respectively. For those aged 65 or older, the corresponding estimated relative risks were 0.73, 0.54, and 0.29, respectively. These two studies suggest that the risk of lung cancer may decline less steeply with increasing abstinence for older ex-smokers.

Multistage Modeling

Multistage models provide a conceptual framework for facilitating understanding of the relationship of lung cancer incidence with amount smoked, duration of smoking, and time since cessation. These models, proposing theoretical constructs of fundamental biologic mechanisms, have been useful for evaluating epidemiologic data in a biologic framework and thereby furthering the understanding of tobacco carcinogenesis. However, fitting these models to epidemiologic data cannot establish the veracity of the underlying biologic theory. Multistage modeling approaches have been used to describe respiratory carcinogenesis and to assess smoking cessation and lung cancer risk. Although a number of different mathematic models of carcinogenesis have been proposed (e.g., two-stage, multicell, multistage), this discussion primarily addresses the Armitage and Doll (1954, 1957) multistage model, which has been used most extensively in studies of lung cancer.

Based on a series of studies examining age-specific mortality rates for various cancers, Armitage and Doll (1954, 1957) proposed a multistage theory of carcinogenesis. Their model assumes that a single cell can generate a malignant tumor only after undergoing a certain number of genetic changes. Animal studies also support the multistage model. Multistage theories also predict the age pattern of occurrence of many tumors induced in experimental animals by continuous exposure to chemical carcinogens. Experimental regimens involving initiation and promotion provide direct evidence of the effect of early- and late-stage events in the carcinogenic process (Stenback, Peto, Shubik 1981a,b,c).

Using data from the British Physicians Study, Doll (1971) showed that when the incidence of lung cancer in cigarette smokers was plotted against duration of smoking, incidence increased approximately in proportion to the fourth power of duration, similar to the slope of the regression line when incidence in never smokers is plotted against age (Figure 3). Thus, a first-stage effect was implicated because the excess lung cancer risk among smokers increased with the same power of duration of smoking as the risk with age among never smokers. Moreover, the lung cancer mortality rates among ex-smokers decreased somewhat initially and then increased slowly in keeping with the increase in risk among never smokers with age (Doll 1971). Armitage (1971) noted that the stabilization of excess lung cancer risk at the level when smoking stopped suggested that smoking also affected a late stage, namely, the penultimate stage in the carcinogenic process.

Day and Brown (1980) conducted a detailed analysis of the pattern of change in cancer risk after cessation of an exposure. The results supported the Armitage–Doll model. In addition, Day and Brown proposed that the stage affected by the agent and the relative magnitude of the effect of the agent on early and late stages of the carcinogenic process are critical in the determination of risk subsequent to cessation of an exposure. To quantify the magnitude of smoking effects on the two stages, Brown

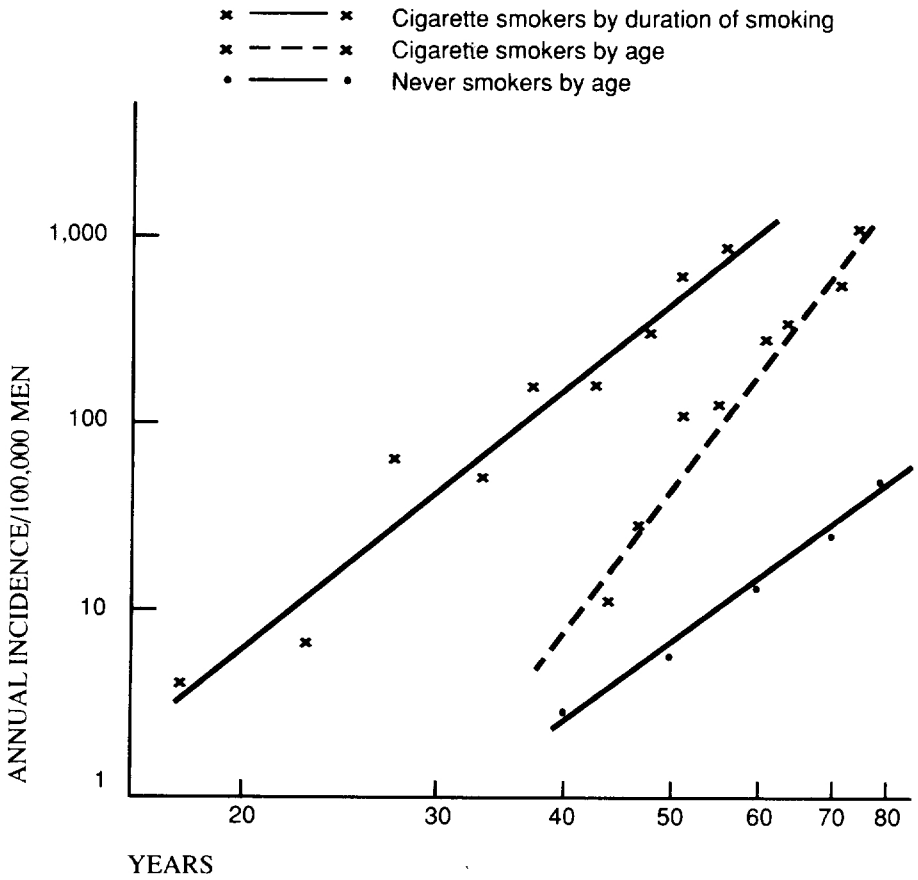

FIGURE 3.—Incidence of bronchial carcinoma among continuing cigarette smokers in relation to age and duration of smoking and among never smokers in relation to age, double logarithmic scale

SOURCE: Doll (1971), with correction of printing error in the original figure.

and Chu (1987) reexamined data on ex-smokers from the European case–control study of lung cancer (Lubin et al. 1984a) and concluded that smoking had an almost double relative effect on late-stage events compared with first-stage events. Using data from a case–control study in New Mexico, Whittemore (1988) developed a predictive model for lung cancer that showed a twofold stronger effect on late-stage than on early-stage events; the model overpredicted cases among ex-smokers and underpredicted cases among current smokers. Therefore, Whittemore suggested that smoking may have an even stronger effect on late-stage events than was assumed in the model.

Alternative models and interpretation of data on former smokers and lung cancer have also been suggested in several recent studies. Freedman and Navidi (1989) tested the

fit of the multistage model to data from ACS CPS-I and the U.S. Veterans Study. These researchers observed that crude rates of lung cancer decreased with increasing years of smoking abstinence although the trend was less steep when average amount of smoking and ages when smoking started and stopped were considered in the analysis. Moreover, the observed lung cancer rates among ex-smokers were compared with the expected rates, which were computed in three ways—risk at the time of quitting, risk at current age with excess risk frozen at the time of quitting, and never smokers of the same age. For each comparison approach, the ratio of observed to expected rates decreased with increasing years of smoking abstinence. Freedman and Navidi (1989) concluded that this pattern was incompatible with the multistage model, which predicts stabilization of excess risk when an individual stops smoking.

Gaffney and Altshuler (1988) reexamined data from the British Physicians Study and found that the best-fitting model among current smokers predicted an increase in the excess incidence among ex-smokers, which was inconsistent with the observed decreased rates. These researchers found that a two-stage model fit the incidence of lung cancer in both current smokers and ex-smokers. Gaffney and Altshuler (1988) then proposed a two-stage model with clonal growth in which cigarette smoke induced the initial transition and promoted clonal growth in these cells initiated by cigarette smoke. Moolgavkar, Dewanji, and Luebeck (1989) questioned the biologic plausibility of the proposal by Gaffney and Altshuler (1988) and noted that their model only fit part of the British physicians data set, did not consider each age–smoking level, and discounted the possibility that smoking affected two transition rates in the carcinogenic process.

Moolgavkar, Dewanji, and Luebeck (1989) reanalyzed the British Physicians Study within the framework of the two-mutation, recessive oncogenesis model. Based on this model, the second-mutation rate would be affected by smoking, and a sudden decline in risk after cessation of smoking would be predicted. However, this model implies that smoking affects the last stage in a multistage process, contrary to current considerations.

In summary, multistage models have been used to describe the interrelationships among number of cigarettes smoked daily, duration, time since exposure ended, and lung cancer incidence. Several investigators have interpreted the data on risk among former smokers in different ways. The epidemiologic data clearly indicate that the risk among former smokers is between that of continuing smokers and never smokers. Various models can be fit to the different data sets. The expected pattern of risk among former smokers is sensitive to the model selected and dependent on the relative magnitude of the effect of smoking on early versus late stages of the process of carcinogenesis. Using multistage models, the data on former smokers are insufficient to allow precise quantification of the relative effects of smoking on the early and late stages of the carcinogenic process, which smoking is assumed to affect. Nevertheless, data indicate that smoking has an effect on the late stages of the carcinogenic process and that cessation reduces lung cancer occurrence.

Cessation After Developing Disease

Individuals who stopped smoking are not a randomly selected group in most studies (Chapter 2). Often, smokers quit as a result of developing symptoms of a life-threatening disease or immediately after diagnosis of cancer. This phenomenon is evidenced by the increase in risk of lung cancer in the immediate period after cessation. Some studies have grouped these former smokers with the continuing smokers or have excluded them from the analysis.

A few epidemiologic studies have assessed the risk of lung cancer among those who quit for health reasons and for non-health-related reasons. In the U.S. Veterans Study, about 10 percent of the smokers quit because of a doctor's orders; these smokers were presumably ill. The lung cancer mortality ratio relative to never smokers for ex-smokers who stopped because of non-health-related reasons was 4.43 compared with 5.83 among ex-smokers who stopped on a doctor's orders and 8.98 among continuing smokers (Kahn 1966). In the European case–control study, Brown and Chu (1987) reported that the relative risk of lung cancer for those who stopped smoking because of health reasons compared with those who stopped for reasons other than health was 1.3 ($p<0.001$). Moreover, the percentage who stopped for health reasons decreased with increasing years of abstinence. Among those who had stopped for 1 year or less, 95.8 percent stopped because of health reasons compared with 65.7 percent of longer term ex-smokers. In ACS CPS-II, men and women who did not have a history of heart disease, stroke, or cancer at the time of interview showed a decreased risk of lung cancer in the first 2 years after smoking cessation when compared with continuing smokers. In contrast, the risks for all subjects combined (i.e., those with and without a history of previous chronic disease) were increased during the first 2 years after smoking cessation when compared with continuing smokers. The lower risks among the group with no history of previous disease compared with the total group persisted for subsequent periods of smoking abstinence (Table 7).

Cessation After Diagnosis of Lung Cancer

Two studies examined the relationship between smoking status and treatment outcome of patients with small cell lung cancer. In the study by Johnston-Early and associates (1980), survival was prolonged in patients who were ex-smokers or who had stopped smoking at diagnosis, whereas no difference in survival by smoking status was detected in the study by Bergman and Sorenson (1988).

The study by Johnston-Early and colleagues (1980) involved 112 patients with small cell lung cancer; 20 had stopped smoking before diagnosis; 35 had stopped at diagnosis; and 57 continued smoking. Therapies included chemotherapy with radiation therapy, with or without thymosin fraction V. The three patient groups were similar in disease extent, pretreatment performance status, pack-years smoked, and age and sex distribution. The patients who had stopped smoking prior to diagnosis had the best survival, followed by those who had stopped at diagnosis, and finally by those who continued smoking; the median survival for the three groups was 70, 52, and 47 weeks, respectively. Overall survival differences remained after individually adjusting for disease

TABLE 7.—Standard mortality ratios of lung cancer among former smokers in ACS-CPS II (relative to never smokers) by years of smoking abstinence, daily cigarette consumption at time of cessation, and history of chronic disease

	No history of chronic disease[a]		All respondents	
	1–20 cig/day	≥21 cig/day	1–20 cig/day	≥21 cig/day
Males				
Current smokers	23.5	31.5	18.8	26.9
Former smokers (yr since stopped)				
<1	16.8	23.4	26.7	50.7
1–2	16.7	25.3	22.4	33.2
3–5	19.7	20.5	16.5	20.9
6–10	8.6	14.2	8.7	15.0
11–15	6.3	13.6	6.0	12.6
≥16	3.3	5.3	3.1	5.5
	No history of chronic disease[a]		All respondents	
	1–19 cig/day	≥20 cig/day	1–19 cig/day	≥20 cig/day
Females				
Current smokers	10.5	24.1	7.3	16.3
Former smokers (yr since stopped)				
<1	3.4	21.1	7.9	34.3
1–2	9.0	18.2	9.1	19.5
3–5	2.5	13.2	2.9	14.6
6–10	1.1	12.0	1.0	9.1
11–15	1.1	2.9	1.5	5.9
≥16	1.6	2.4	1.4	2.6

[a]No history of cancer, heart disease, or stroke.

SOURCE: Unpublished tabulations, American Cancer Society.

extent, performance status, and type of protocol treatment. Similarly, statistical significance was maintained after simultaneous adjustment for both thymosin and radiation therapy.

The study by Bergman and Sorenson (1988) involved 154 small cell lung cancer patients who received combination chemotherapy. Thirty-two had stopped smoking at least 6 months before the initiation of treatment or had never smoked, 51 patients stopped smoking less than 6 months prior to the start of treatment, and 71 patients continued to smoke during the treatment period; the median survival was 39, 42, and 40 weeks, respectively. Reasons for differences in results between the two studies are not clear. Overall, patients in the study by Bergman and Sorenson (1988) had smoked fewer pack-years, but the median survival and performance status of each of the three

smoking status groups were poorer than for the comparable smoking status groups in the study by Johnston-Early and associates (1980).

LARYNGEAL CANCER

Pathophysiologic Framework

Smoking has been firmly established as a cause of laryngeal cancer (US DHHS 1982, 1989) based on numerous epidemiologic studies. These studies have employed diverse methodologies and have been performed in different countries and covered various time periods. Tobacco smoke exposure has been measured by number of cigarettes smoked per day, number of years of smoking, age when started to smoke, type of cigarettes smoked, and depth of inhalation (US DHHS 1982).

In the larynx, as in the bronchus, a sequence of histologic changes occurs with continued smoking. These changes progress from cells with atypical nuclei, to carcinoma in situ, to invasive carcinoma. Autopsy studies show that recovery of the laryngeal epithelium can follow smoking cessation. Auerbach, Hammond, and Garfinkel (1970) studied postmortem specimens of laryngeal epithelium from 942 men (644 current cigarette smokers, 94 cigar and/or pipe smokers, 116 ex-cigarette smokers, and 88 never smokers). Ex-smokers in this study had stopped smoking for at least 5 years. Compared with current smokers, ex-smokers showed fewer histologic changes; 75 percent of ex-smokers and never smokers showed no cells with atypical nuclei, whereas almost all current smokers showed some cells with atypical nuclei.

Similar findings were reported by Muller and Krohn (1980), who obtained laryngeal epithelial specimens from autopsy. Of the 148 cases in the study, 24 were never smokers and 24 were ex-smokers who had stopped smoking for at least 5 years. Table 8 shows the relative distribution of selected histologic features by smoking status. Occurrence of all histologic changes was lowest among never smokers, intermediate among ex-smokers, and highest among current smokers. However, the histologic findings of ex-smokers in this study were more similar to those of light current smokers (<10 cig/day) than to those of never smokers.

Smoking Cessation and Laryngeal Cancer Risk

A few studies provide data on the relationship between smoking cessation and risk of laryngeal cancer (Table 8). Former smokers are at less risk than current smokers, but have about six times the risk of never smokers. The relative risk of laryngeal cancer is higher immediately after smoking cessation (i.e., 1–3 years after quitting) compared with continuing smokers. However, after approximately 3 to 4 years of smoking abstinence, former smokers show lower relative risks with increasing years of smoking abstinence (Table 8). Based on a case–control study of laryngeal and hypopharyngeal cancer conducted in Europe, Tuyns and colleagues (1988) suggested that the benefit of smoking cessation seemed to appear sooner after cessation for cancer of the hypopharynx/epilarynx than for the larynx.

TABLE 8.—Histologic changes in laryngeal epithelium by smoking status

Smoking status	Histologic change (% relative frequencies)			
	Normal squamous epithelium	Keratinizing squamous epithelium	Hyperplastic squamous epithelium	Squamous metaplasia
Never smokers	83	4	8	21
Ex-smokers	54	33	29	33
Current smokers				
Light	56	25	12	58
Moderate	46	36	26	46
Heavy	31	44	33	52

SOURCE: Abstracted from text and figures 2–5 in Muller and Krohn (1980).

Risk reduction pattern by years of smoking abstinence and number of cigarettes smoked daily was examined in a few studies (Table 9). In the U.S. Veterans Study, the risk of death from laryngeal cancer was lower among ex-smokers who smoked 10 to 20 or 21 to 39 cigarettes per day than among current smokers, but it was not lower among those smoking 1 to 9 or 40 cigarettes or more per day. However, there were very few laryngeal cancer deaths in the lowest and highest consumption levels (two and one, respectively) (Kahn 1966). In ACS CPS-II, ex-smokers who smoked less than 21 cigarettes per day showed a greater reduction in laryngeal cancer mortality for all durations of smoking abstinence compared with ex-smokers who smoked 21 cigarettes or more per day relative to current smokers. In a case–control study conducted in the Texas Gulf Coast region (Falk et al. 1989), there was no consistent pattern of greater proportion of reduction in risk among those who had smoked fewer cigarettes per day prior to smoking abstinence. Moreover, there was still a threefold increased risk among those who had smoked more than 30 cigarettes daily after 10 years of smoking abstinence (Table 9).

The effect of smoking duration prior to smoking cessation was not considered in the studies mentioned above. There is some indication that the average age at which the ex-smoker developed clinical laryngeal cancer was about 10 years older (68.7) than that of the current smoker (Wynder et al. 1976).

Alcohol has been shown to have an independent effect on risk of laryngeal cancer, but the relationship is weaker than the one between smoking and laryngeal cancer. The relative risks for joint exposure to alcohol and tobacco are consistent with a multiplicative interaction of the two agents (Flanders and Rothman 1982; Elwood et al. 1984; Olsen, Sabroe, Fasting 1985). In this review of the literature, no studies were found that accounted for the effects of alcohol intake in examining risk of laryngeal cancer after smoking cessation.

TABLE 9.—Relative risks of laryngeal cancer by smoking status

Reference	Population	Smoking status	Relative risks				
Kahn (1966)	US veterans	Never smokers	1.0				
		Current smokers	9.5				
		Former smokers	7.2				
Wigle, Mao, Grace (1980)	Alberta, Canada, cancer patients	Never smokers	1.0				
		Current smokers	7.8				
		Former smokers	6.3				
ACS (unpublished tabulations)	ACS CPS-II		Males	Females			
		Never smokers	1.0	1.0			
		Current smokers	12.8	9.5			
		Former smokers	6.7	6.5			
Falk et al. (1989)	Texas	Never smokers	1.0				
		Current smokers	9.0				
		Former smokers	3.2				
			Cig/day				
		(yr since stopped)[a]	1–10	11–20	21–30	31–40	>40
		3–9	3.0	3.6	4.0	7.2	0.9
		≥10	2.8	1.2	1.0	3.1	3.5

TABLE 9.—Continued

Reference	Population	Smoking status	Relative risks	
Wynder and Stellman (1977)	6 US cities	Former smokers (yr since stopped)	Males	Females
		1–3	17.9	6.9
		4–6	8.5	2.6
		7–10	4.0	—
		11–15	3.4	8.8
		≥16	2.5	—
		Current smokers	14.3	11.6
		Never smokers	1.0	1.0
Tuyns et al. (1988)	European countries	Former smokers (yr since stopped)	Males	
			Endolarynx	Hypopharynx
		1–4	1.51	1.09
		5–9	0.52	0.28
		≥10	0.28	0.32
		Current smokers	1.0	1.0

NOTE: ACS CPS II=American Cancer Society Cancer Prevention Study II.

[a]Reference category is never smokers.

CONCLUSIONS

1. Smoking cessation reduces the risk of lung cancer compared with continued smoking. For example, after 10 years of abstinence, the risk of lung cancer is about 30 to 50 percent of the risk for continuing smokers; with further abstinence, the risk continues to decline.

2. The reduced risk of lung cancer among former smokers is observed in males and females, in smokers of filter and nonfilter cigarettes, and for all histologic types of lung cancer.

3. Smoking cessation lowers the risk of laryngeal cancer compared with continued smoking.

4. Smoking cessation reduces the severity and extent of premalignant histologic changes in the epithelium of the larynx and lung.

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CHAPTER 5
SMOKING CESSATION AND NONRESPIRATORY CANCERS

CONTENTS

INTRODUCTION

Lung cancer, the first neoplasm causally linked to cigarette smoking, has been the cancer most thoroughly studied with respect to exposure–response relationships and benefits of cessation (US DHHS 1982). Subsequently, cigarette smoking has been established as a cause of cancer at diverse other sites. For some sites (e.g., oral cavity), the target cells are exposed directly to the various constituents of tobacco smoke. For other sites (e.g., urinary bladder), absorption, transport, and metabolic activation of carcinogens in tobacco smoke result in exposure of target tissues. This Chapter reviews the evidence on smoking cessation and cancer risk at various nonrespiratory sites. The sites selected for review are those for which cigarette smoking has been determined to be a cause of cancer, or contributing cause, or those for which evidence indicates a possible association.

Methodologic issues encountered in inferring causality on the effects of smoking cessation have been discussed in Chapter 2 and will not be reviewed in detail in this Chapter. Potential confounding by differences in prior tobacco exposure at the time of quitting, and by differences between former smokers and continuing smokers in other cancer-related risk factors may pose a greater obstacle to causal inference for the nonrespiratory cancers than for cancers of the lung or larynx; the smoking effects are generally smaller for nonrespiratory cancers, and the potential confounding factors are more numerous.

REVIEW OF SPECIFIC SITES

Oral Cancer

Tobacco use is a major cause of oral cancer (US PHS 1964; US DHHS 1982, 1989). An exposure–response relationship has been identified between the amount of tobacco consumed and the risk of cancer of the oral cavity after considering the effects of alcohol consumption. The proportion of 1985 oral cancer deaths attributable to cigarette smoking in the United States has been estimated to be 92 percent for men and 61 percent for women (US DHHS 1989). The oral cavity, like the lung, receives direct exposure to cigarette smoke. Presumably, the causal association of cigarette smoking with cancer of the oral cavity reflects this contact and the same initiating and promoting agents that are considered to determine the development of lung cancer.

Table 1 summarizes studies that have examined the relationship between smoking cessation and oral cancer risk. In these studies, the risk of oral cancer among current smokers ranges from 2.0 to 18.1 times (median of approximately 4) the risk among never smokers. Oral cancer risks for women who are currently smoking seem lower than those for men in studies conducted prior to the mid-1970s, but little difference by gender has been noted in more recent research. This gender pattern may be because of the initiation of smoking at an older age among earlier birth cohorts of women (US DHHS 1989) born during this century and the resultant low cumulative lifetime exposure of such women.

TABLE 1.—Studies of oral cancer and smoking cessation

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
Kahn (1966)	U.S veterans (1954–62)	Prospective (248,195)	Male	3.8	1.9	NP	Excludes "doctor's orders" quitters Cancer mortality
Cederlot et al. (1975)	Sweden (1963–72)	Prospective					
		(27,300)	Male	2.7	0.8	NP	Cancer incidence
		(27,700)	Female	2.0	0	NP	
Wynder and Stellman (1977)	6 US cities (1969–75)	Case:control	Male	8.9	9.0	1–3	
		(497:6,534)			3.5	4–6	
					3.2	7–10	
					3.4	11–15	
					1.6	≥16	
		(270:6,522)	Female	4.4	3.8	1–3	
					2.2	4–6	
					1.4	7–10	
					0.6	11–15	
					0.8	≥16	
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (293,958)	Male	4.2	1.7	NP	Excludes "doctor's orders" quitters Cancer mortality Extension of US Veterans Study

TABLE 1.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers: Current smokers	Risk relative to never smokers: Former smokers	Yr since quitting	Comments
Wigle, Mao, Grace (1980)	Alberta, Canada (1971–73)	Case:control (84:1,002)	Male	8.7	3.5	NP	
		(41:674)	Female	4.3	0.8	NP	
Spitz et al. (1988)	Houston, TX (1985–87)	Case:control (121:127)	Male	4.5[a]	6.1	<5	
					2.2	5–14	
					1.0	≥15	
		(50:49)	Female	5.5[a]	9.8	<5	
					4.5	5–14	
					1.5	≥15	
Blot et al. (1988)	4 areas in United States (1984–85)	Case:control (762:837)	Male	3.4	1.1	1–9	Adjusted for alcohol consumption
					1.1	10–19	
					0.7	≥20	
		(352:431)	Female	4.7	1.8	1–9	
					0.8	10–19	
					0.4	≥20	
Franco et al. (1989)	Brazil (1986–88)	Case:control (232:464)	Male and female	9.3	2.9	<10	Data for commercially produced cigarettes only
					0.6	≥10	

TABLE 1.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers: Current smokers	Risk relative to never smokers: Former smokers	Yr since quitting	Comments
Kabat and Wynder (1989)	18 US cities (1976–83)	Case:control (511:1,057)	Male	5.5[a]	2.1	≥1	Adjusted for alcohol
		(226:453)	Female	4.1[a]	1.5	≥1	
Kabat, Hebert, Wynder (1989)	7 US cities (1983–87)	Case:control (125:107)	Female	2.0	1.0	NP	Adjusted for alcohol and previous number of cig/day
ACS CPS-II (unpublished tabulations)	United States (1982–86)	Prospective (421,623)	Male	18.1	6.4	NP	Cancer mortality
		(605,758)	Female	5.8	2.5		

NOTE: NP=not provided; ACS CPS-II=American Cancer Society Cancer Prevention Study II.

[a]Computed as a weighted average from cigarette dose-specific relative risks presented in the paper. Weights are the number of controls within each stratum of smoking.