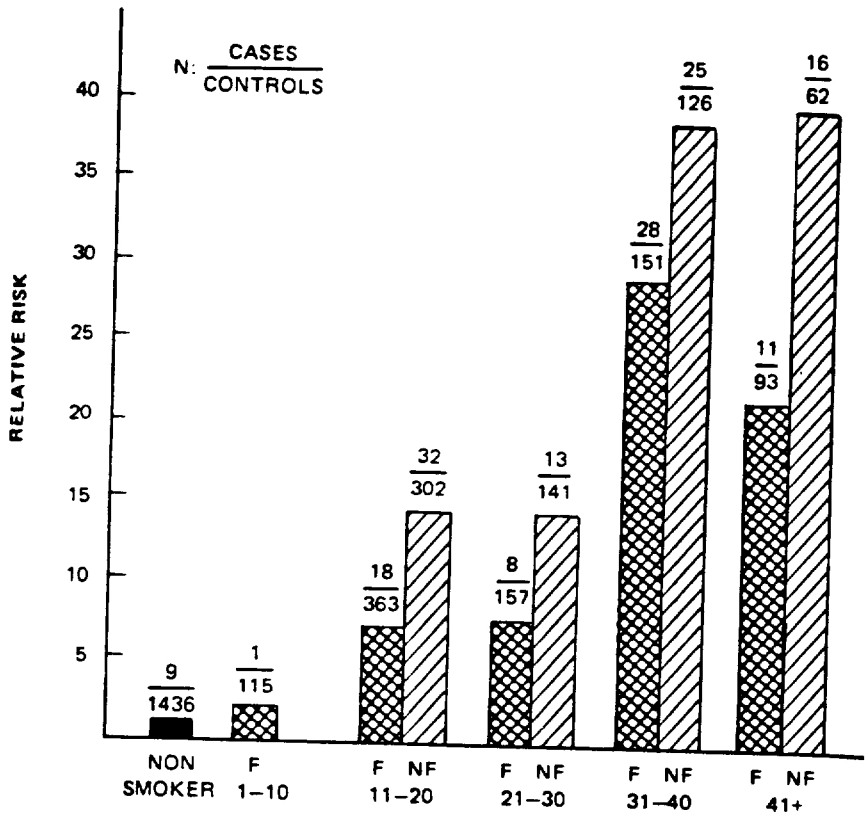

FIGURE 21.—Relative risk of developing larynx cancer for males, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

the mortality ratios of laryngeal cancer in comparison with other cancers (Appendix Tables A and B).

Temporal Relationship of the Association

This criterion is supported by the major prospective studies (Table 19) that examined the occurrence of laryngeal cancer in initially healthy groups of smokers and nonsmokers. The temporal relationship of the association is strengthened by data from post mortem studies that have evaluated vocal cord histology in groups of smokers and nonsmokers (*11, 56, 190, 228*). A spectrum of premalignant changes is seen in laryngeal tissue of smokers; this is not found in nonsmokers (see below).

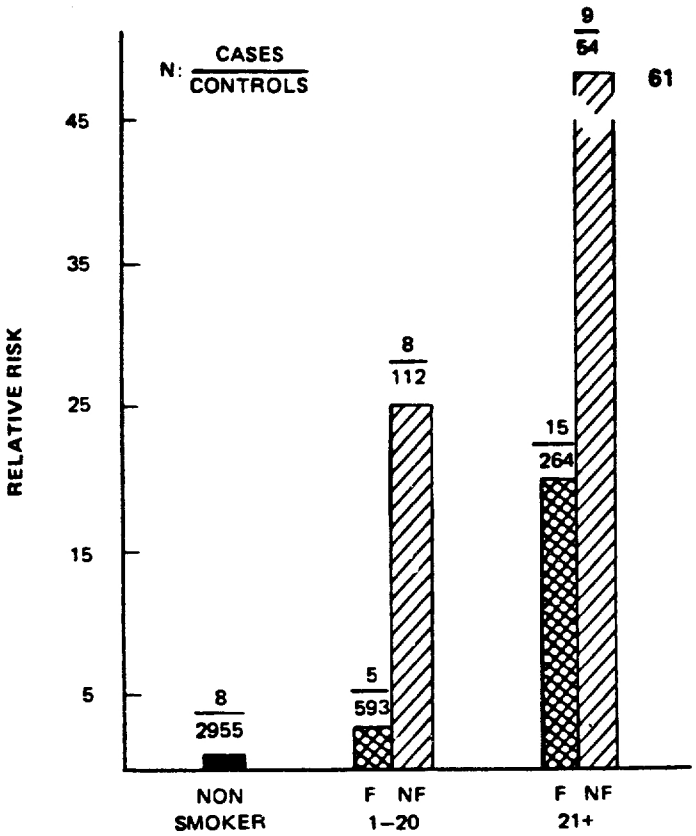

FIGURE 22.—Relative risk of developing larynx cancer for females, by number of cigarettes smoked per day and use of filter (F) and nonfilter (NF) cigarettes

SOURCE: Wynder (*327*).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship between smoking and laryngeal cancer incidence and mortality in retrospective and prospective studies strongly supports a causal association. Smoke exposure has been measured by the number of cigarettes smoked per day, the tar and nicotine content of the cigarettes smoked, the depth of inhalation, the number of years smoked, and the age at initiation (*269, 276*), all of which support a direct causal relationship.

TABLE 21.—Laryngeal cancer mortality ratios, by amount smoked

Population	Cigarettes/day	Mortality rates		Comments
U.S. Veterans Study	Nonsmoker	1.00		
	1–9	5.28*		*Based on less than 20 deaths
	10–20	9.20		
	21–39	14.78		
	> 40	32.14*		
Japanese Study	Nonsmoker	1.00		
	1–19	19.23		
	20–39	27.43		
	40+	34.13		
British Physicians		Male	Female	
	Nonsmoker	1.00	1.00	Includes larynx and other respiratory sites
	1–14	5.00	—	
	15–24	7.00	4.00	
	25+	33.00	6.50	

Correlation of Sex Differences in Laryngeal Cancer With Different Smoking Habits

Laryngeal cancer is predominantly a disease of males, although the mortality among females has increased over the past 20 years. A male-to-female ratio of 14.9:1 was reported in 1956 (*312*). The sex ratio decreased to 4.6:1 by 1976. This time trend is consistent with the later adoption of cigarette smoking by females (*270*) and a possible increase in female alcohol consumption, given the synergy between the two exposures. The greater alcohol consumption among males and the strong association between laryngeal cancer and alcohol consumption (see below) are considered to contribute to the excess of male to female laryngeal cancer mortality.

Correlation of Laryngeal Cancer Mortality Among Populations With Different Tobacco Consumption

In studies of populations with low proportions of smokers (e.g., Mormons and Seventh Day Adventists), the incidence of laryngeal cancer is substantially lower (*79, 165, 166, 211, 294*), supporting the causal relationship between smoking and laryngeal cancer.

Laryngeal Cancer Mortality and Cessation of Smoking

A few studies have examined the relationship between cigarette smoking cessation and risk for laryngeal cancer. One retrospective study found a marked reduction in risk following cessation among males and females (Figures 23 and 24) and suggested that "10 to 15 years of cessation are required before the long-term smoker's risk approaches that of a nonsmoker" (*327*). In the U.S. Veterans and British Physicians studies, ex-smokers had approximately 40 percent

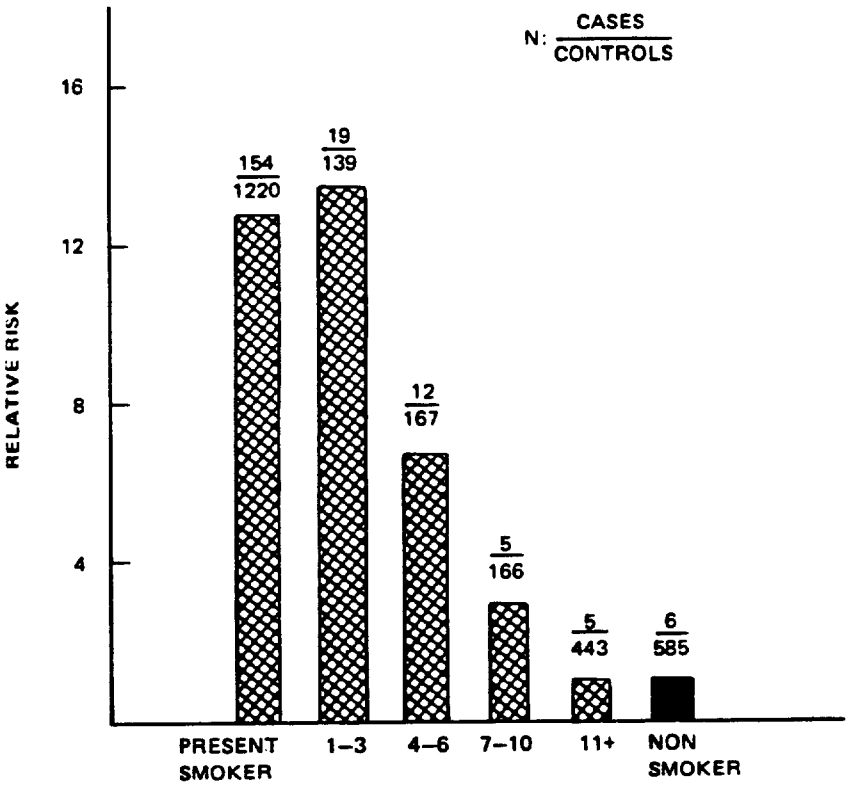

FIGURE 23.—Relative risk of developing larynx cancer for male ex-smokers, by years of smoking cessation

SOURCE: Wynder (*327*).

of the risk of current smokers for laryngeal cancer; however, the risk was still roughly five times that of the nonsmoker (*68, 224*). Because data were not presented by the number of years off cigarettes, the higher relative risk may be due to higher mortality rates often observed in former smokers (even compared to continuing smokers) during the initial years of smoking cessation.

Smoking and Histologic Changes in the Larynx

The relationship of smoking habits to precancerous lesions of the larynx was examined in an autopsy series of 148 cases, 24 of whom were nonsmokers (*190*). Precancerous lesions (dysplasia and carcinoma *in situ*) and carcinoma occurred least frequently among nonsmokers (4.2 percent). The frequency of these lesions increased from 12.5 percent in light smokers to 22.9 percent in moderate smokers and to 47.2 percent in heavy smokers. Similar findings were reported

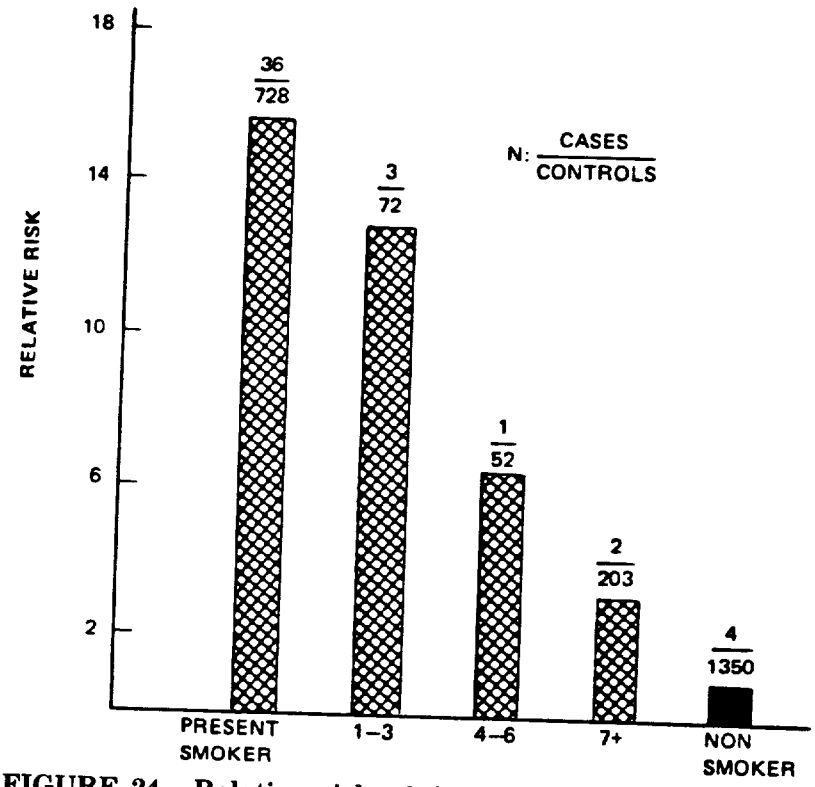

FIGURE 24.—Relative risk of developing larynx cancer for female ex-smokers, by years of smoking cessation

SOURCE: Wynder (*327*).

from a study of histological changes in the larynx of 942 males aged 21 to 95 (*11*). These findings lend support to a causal nature of the relationship.

Laryngeal Cancer and Non-Cigarette Tobacco Use

A few epidemiological studies have examined the relationship between other forms of tobacco use and cancer of the larynx (*60, 68, 98, 131*). Pipe and cigar smokers develop cancer of the larynx at rates comparable to those of cigarette smokers (i.e., several times those of nonsmokers) (Tables 22 and 23). The similarities of the mortality ratios of cancer of the larynx for smoking of non-cigarette tobacco products suggests that the carcinogenic potentials of smoke from cigars, pipes, and cigarettes are quite similar at this site.

The association of smoking of non-cigarette tobacco products to histological changes in the larynx has been examined (*11*). Among males who smoked cigars and pipes but not cigarettes, only 1 percent

TABLE 22.—Mortality ratios for cancer of the larynx 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	—	—	2.00	1.00	0.60
ACS 25-State Study	1.00	—	—	3.37	[3]6.09	—
U.S. Veterans	1.00	10.33	—	7.28	11.49	—

[1] Combines data for oral, larynx, and esophagus.
[2] Ratios: relative to cigarette smokers.
[3] Only mortality ratios for ages 45 to 64 are presented.

had no atypical cells and more than 75 percent of the subjects had lesions with 50 to 69 percent atypical cells. Four of the cigar and pipe smokers had carcinoma *in situ*. Of those who never smoked regularly, 75 percent had no atypical cells. The cigar and pipe smokers had a percentage of cells with atypical nuclei similar to that of cigarette smokers who smoked one to two packs per day.

Synergistic Role of Alcohol for Laryngeal Cancer

Laryngeal cancer occurs much more frequently in alcoholics than in nonalcoholics (*183, 208, 239*). Although part of this increased risk for laryngeal cancer among alcohol abusers may be attributed to heavier smoking by this group, there remains a substantial excess risk associated with alcohol use (*227*). The relative risks of laryngeal cancer by daily consumption of alcohol and cigarettes in 239 male cases and 4,725 controls (Figure 25) suggest a synergy when tobacco usage is combined with chronic alcohol consumption (*179*). Male smokers of from 11 to 20 and from 21 or more cigarettes per day who consumed 7 ounces or more of alcohol per day had relative risks for laryngeal cancer of 26.8 and 27.2 respectively. The corresponding risks for nondrinking smokers were 6.6 and 12.0. This synergy has also been demonstrated using the Third National Cancer Survey, which suggests that the laryngeal cancer risk for smoking drinkers is approximately 50 percent greater than the sum of the excess risks posed by either behavior alone (*85*). The mechanism(s) by which these two factors interact is unclear (*179, 226, 242*).

Experimental 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 due not to an unusual susceptibility of the larynx for tumor induction, but rather to the distribution of smoke aerosol precipitation within the upper

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