Synergistic Role of Alcohol for Esophageal Cancer

Numerous investigators have found a synergistic relationship between the use of tobacco in various forms, alcohol consumption, and the development of cancer of the esophagus (*119, 132, 143, 241, 243, 263, 299, 307, 323*). Some investigators report that tobacco is a more important carcinogen than alcohol, but others report that the reverse is true. Most of the studies report a synergism with the combined use of tobacco and alcohol, resulting in higher rates of cancer of the esophagus than would be observed by the addition of the two exposures. The mechanisms by which these two factors interact are not known. Alcohol may act as a solvent for carcinogenic hydrocarbons in the tobacco smoke or may alter microsomal enzymes in the mucosal cells of the esophagus (*306*). This hypothesis has received support from experimental observations (*150*). It has been noted, however, that alcoholism may be accompanied by severe nutritional deficiencies, which also may predispose an individual to certain diseases (*271*).

Experimental 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 carcinoma. These studies and others are presented in the Part of this Report on mechanisms of carcinogenesis.

Conclusion

1. Cigarette smoking is a major cause of esophageal cancer in the United States. Cigar and pipe smokers experience a risk of esophageal cancer similar to that of cigarette smokers.
2. The risk of esophageal cancer increases with increased smoke exposure, as measured by the number of cigarettes smoked daily, and is diminished by discontinuing the habit.
3. The use of alcohol in combination with smoking acts synergistically to greatly increase the risk for esophageal cancer mortality.

Cancer of the Urinary Bladder

Introduction

It is estimated that in 1982 in the United States there will be 37,100 new cases and 10,600 deaths from cancer of the bladder (*2*). The average annual incidence for males is almost three times that for females.

Cancer of the bladder resulted in 6,401 deaths in 1950 and 9,812 deaths in 1977 in the United States. The age-adjusted rate fell from 3.7 to 2.9 per 100,000.

The age-adjusted mortality rate fell in all four color-sex groups (Figure 39). The rate for white males, who had the highest mortality from this disease, decreased by 5.7 percent between 1950 and 1977. Among other than white males, who had the second highest mortality rate from this disease, mortality declined by 2.6 percent. In contrast, the age-adjusted death rate for white females decreased by 36.4 percent, and that of other than white females fell 25.9 percent.

White males between 45 and 74 years of age had lower death rates from cancer of the bladder in 1977 than in 1960, but older males had higher mortality. Among white females 45 years of age and older, mortality decreased over the study period. The death rate increased in other than white males 65 years of age or older and in other than white females 75 years of age or older (Figures 40 and 41).

The age-specific death rates show no significant increases in either white males or white females when plotted on a three-dimensional graph for the period 1950–1977 (Figures 42 and 43).

Most cancers of the bladder are transitional or squamous cell carcinomas. Unless these produce hematuria or obstruct the bladder outlet, they remain undiagnosed until quite late, making cure less likely. Five-year survival rates range from 4 percent for individuals with distant metastasis, to 21 percent for individuals with regional involvement, and to 72 percent with localized disease (2). For patients diagnosed with bladder cancer from 1960 to 1973, the overall 5-year survival rate was approximately 60 percent for whites and 30 percent for other than white (313).

Certain occupational exposures are associated with an elevated risk for bladder cancer. Many of these are related to the exposure to certain aromatic amines in the work place. The first report of an association between cigarette smoking and human bladder cancer in the United States was based on a retrospective study of 321 men with bladder cancer (157). In the ensuing 35 years, other epidemiological and experimental data have established an association between cigarette smoking and bladder cancer.

Several authors have conservatively calculated the percentage of bladder cancers that can be attributed to cigarette smoking. One study (313) estimated that 40 percent of male bladder cancers and 31 percent of female bladder cancers in the United States may be attributed to smoking cigarettes. This is in agreement with the estimate by Cole et al. (48) of 39 percent in males and 29 percent in females. A Canadian study reported a population-attributable risk of bladder cancer due to cigarette smoking of 61 percent in males and 26 percent in females (129).
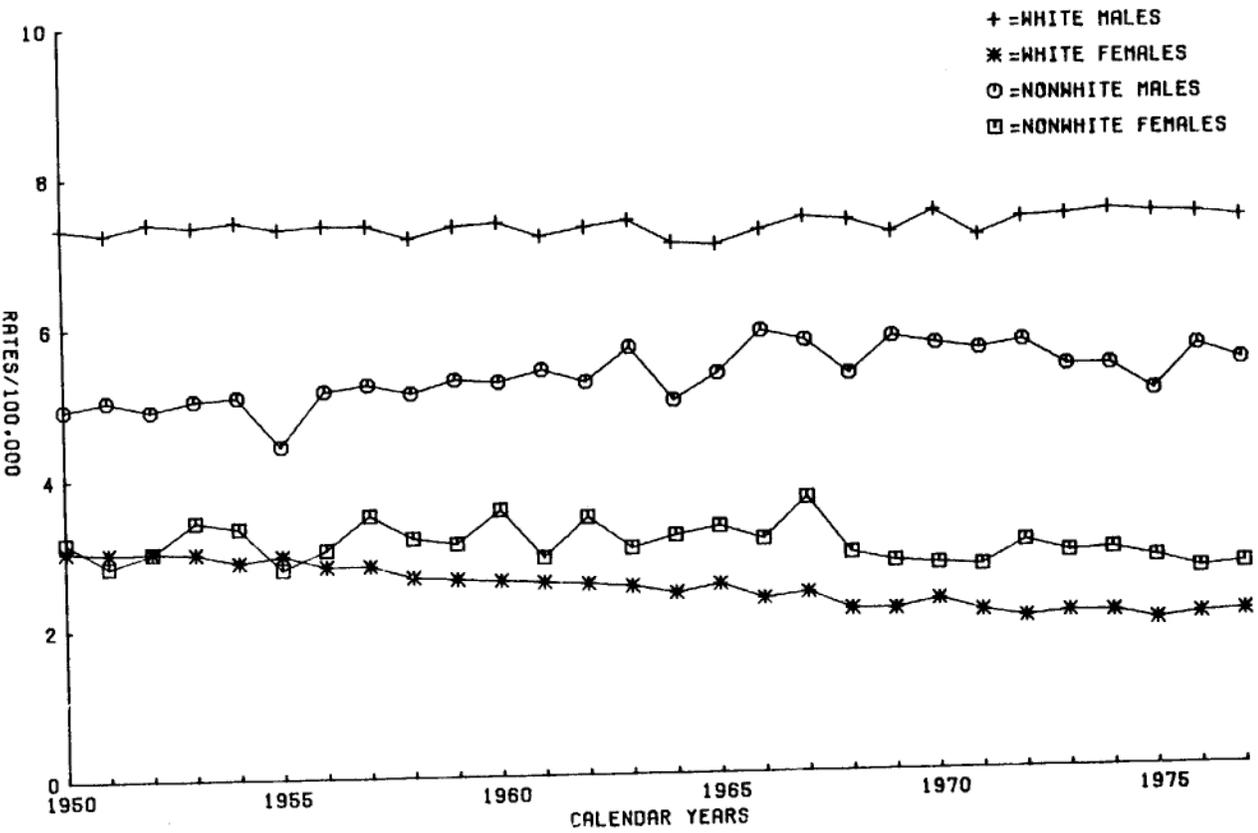
FIGURE 39.—Age-adjusted* mortality rates for cancer of the bladder and other urinary glands, by race and sex, United States, 1950–1977

* 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.
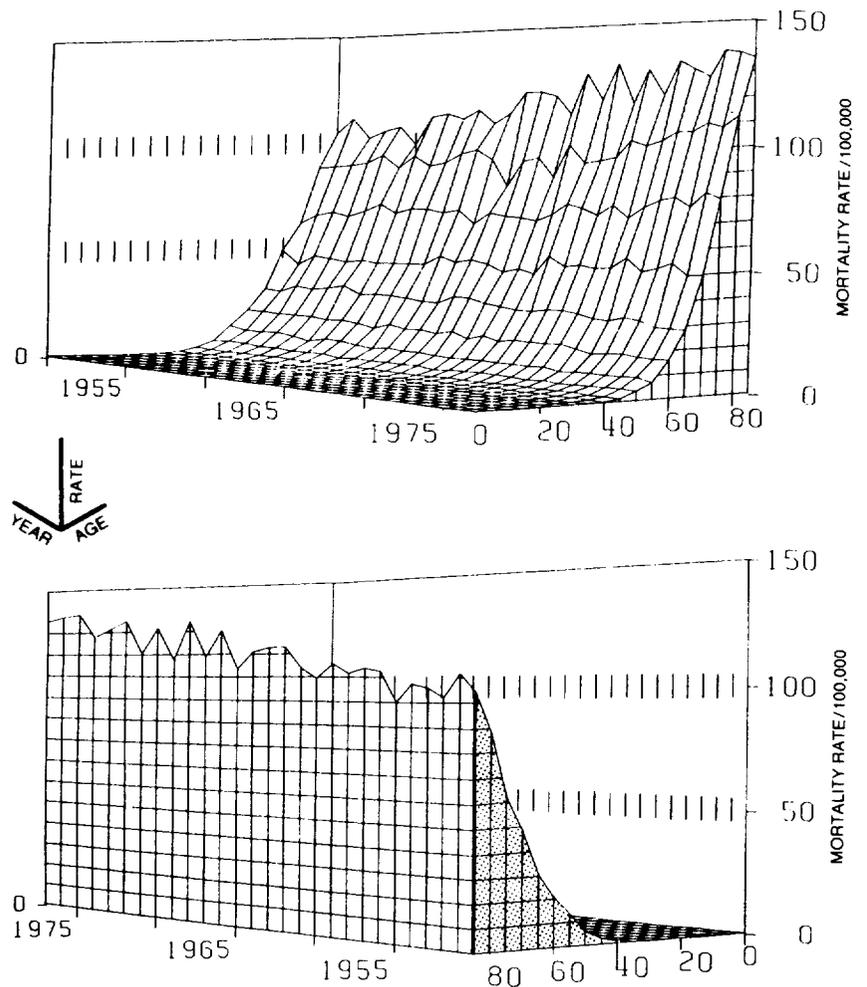
SOURCE: National Cancer Institute (1/98).

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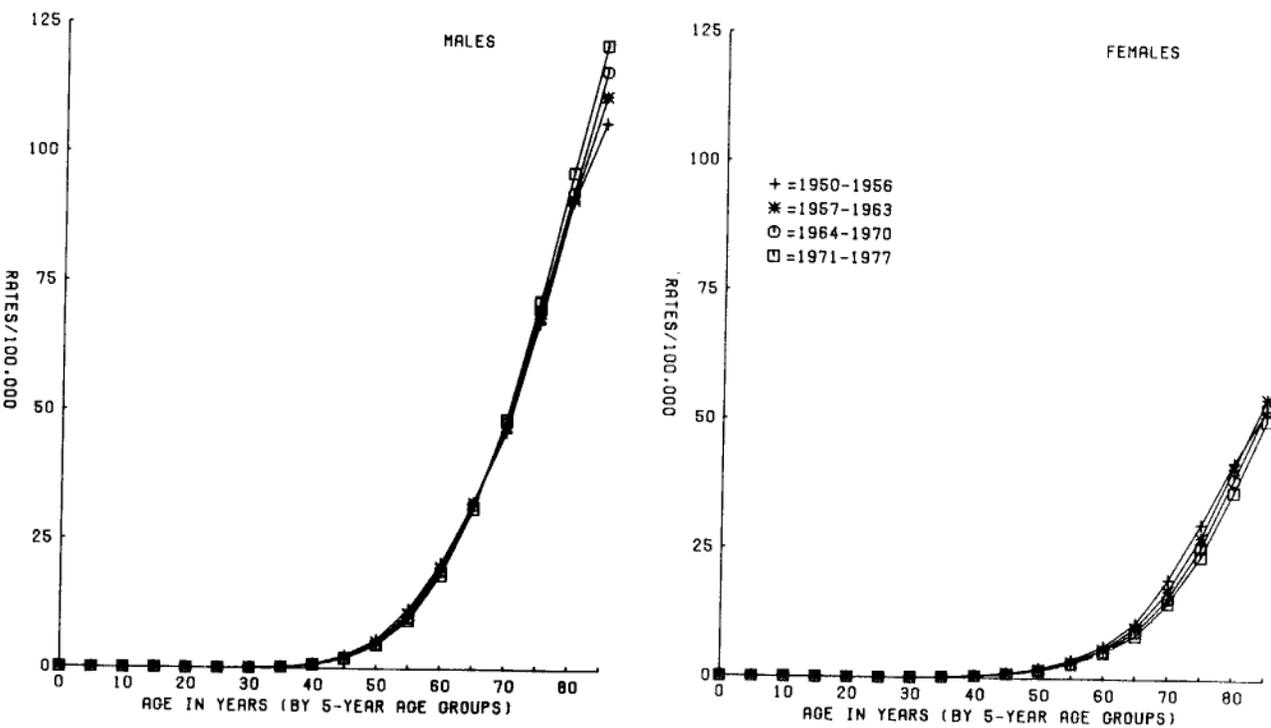
FIGURE 40.—Age-specific mortality rates for whites in the United States for cancer of the bladder and other urinary glands

SOURCE: National Cancer Institute (1980).
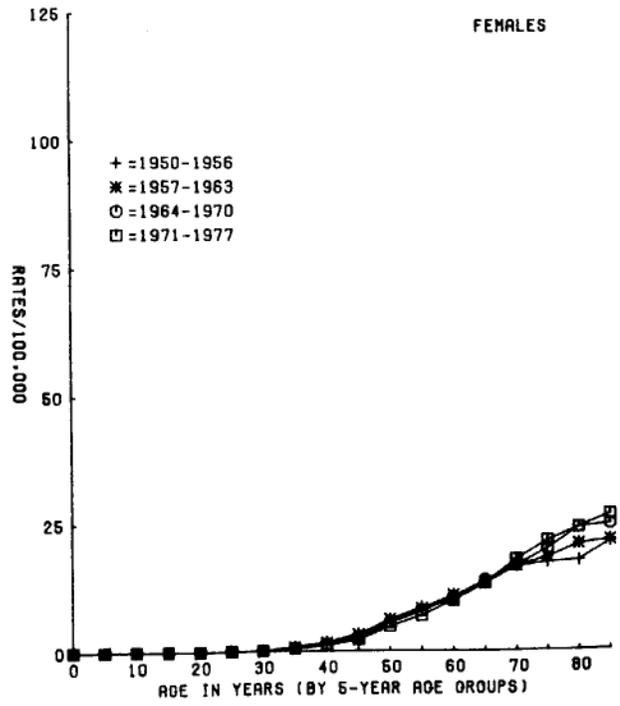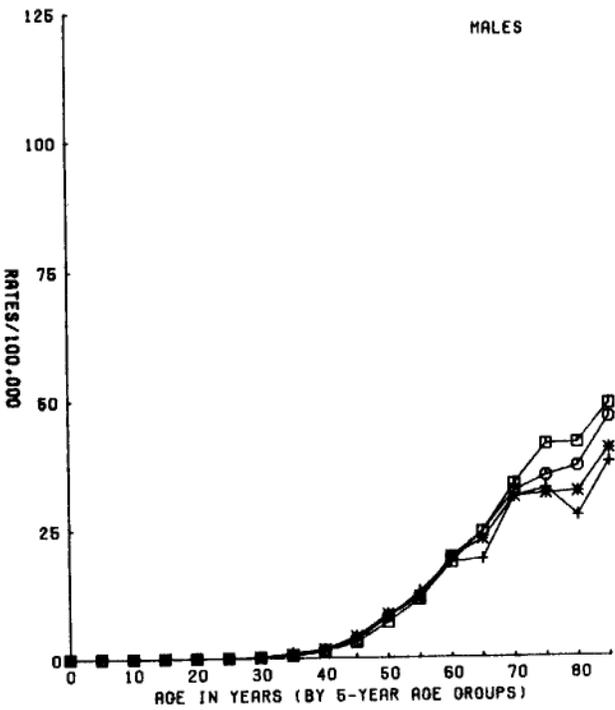
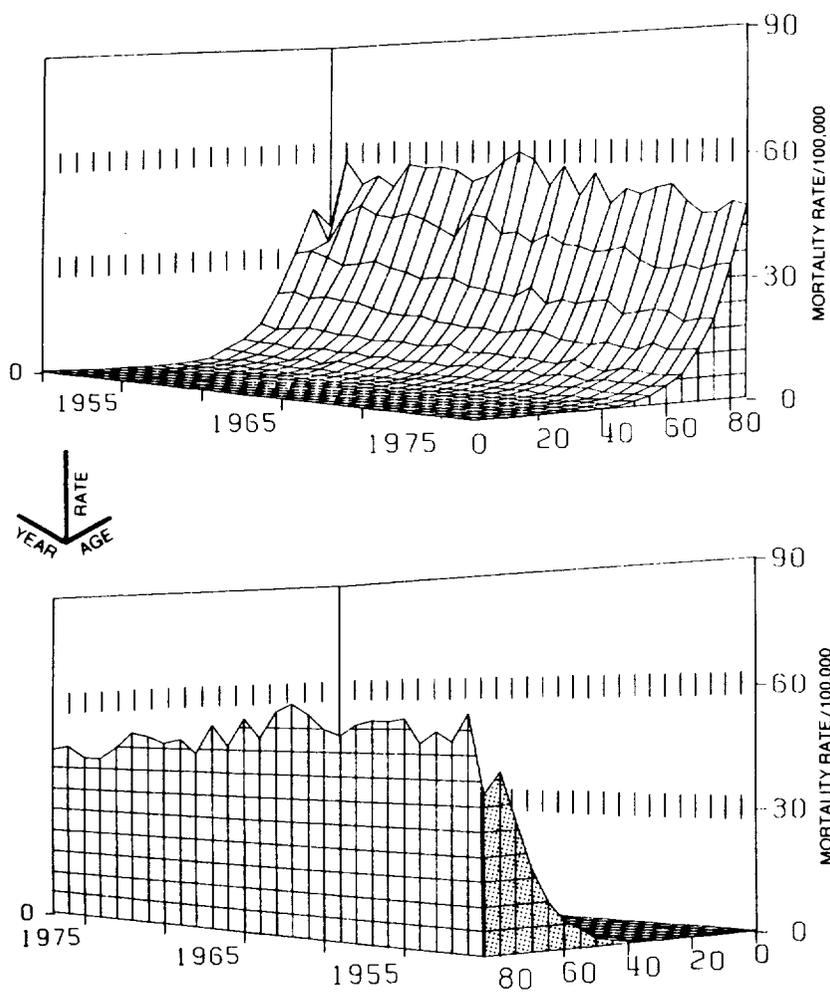FIGURE 41.—Age-specific mortality rates for nonwhites in the United States for cancer of the bladder and other urinary glands

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FIGURE 42.—Age-specific mortality rates by 5-year age groups for cancer of the bladder and other urinary glands for white males, United States, 1950–1977

SOURCE: National Cancer Institute (198).

Causal Significance of the Association

Consistency, Strength, and Specificity of the Association

There have been numerous retrospective studies of the relationship between smoking and bladder cancer (*3, 46, 48, 55, 75, 139, 141, 157, 159, 188, 247, 253, 267, 313, 325, 327, 330*). Almost all of these studies have found an association between smoking and cancer of the

FIGURE 43.—Age-specific mortality rates by 5-year age groups for cancer of the bladder and other urinary glands for white females, United States, 1950–1977

bladder with relative risk ratios for the smoker averaging two to three times that of the nonsmoker (Table 31). A retrospective population-based study of 470 confirmed cases of transitional cell or squamous cell cancers of the bladder found a positive relationship between cigarette smoking and bladder cancer (*48*). A dose-response

relationship was demonstrated for both the number of cigarettes smoked per day and different degrees of inhalation.

In the TNCS study (299), a significant association was found between cigarette smoking and bladder cancer. The Hawaiian study of five ethnic groups (113) also disclosed a positive association between smoking and bladder cancer. In a Canadian population-based retrospective study of 632 case-controlled pairs (129), the relative risk for developing bladder cancer for those who had ever used cigarettes versus those who had never used cigarettes was 3.9 for males and 2.4 for females. A dose-response relationship was demonstrated, and reduced risk was associated with the use of filter cigarettes as compared with the use of nonfilter cigarettes. Several of the retrospective studies found a dose-response relationship of cigarette smoking for bladder cancer, with the risk increasing with increased number of cigarettes smoked per day, duration of cigarette smoking, or lifetime number of cigarettes. Further, a study of successive birth cohorts in four countries, including the United States, found increasing rates of bladder cancer with increasing smoking exposure, for both males and females (128).

Several of the large prospective epidemiological studies have examined the relationship between cigarette smoking and bladder cancer and are summarized in Table 32. On the average, cigarette smokers are twice as likely to die from cancer of the bladder as are nonsmokers. Several of these studies also show a moderate dose-response relationship; however, this relationship is not as strong as that noted between smoking and lung, laryngeal, oral, and esophageal cancers (Table 33). Comparisons of mortality ratios for selected causes of disease suggest that the specificity of the association is not as great as that noted for the above cancers (Appendix Tables A and B). The American Cancer Society 25-State Study (155) reported a reduced risk for bladder cancer among smokers of lower tar and nicotine cigarettes, a reduction which was statistically significant among females but not among males.

The lower order of strength and specificity for bladder cancer than for cancers of the lung, larynx, oral cavity, or esophagus suggests that factors other than smoking may also be associated etiologically with bladder cancer.

Bladder Cancer Mortality and Cessation of Smoking

Wynder and Stellman (326) reported that the risk of bladder cancer decreased almost to the level of nonsmokers after about 7 years of cessation (Figure 44). More recent data from the U.S. Veterans and British Physicians prospective studies show bladder cancer mortality ratios for ex-smokers only half those for continuing smokers (68, 224).

TABLE 31.—Review of literature on smoking and bladder cancer reported since 1963—retrospective studies

Country	Years of study	Authors	Relative risk smokers: nonsmokers	Number of subjects Cases	Controls	Study population
U.S.A.	1957–60	Wynder et al. (325)	3.5[a]	300	300	Male patients
U.S.A.	1951–61	Cobb and Ansell (46)	7.3[a]	131	120	Male VA hospital patients
Poland	1958–64	Staszewski (253)	2.7	150	750	Male patients
U.S.A.	1958–64	Dunham et al. (75)	1.4[a]	334	350	Male patients
			1.2[a]	159	177	Female patients
U.K.	1958–67	Anthony and Thomas (4)	<1	381	275	Male patients
U.S.A.	1967–68	Cole et al. (48)	1.9	360	381	Male patients
			2.0	108	117	Female patients
U.S.A.	1965–71	Simon et al. (141)	1.6	135	390	Female patients
Egypt	1966–71	Makhyoun (157)	1.3[a]	278	278	Bilharzial male patients
			1.7	87	87	Nonbilharzial male patients
Canada	1972–73	Morgan and Jain (188)	6.4[b]	158	158	Male patients
			4.4[b]	74	74	Female patients
Austria	1972–75	Flamm et al. (84)	1.6	150	—	Male patients; Austrian population controls
			3.0	40	—	Female patients; Austrian population controls

[a] Recalculated from author's data.

[b] Heavy smokers (≥ 25 cigarettes per day) compared with nonsmokers.

SOURCE: Wynder and Goldsmith (313).

TABLE 32.—Bladder cancer mortality ratios—prospective studies

| Population	Study size	Non-smokers	All cigarette smokers	Comments
ACS Males in 9-State Study	187,783 White Males	1.00	2.00	Smokers of 10–20 cigarettes Includes all urinary tract cancers. Includes Prostate.
British Physicians	34,000 Male Doctors	1.00	2.11	
Canadian Veterans	78,000 Males	1.00	1.40	Genitourinary cancers considered as a group
ACS 25 State Study	358,000 Males and 483,000 Females	1.00 1.00	2.55 2.80	
U.S. Veterans	2,265,000 Person-Years	1.00	2.15	
California Males in 9 occupations	68,153 Males	1.00	2.89	
Japanese study	265,118 Males and Females	1.00 1.00	2.00 (Males) 2.55 (Females)	
Swedish Study	55,000 Males and Females	1.00 1.00	1.80 (Males) 1.60 (Females)	Bladder + other urinary organs

For male ex-smokers, the risk after 15 years of not smoking was less than one-half that of current male smokers (*129*).

Temporal Relationship of the Association

Evidence for the temporal relationship of the association is provided by the prospective studies in which populations of initially disease-free subjects were followed for the development of bladder cancer. Reliable histological studies of bladder epithelium in smokers compared with nonsmokers have not been reported.

TABLE 33.—Bladder cancer mortality ratios by amount smoked—prospective studies

Study	Population	Amount Smoked per Day	Ratio	Comments
U.S. Veterans	290,000	Nonsmoker	1.00	
		1–9	1.22	*Based on
		10–20	2.18	less than
		21–39	2.78	20 deaths
		≥40*	2.29	
British Physicians	34,000 males	Nonsmoker	1.00	Grams of
		1–14	2.20	tobacco
		15–24	2.20	per day
		25 +	1.40	
California males in 9 occupations	68,000 males	Nonsmoker	1.00	
		about ½ pk	1.52	
		about 1 pk	2.81	
		about 1½ pk	5.41	

Study	Population	Males		Females	
Swedish Study	55,000 males and females	NS	1.00	NS	1.00
		1–7 gm/day	1.50	1–7	1.20
		8–15	1.60	8–15	2.10
		16 +	2.70	16 +	0.80
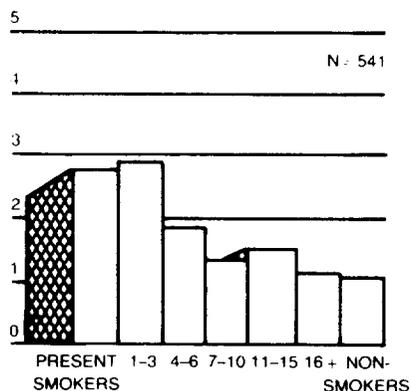
FIGURE 44.—Relative risk of male ex-smokers for cancer of the bladder by years since quitting smoking

SOURCE: Wynder and Stellman (326).

Coherence of the Association

Dose-Response Relationship

The finding of a dose-response relationship in both retrospective

and prospective studies (see page 106–107) strengthens the coherence of the association of smoking and bladder cancer.

Correlation of Sex Differences in Bladder Cancer With Different Smoking Habits

Two investigators (128, 185), reporting 10 years apart, found an association between time trends in smoking patterns and bladder cancer mortality among both males and females. Each found an increasing risk of bladder cancer with increasing smoking exposure.

Correlation of Bladder Cancer Among Populations With Different Tobacco Consumption

Coherence of the association is also illustrated by data showing a low prevalence of this disease in groups with small proportions of smokers (e.g., Mormons and Seventh Day Adventists) (79, 165, 166, 211, 294).

Bladder Cancer Mortality and Cessation of Smoking

Cessation of smoking decreases the risk of bladder cancer compared to that of continuing smokers. A study of male ex-smokers (129) found a risk of less than one-half that of continuing smokers 15 years after quitting smoking; a similar finding was observed in two of the major prospective studies (68, 224).

Bladder Cancer and Non-Cigarette Tobacco Use

Two prospective studies have noted a relationship between pipe and cigar smoking and cancer of the bladder (68, 131). In the British Physicians Study, a mortality ratio of 1.5 was observed for the combined category of pipe/cigar smokers, whereas in the U.S. Veterans Study, a relationship was noted only for pipe smokers (ratio 1.20).

Synergistic Role of Other Substances for Bladder Cancer

The relationship between cigarette smoking and occupational exposure(s) is complex and has not been clearly elucidated. A number of carcinogens specific for the human bladder have been identified (45). Some of these compounds are found in cigarette smoke in very low concentrations. Cigarette smoking probably acts as an independent agent in the development of bladder cancer; however, there may also be additive or synergistic interactions between cigarette smoking and substances present in the work place.

Those who work with dye stuffs, rubber, leather, print, paint, petroleum, and other organic chemicals are at higher risk for bladder cancer than workers not exposed.

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Conclusion

1. Cigarette smoking is a contributory factor in the development of bladder cancer in the United States. This relationship is not as strong as that noted for the association between smoking and cancers of the lung, larynx, oral cavity, and esophagus. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers at this site.

Cancer of the Kidney

Introduction

Over the period 1950–1977, the age-adjusted mortality rate for kidney cancer rose from 2.2 to 2.6. The annual number of deaths due to cancer of the kidney increased from 3,643 to 7,373. It is estimated that in 1982 there will be 18,100 new cases and 8,300 deaths due to kidney and other urinary tract cancers in the United States (other than bladder cancer) (2).

The death rate of white males was higher than that of the other three color-sex groups (Figure 45). While age-adjusted death rates increased, although at a decelerating pace, among white males throughout this period, rates among other than white males actually decreased slightly after 1967. Among white females, the age-adjusted rate increased between 1950 and 1957, when it stabilized. Among other than white females, who had the lowest age-adjusted rate of death from this disease, mortality rose from 1.2 to 1.4 per 100,000.

In the white population, the mortality sex ratio (male/female) increased from 1.75 in 1950 to 2.24 in 1977, reflecting the rise in the male death rate and the relative stability of the female rate. In the other than white populations, the mortality sex ratio was slightly lower during the 28-year period.

White males and white females were at greater risk from this disease than were their counterparts, although the white to other-than-white differential narrowed throughout the study period. In all four color-sex groups, death rates moved generally upward in the population between 45 and 84 years of age (Figures 46 and 47). In 1977, both white and other than white males had higher death rates from this disease than did white and other than white females in the 10-year age group from 35 to 44.
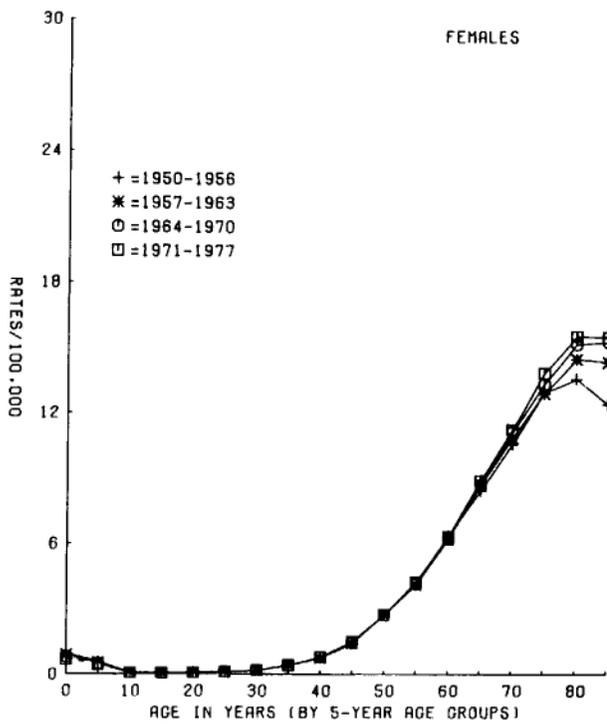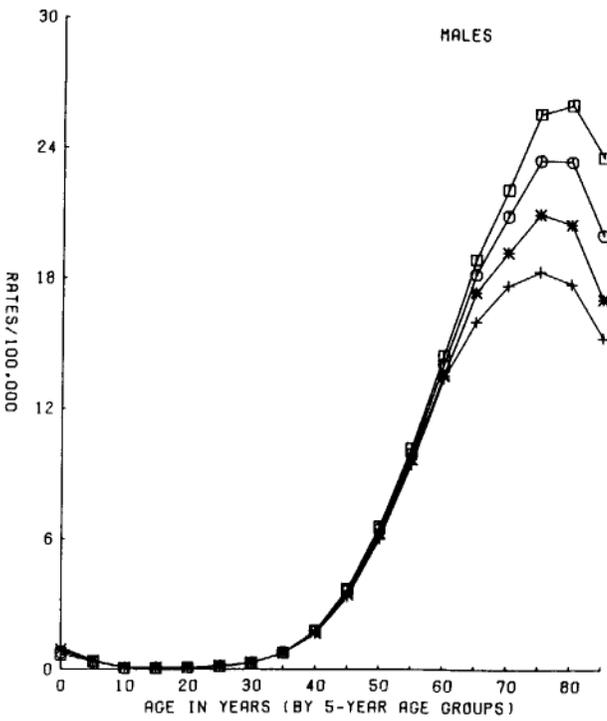
The age-specific death rates for cancer of the kidney show an upward trend in the older age groups, without a significant increase in the rates for the younger age groups when plotted on a three-dimensional graph for the period 1950–1977 (Figures 48 and 49).

There are four primary histological types of kidney cancer: (1) renal cell carcinoma, (2) nephroblastoma (Wilm's tumor), (3) sarco-
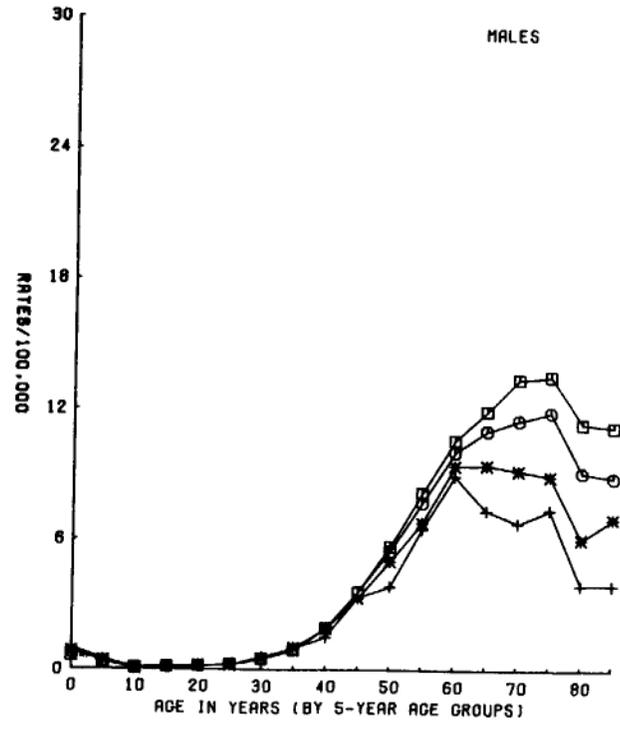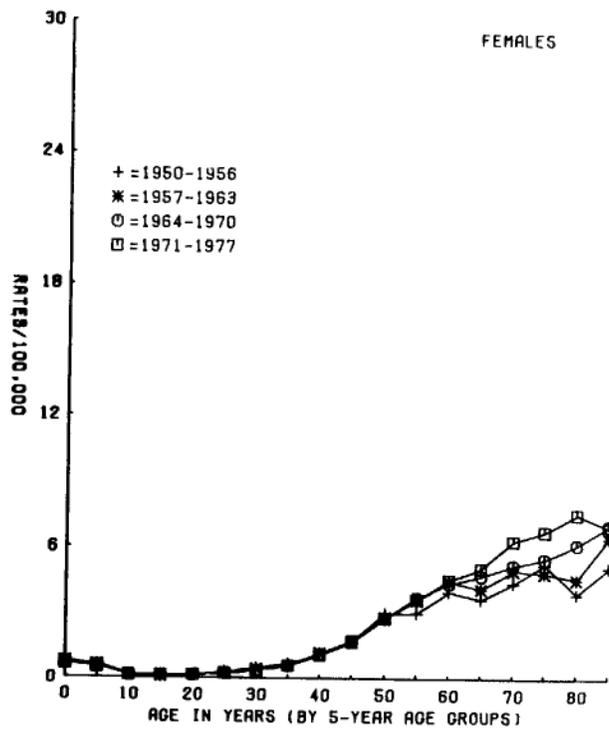
113

RATES/100,000
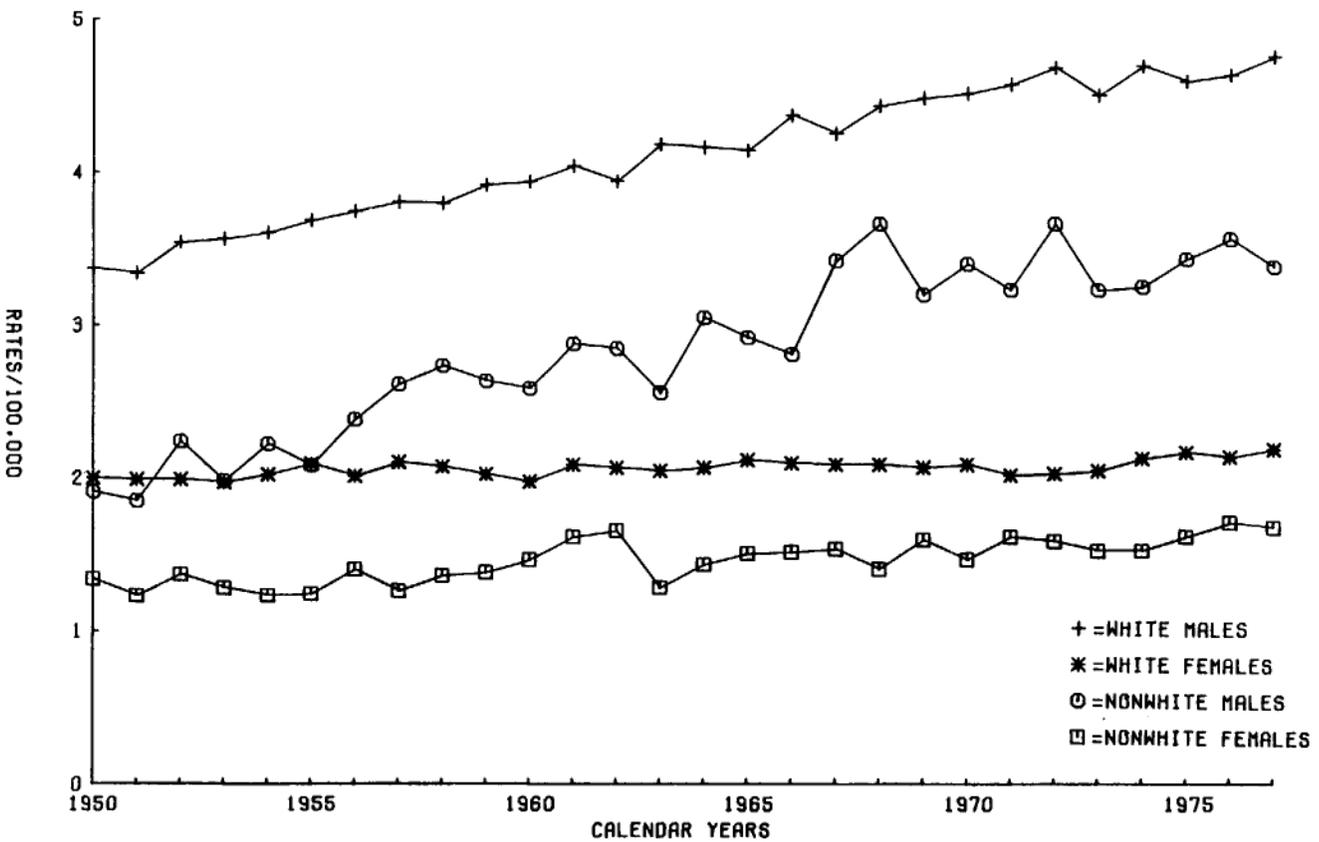
FIGURE 45.—Age-adjusted* mortality rates for cancer of the kidney, by race and sex, United States, 1950-1977

* 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.
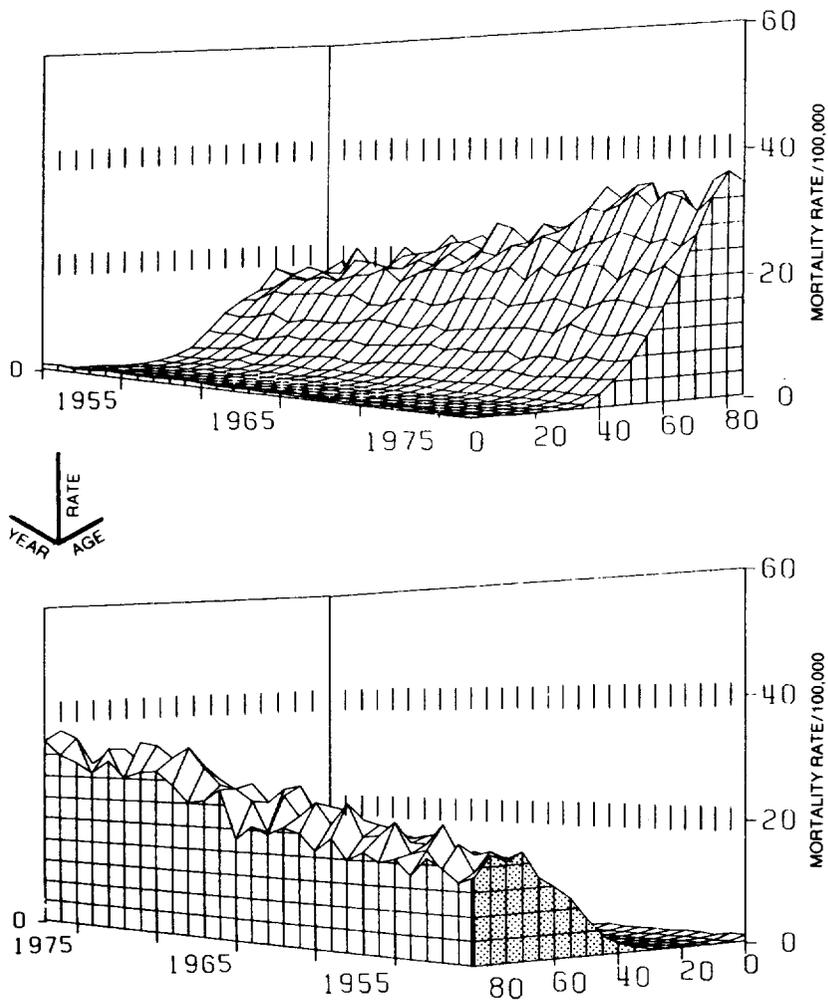
SOURCE: National Cancer Institute (198).

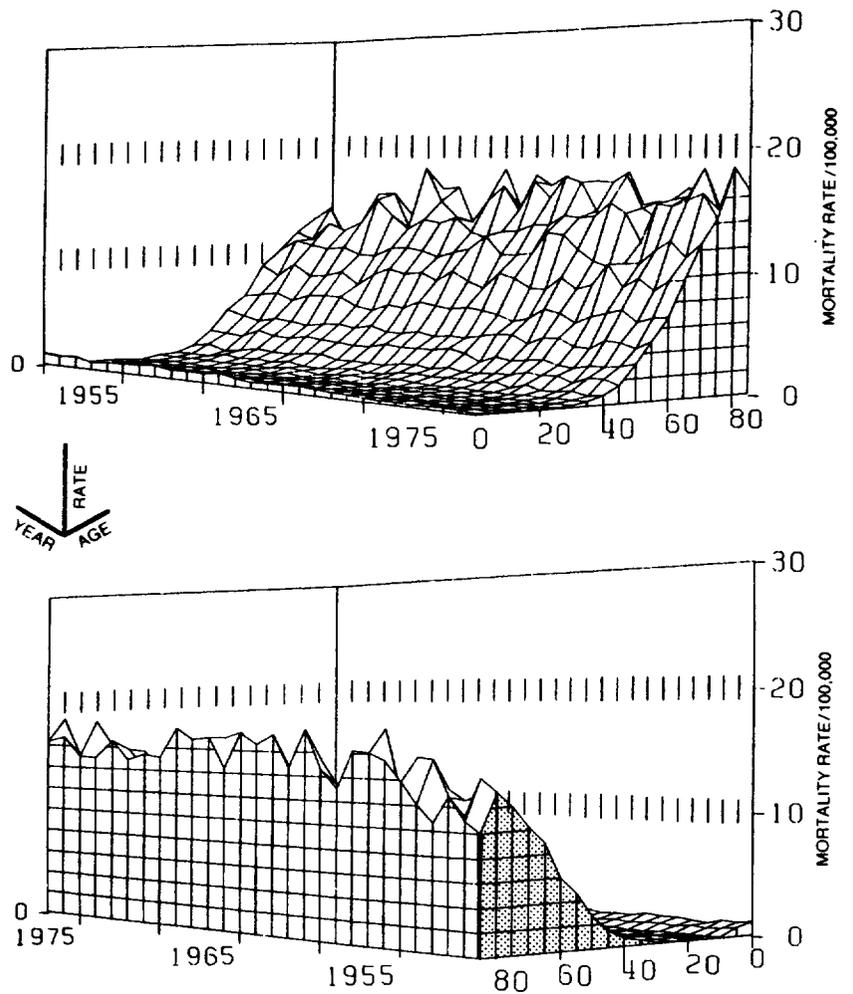**FIGURE 46.—Age-specific mortality rates for whites in the United States for cancer of the kidney**

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FIGURE 47.—Age-specific mortality rates for nonwhites in the United States for cancer of the kidney

SOURCE: National Cancer Institute (198).

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FIGURE 48.—Age-specific mortality rates by 5-year age groups for cancer of the kidney for white males, United States, 1950–1977

SOURCE: National Cancer Institute (*198*).

ma, and (4) epithelial tumors of the renal pelvis. Renal cell carcinomas comprise about 90 percent of kidney tumors and generally affect individuals after age 40 (average 55 to 60) (*197*). This tumor may be silent until far advanced. The median survival time for kidney cancer in the adult is about 2.7 years for those aged 35 to 54 at the time of diagnosis and 1 year for those 65 or older (*197*).

FIGURE 49.—Age-specific mortality rates by 5-year age groups for cancer of the kidney for white females, United States, 1950–1977

SOURCE: National Cancer Institute (1981).

Epidemiological studies have established an association between cigarette smoking and kidney cancer.

Causal Significance of the Association

Consistency, Strength, and Specificity of the Association

Several retrospective studies have examined the relationship between smoking and kidney carcinoma. Data from these studies

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(Table 34) show a positive association between smoking and kidney cancer with relative risks ranging from 1.06 to over 5, with one study of renal pelvis cancer reporting a tenfold risk for heavy cigarette smokers. Other studies also reported an increasing relative risk of renal adenocarcinoma and cancer of the renal pelvis in cigarette smokers (20, 21, 130, 238); the increase of relative risk of renal adenocarcinoma among cigarette smokers was found for both males and females (320). A significant positive association between cigarette smoking and renal cancer was noted in the TNCS study (299) and in the Hawaiian Study of Five Ethnic Groups (113).

In most of the prospective studies, cancer of the kidney refers to tumors arising from the renal parenchyma as well as to tumors in the renal pelvis and ureter. In several of the large prospective studies (Table 34), an association was found between cigarette smoking and cancer of the kidney. The mortality ratios for all cigarette smokers varied from 1.20 to almost 3, compared with nonsmokers. Four of the prospective studies have noted a dose-response relationship as measured by the number of cigarettes smoked per day for kidney cancer (68, 105, 224, 290). Data from these studies are presented in Table 35. Generally, heavy smokers have mortality ratios two to three times greater than nonsmokers. In the U.S. Veterans Study, Rogot and Murray observed a decline in kidney cancer mortality among ex-cigarette smokers with a mortality ratio of 1.21 versus 1.41 for continuing smokers. Thus, the strength of the association of cigarette smoking related to kidney cancer risk is less marked than that for cancer of the other sites discussed above.

Chemical elements such as lead and cadmium, hormones, ionizing radiation, genetic susceptibilities, as well as tobacco smoke have each been suggested as potential etiologic factors in this disease (322). Several studies (21, 32, 130, 214) have shown that a substance present in tobacco smoke, di-methylnitrosamine, causes kidney tumors in rats.

Temporal Relationship

The prospective studies provide support for the temporal relationship of the association.

Coherence of the Association

Dose-Response Relationship

The dose-response relationship noted in four of the prospective studies lends support to the coherence of the association between smoking and cancer of the kidney.

TABLE 34.—Kidney cancer mortality, ratios and relative risks, prospective and selected retrospective studies

Population	Study size	Number of kidney cancer deaths	Mortality ratio or relative risk ratio		Comments
			Non-smokers	Cigarette smokers	
Prospective Studies					

Prospective Studies

Population	Study size	Number of kidney cancer deaths	Non-smokers	Cigarette smokers	Comments
ACS 9-State Study	188,000 white males	54	1.00	1.58	Based on 54 microscopically proved cases
ACS 25-State Study	440,558 males	104	1.00	1.42 1.57	Age 45–64 Age 65–79
U. S. Veterans	290,000	257	1.00	1.41	
California males in 9 occupations	68,153 males	27	1.00	2.46	
Japanese Study	122,261 males	30	1.00	1.20	
British Physicians	34,000 males	46	1.00	2.66	All smokers

Retrospective Studies

Population	Study size	Number of kidney cancer deaths	Non-smokers	Cigarette smokers	Comments
Bennington Laubscher (20, 21)	renal adenocarcinoma 100 cases 190 controls	100	1.00	5.1	Risk ratio for pipe - 10.3 cigar - 12.9
Schmauz and Cole (238)	43 cases of renal pelvis or ureter 451 controls	18	1.00	10.0	For smokers of more than 2½ pks/day
Armstrong (5a)	106 adenocarcinoma of kidney	106	1.00	1.06	
	30 carcinoma of renal pelvis 139 controls	30	1.00	1.80	
Wynder et al. (322)	202 adenocarcinoma of kidney		1.00	2.00	(males)
	394 controls		1.00	1.50	(females)

Correlation of Sex Differences in Kidney Cancer With Different Smoking Habits

There has been an increase in the white male to female ratio of deaths from kidney cancer. This trend does not demonstrate an

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TABLE 35.—Kidney cancer mortality ratios by amount smoked per day—prospective studies

Amount per Day	Study/Ratio	Comments
	U.S. Veterans	
Nonsmoker	1.00	*Less than
1–9	0.95	20 deaths
10–19	1.32	
20–39	1.63	
40+	2.59*	
All smokers	1.41	
	British Physicians**	
Nonsmoker	1.00	**Grams of
1–14	2.66	tobacco
15–24	3.00	per day
25+	3.00	
All smokers	2.66	
	ACS 9-State Study***	
Nonsmokers	1.00	***Includes
1–9	1.90	genitourinary
10–20	1.8	
21+	2.94	
All smokers	1.90	
	California Males in Various Occupations	
Nonsmoker	1.00	
about 10	0.86	
about 20	3.30	
Over 30	2.57	
All smokers	2.46	

effect of the later initiation of smoking by females as evidenced so clearly by the recent increases in female lung and laryngeal cancer risks.

Correlation of Kidney Cancer Mortality Among Populations With Different Tobacco Consumption

The relative risk of kidney cancer is reduced in populations with a low proportion of smokers (79, 165, 166, 211, 294), although this reduction is not as great as that observed for lung, larynx, esophageal, and oral cancer.

Smoking and Histologic Changes in the Kidney

No human autopsy studies have been published which examine histologic changes in the kidney among smokers compared to nonsmokers.

Kidney Cancer and Non-Cigarette Tobacco Use

An elevated relative risk of from tenfold to twelvefold has been reported for smokers of pipes or cigars in one study (21). The U.S. Veterans Study noted an association for pure pipe smokers (ratio 1.32) and for mixed smokers of pipe and cigars (ratio 1.52) and kidney cancer, but not for pure cigar smokers.

Conclusion

Cigarette smoking is a contributory factory in the development of kidney cancer in the U.S. The term "contributory factor" by no means excludes the possibility of a causal role for smoking in cancers of this site.

Carcinoma of the Pancreas

Introduction

In 1982, it is estimated that there will be 24,800 new cases and 22,300 deaths from carcinoma of the pancreas in the United States (2).

Pancreatic cancer caused the deaths of 8,953 persons in 1950 and 20,465 persons in 1977 (the data for 1977 include deaths coded under ICD No. 157). The age-adjusted death rate rose from 5.3 per 100,000 in 1950 to a peak of 6.8 in 1968, and has remained stable since, at about 6.7. After 1968, the age-adjusted death rate from this disease actually decreased slightly from 6.8 to 6.7 per 100,000.

Increases in the age-adjusted rate between 1950 and 1967 resulted from increases in the mortality rates of all four color-sex groups (Figure 50), with white females showing the smallest increase and other than white males showing the largest. In 1950, white males and females had higher death rates from this disease than did males and females of other races. By 1977, the age-adjusted rate for whites was 22 percent lower than the rate for others.

The age-adjusted death rate of white males increased from 6.4 to 8.3 per 100,000 over the study period, and that of white females rose slowly from 4.3 to 5.2. Rates nearly doubled in the other populations, rising from 3.4 to 6.6 in females and from 5.3 to 10.5 in males.

Among white males 25 to 84 years of age, there was an increase in mortality from 1950 until 1967 (Figure 51). Thereafter, this trend was reversed, except in males 75 or older. Among other than white males, rates rose steadily during the 1950s and early 1960s and then leveled off or declined, except among those 55 or older, whose mortality rates continued to increase through 1977 (Figure 52). Both white and other females of most ages had increasingly higher mortality rates over the entire 1950–1977 period.

Generally, the mortality sex ratio decreased with advancing age in both the white and the other than white populations. The age-specific death rates over time show an increase in the older age

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RATES/100,000
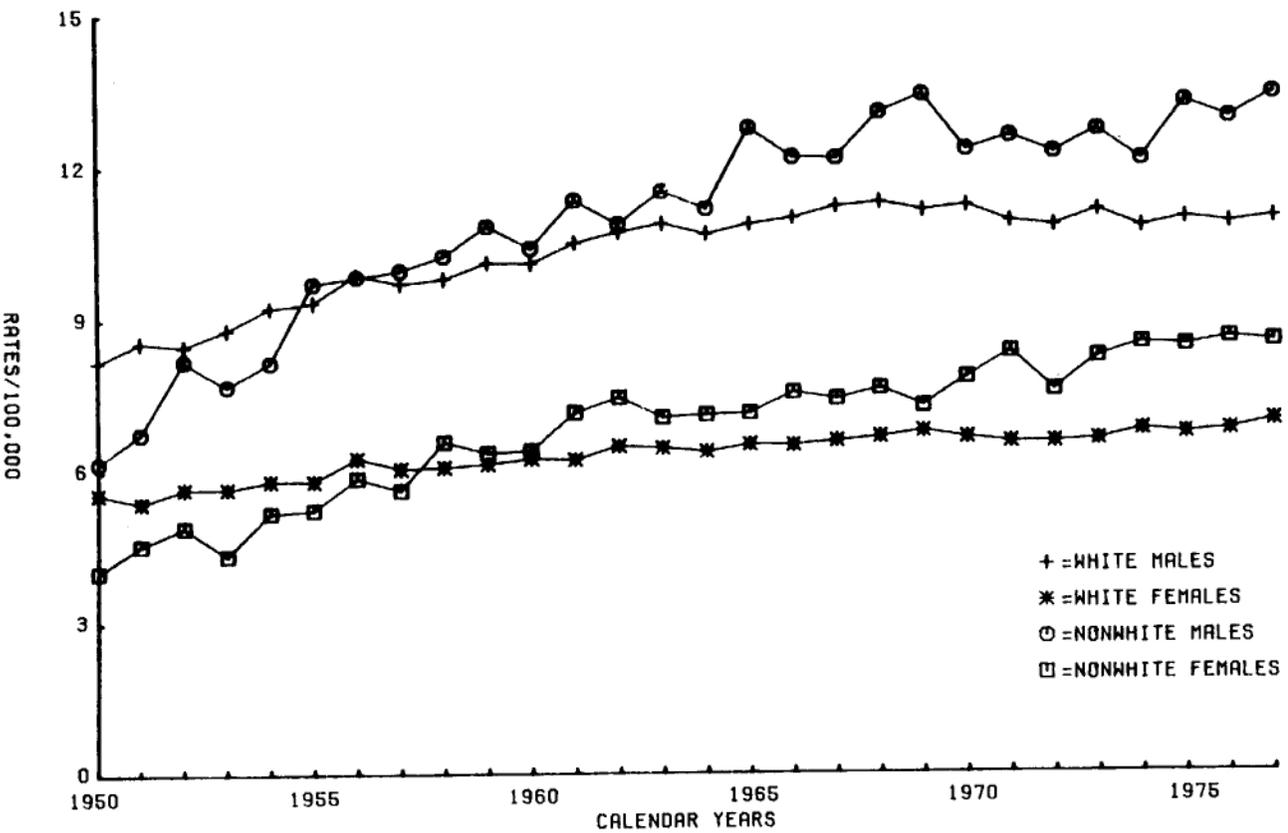
FIGURE 50.—Age-adjusted* mortality rates for cancer of the pancreas, by race and sex, United States, 1950–1977

+ =WHITE MALES
✳ =WHITE FEMALES
☉ =NONWHITE MALES
⊡ =NONWHITE FEMALES

CALENDAR YEARS

* 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).
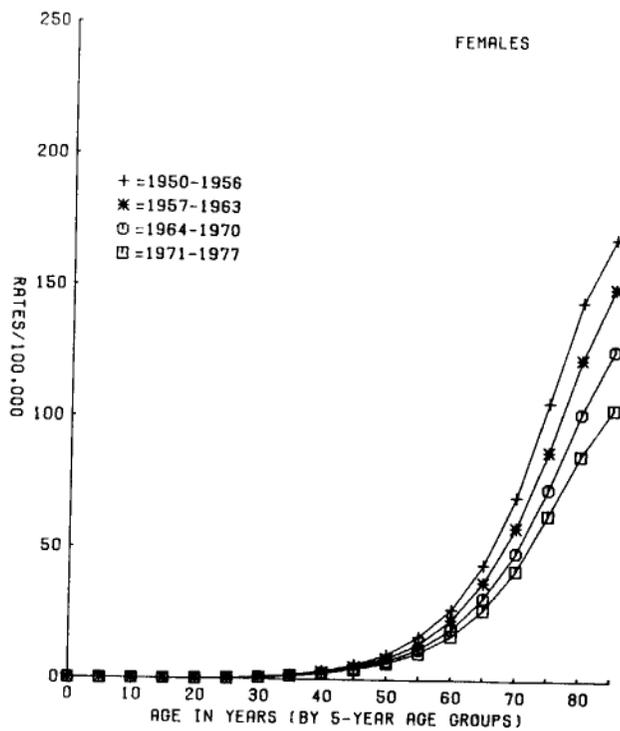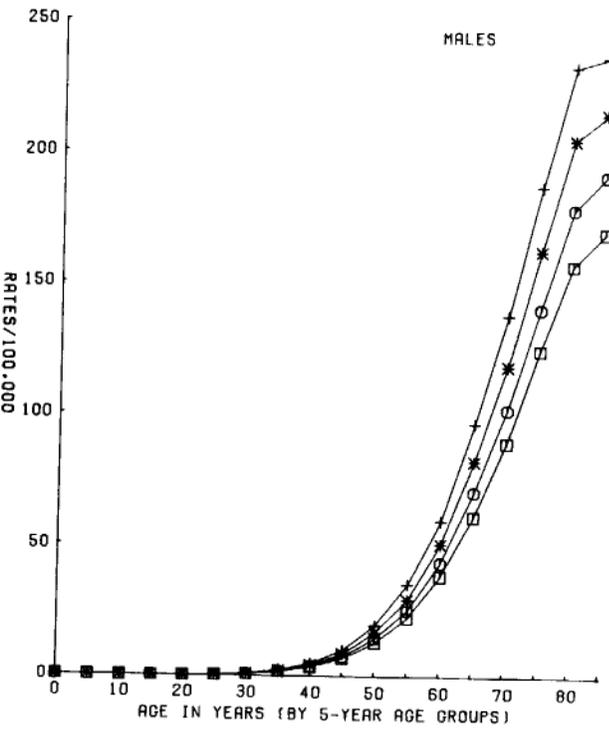
FIGURE 51.—Age-specific mortality rates for whites in the United States for cancer of the pancreas

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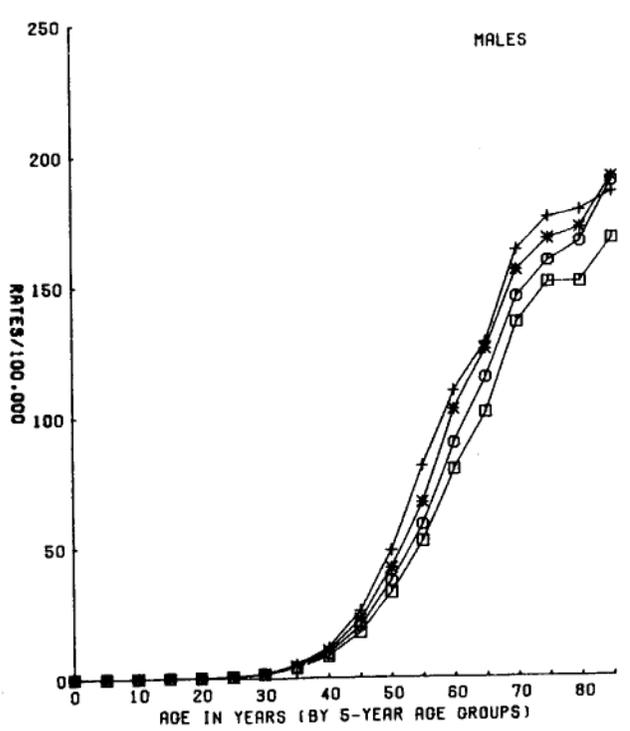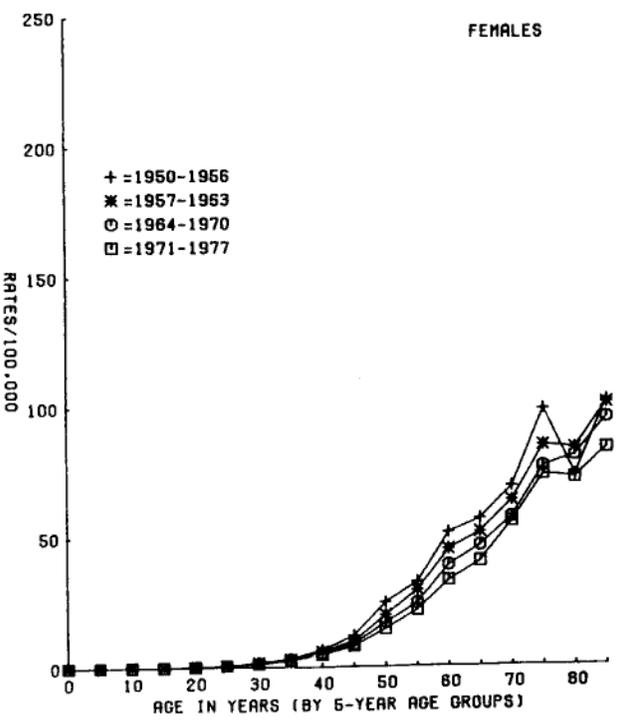
FIGURE 52.—Age-specific mortality rates for nonwhites in the United States for cancer of the pancreas

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