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CHAPTER 4
SMOKING CESSATION AND RESPIRATORY CANCERS

CONTENTS

LUNG CANCER

Epidemiologic studies have provided overwhelming evidence for a causal association of cigarette smoking with lung cancer (US PHS 1964; US DHEW 1979; US DHHS 1989). The plausibility of this association is supported by the presence of numerous carcinogens in tobacco smoke. Compared with the risk among never smokers, the risk of lung cancer for smokers may be increased twentyfold or more for heavy smokers (US DHHS 1989). Risk of lung cancer increases with the number of cigarettes smoked daily and the duration of cigarette smoking; risk declines after cessation (US DHHS 1982, 1989). For example, in an analysis of data from the British Physicians Study, Doll and Peto (1978) indicated that among subjects who persisted in smoking, lung cancer incidence increased with the fourth or fifth power of the duration of smoking and with approximately the square of daily cigarette consumption. In 1985, estimated attributable risks of lung cancer from cigarette smoking were 90 percent for males and 79 percent for females in the United States (US DHHS 1989).

This Section considers the effects of cigarette smoking on the epithelium of the airways of the lungs, the site from which most lung cancers stem, and the evolution of the smoking-related changes after cessation. The epidemiologic evidence on lung cancer risk after smoking cessation is comprehensively reviewed; the change in risk over time following cessation is described; and factors modifying the effect of cessation are considered. The Section includes discussion of the application of multistage modeling to data on smoking cessation.

Pathophysiologic Framework

Previous Surgeon General's reports have provided extensive reviews on carcinogenic components of tobacco smoke and on experimental carcinogenesis with tobacco smoke (US DHEW 1979; US DHHS 1982, 1986). Tobacco smoke contains numerous carcinogenic agents with both initiating and promoting activity. Although the specific mechanisms of respiratory tract carcinogenesis by tobacco smoke are not yet fully characterized, the plausibility of the smoking–lung cancer relation has been considered to be well supported by the available information (US PHS 1964; US DHHS 1982).

Carcinogenesis in the respiratory tract is widely considered to be a multistep process involving sequential changes in a cell from the normal to the malignant state. Extensive experimental and human evidence is consistent with the multistage hypothesis, and application of the new molecular and cellular biology techniques to the study of lung cancer is providing further insights into the genetic mechanisms underlying the development of this disease (Birrer and Minna 1988). Experiments with animals have shown that agents may initiate or promote cancer. In animal experiments involving a sequence of exposures to agents, those agents that cause cancer when administered initially are referred to as initiators, whereas agents that promote the growth of initiated cells are referred to as promoters.

Diverse multistep models of carcinogenesis have been developed (Farber 1984). The age–incidence patterns for epithelial cancers such as lung cancer, which show that the rates usually increase as a power of age, are also consistent with a multistage process

(Doll 1971; Doll and Peto 1978; Peto 1984; Day 1984). The bronchial epithelia of sustained smokers show a progression of abnormality (Saccomanno et al. 1974). The pseudostratified, ciliated epithelium becomes metaplastic and then dysplastic. Carcinoma in situ may develop and eventually become invasive (McDowell, Harris, Trump 1982). To the extent that cigarette smoking affects late as well as early stages in this process, smoking cessation would be expected to have beneficial consequences on lung cancer incidence. The epidemiologic evidence provides strong support for the anticipated benefits of smoking cessation.

Cigarette smoking is associated with changes in the large and small airways, in the respiratory epithelium and parenchyma, and in the numbers, type, and functional capacities of inflammatory cells. The reversibility of these changes after smoking cessation is germane to respiratory carcinogenesis and to the health consequences of smoking cessation. This Section focuses on studies that have examined the effect of smoking on the respiratory epithelium and on the cells in the lungs of current, former, and never smokers. Additional relevant information is reviewed in Chapter 7 and in previous reports of the Surgeon General (US DHHS 1984, 1986).

Smoking and Histopathology of the Airways

Extensive histopathologic evidence is available on the effects of smoking on the airways of the lung. The association between smoking and premalignant changes in the bronchial epithelium has been addressed by many investigators (US DHHS 1982). Based on sequential examinations of exfoliative cytologic specimens from uranium miners over a period of many years, Saccomanno and colleagues (1974) reported evidence of squamous metaplasia progressing through increasing atypia to carcinoma in situ and invasive bronchogenic carcinoma. Detailed observations have been made on the histopathology of lung specimens obtained at autopsy (Auerbach et al. 1957, 1962a,b, 1963, 1964, 1972; Auerbach, Garfinkel, Hammond 1974).

In 1962, Auerbach and coworkers (1962a) reported that the frequency and intensity of epithelial changes increased with the number of cigarettes smoked daily. In addition, these investigators assessed changes following smoking cessation in postmortem bronchial epithelial specimens from 72 ex-smokers and controls matched individually with 2 controls per case (Auerbach et al. 1962b). One control was a current smoker matched with an ex-smoker on age, occupation, residence, and smoking history. The second control was a lifetime nonsmoker also matched with an ex-smoker on age, occupation, and residence. Some type of epithelial abnormality was found in 98 percent of histologic sections from current smokers, 67 percent from ex-smokers, but only 26 percent from never smokers. This pattern persisted for many specific types of epithelial abnormalities including absence of ciliated cells, presence of atypical cells, and presence of hyperplasia and goblet cells in glands (Table 1). The occurrence of unciliated atypical cells, the most severe change before invasive carcinoma, was similar among ex-smokers and never smokers but was considerably greater among current smokers. The number of cells with atypical nuclei was reported to decrease with increasing number of years since smoking cessation. When current smokers were matched with former smokers of the same age at time of cessation, former smokers

TABLE 1.—Histologic changes (%) in bronchial epithelium by smoking status

	Smoking status		
	Current smokers	Ex-smokers	Never smokers
Sections with 1 or more epithelial lesions	97.8	66.6	25.7
Cilia present on 3 or more cell rows	92.7	57.3	12.1
Cilia absent	20.5	15.1	14.8
Atypical cells present	93.2	6.0	1.2
Unciliated atypical cells	19.0	0.9	0.1

SOURCE: Auerbach et al. (1962b).

showed fewer lesions, suggesting that the number of lesions decreased rather than merely failed to increase after cessation of smoking.

Auerbach and colleagues (1964) also reported that among cigarette smokers, there was a high degree of association between all types of histologic changes in the bronchi and in the lung parenchyma. However, the lungs of ex-smokers were more similar to those of never smokers than to those of current smokers with respect to cells with atypical nuclei. In this study of 46 ex-smokers, 32 had few atypical cells in their bronchial epithelium. Auerbach and associates (1964) suggested that with cessation of smoking, cells with atypical nuclei gradually disappeared from the bronchial epithelium and were replaced with normal cells.

Other Changes

Several reports have described levels of DNA adducts formed by the combination of chemical carcinogens or their metabolites with DNA in the tissues of never, former, and current smokers. Decline of DNA adduct levels in human lungs after smoking cessation has been reported by Phillips and coworkers (1988). These investigators utilized autoradiographs of chromatograms of ^{32}P-postlabeled digests of DNA from lungs of current, former, and never smokers. A linear relationship was observed between number of cigarettes smoked per day and DNA adduct levels (Pearson correlation coefficient, $r=0.72$, $p<0.001$). In addition, ex-smokers who had quit smoking 1 to 3 months previously had adduct levels typical of the current smokers (12–14 adducts/10^8 nucleotides), whereas those who had not smoked for 5 years or more had adduct levels similar to those of never smokers (1.7–4.9 adducts/10^8 nucleotides). These investigators suggested that the reduced risk of lung cancer among ex-smokers may be due to loss of the promutagenic lesions that initiate the process, in addition to late-stage effects.

Randerath and colleagues (1989) also used a ^{32}P-postlabeling assay to study DNA damage in relation to cigarette smoking. Adduct profiles and levels were determined in nontumorous surgical specimens taken from patients with lung or laryngeal cancer.

Characteristic profiles were found in the laryngeal and lung tissues; levels of adducts tended to increase with the amount of cumulative smoking. The study included only three long-term former smokers with duration of abstinence ranging from 10 to 14 years. These subjects had low levels of adducts compared with current smokers.

Smoking Cessation and Lung Cancer Risk

Pattern of Changing Risk After Cessation

Numerous cohort and case–control studies have documented a reduction in the relative risk of lung cancer among former smokers compared with current smokers. The findings of selected studies are presented in Table 2. Former smokers in these studies experienced a 10- to 800-percent increase in risk of lung cancer compared with never smokers; however, compared with current smokers, former smokers showed a 20- to 90-percent reduction in risk.

The relative risk estimates provided in Table 2 group former smokers with varying durations of abstinence from smoking. However, the number of years since cessation has a strong effect on risk of lung cancer among former smokers; in studies assessing risk by duration of abstinence, the reduced risk has been evident within 5 years of cessation compared with continued smoking, and the benefit of cessation has increased as the duration of abstinence lengthened. However, in most of the studies, the risk of lung cancer among former smokers remained elevated above the risk among never smokers, even in the longest periods of abstinence evaluated. In many studies, risks among former smokers were higher than among continuing smokers during the first few years after stopping smoking. This pattern of risk reflects cessation by individuals who quit smoking because of symptoms and illness before the clinical diagnosis of lung cancer (Chapter 2; Haenszel, Loveland, Sirken 1962; Doll and Hill 1964; Kahn 1966).

Table 3 summarizes standardized mortality ratios of lung cancer among former smokers by years of abstinence, as reported in five cohort studies: British physicians, U.S. veterans, Japanese males, and the American Cancer Society Cancer Prevention Studies, ACS CPS-I and ACS CPS-II. These studies varied in the length of followup, the extent of information obtained on smoking history, and the number of lung cancer cases. Compared with never smokers, former smokers who had been abstinent for 10 to 20 years or more showed a varying extent of risk reduction among the studies. In the British Physicians Study, U.S. Veterans Study, and ACS CPS-II, former smokers who had been abstinent for 15 years or more showed an 80- to 90-percent reduction in risk compared with current smokers. The percentage reduction in risk was slightly lower among the Japanese cohort and higher in ACS CPS-I.

Results from selected case–control studies are shown in Table 4. As in the cohort studies, former smokers who had been abstinent the longest experienced increased risk compared with never smokers, but substantially reduced risk in most studies compared with current smokers.

Thus, reduction in risk of lung cancer after smoking cessation has been observed in numerous cohort and case–control studies conducted in the United Kingdom (Doll and Peto 1976; Alderson, Lee, Wang 1985), the United States (Kahn 1966; Hammond 1966;

TABLE 2.—Relative risks of lung cancer among never, former, and current smokers in selected epidemiologic studies

Reference	Population	Subgroup	Smoking status				
			Never smokers	Former smokers		Current smokers	
				1–19 cig/day	≥20 cig/day	1–19 cig/day	≥20 cig/day
Hammond (1966)	ACS CPS-I		1.0	2.0	7.9	6.5	13.7
Kahn (1966)	US veterans		1.0	4.7		10.9	
Canadian Department of National Health and Welfare (1966)	Canadian males		1.0	6.1		14.9	
Cederlof et al. (1975)		Males	1.0	6.1		7.8	
		Females	1.0	1.5		4.5	
Doll and Peto (1976)	British male physicians		1.0	4.3		10.4	
Doll et al. (1980)	British female physicians		1.0	3.3		6.4[a]	
Wigle, Mao, Grace (1980)	Alberta (Canada) cancer patients	Males	1.0	6.5		10.4	
		Females	1.0	2.1		5.2	
Wu et al. (1985)	Los Angeles (CA) whites	Squamous	1.0	7.7		35.3	
		Adenocarcinoma	1.0	1.2		4.1	
Carstensen, Pershagen, Eklund (1987)	Swedish males		1.0	1.1		7.5[b]	
ACS (unpublished tabulations)	ACS CPS-II	Males	1.0	8.9		21.3	
		Females	1.0	4.8		12.1	

NOTE: ACS CPS-I and II=American Cancer Society Cancer Prevention Studies I and II.
[a]15–24 cig/day.
[b]8–15 cig/day.

TABLE 3.—Lung cancer mortality ratios among never, current, and former smokers by number of years since stopped smoking (relative to never smokers), prospective studies

Reference	Population	Smoking status and yr since stopped smoking	Mortality ratios (N)[a]	Comments
Doll and Peto (1976)	British male physicians	Never smokers	1.0 (7)	1951–71, 20-yr followup; data on former smokers in summary form
		Current smokers	15.8 (123)	
		Former smokers		
		1–4	16.0 (15)	
		5–9	5.9 (12)	
		10–14	5.3 (9)	
		≥15	2.0 (7)	
Rogot and Murray (1980)	US veterans[b]	Current smokers	11.3 (2,609)	1954–69, 16-yr followup
		Former smokers		
		1–4	18.8 (47)	
		5–9	7.7 (86)	
		10–14	4.7 (100)	
		15–19	4.8 (115)	
		≥20	2.1 (123)	
US DHHS (1982)	Japanese males	Current smokers	3.8	
		Former smokers		
		1–4	4.7	
		5–9	2.5	
		≥10	1.4	

TABLE 3.—Continued

Reference	Population	Smoking status and yr since stopped smoking	Mortality ratios (N)[a]		Comments
Hammond (1966)	ACS CPS-I males		1–19 cig/day	≥20 cig/day	1959–63, 3.5-yr followup, men aged 50–69
		Never smokers	1.0 (32)	1.0 (32)	
		Current smokers	6.5 (80)	13.7 (351)	
		Former smokers			
		<1	7.2 (3)	29.1 (33)	
		1–4	4.6 (5)	12.0 (33)	
		5–9	1.0 (1)	7.2 (22)	
		≥10	0.4 (1)	1.1 (5)	
ACS (unpublished tabulations)	ACS CPS-II males		1–20 cig/day	≥21 cig/day	
		Never smokers	1.0 (81)	1.0 (81)	
		Current smokers	18.8 (608)	26.9 (551)	
		Former smokers			
		<1	26.7 (33)	50.7 (64)	
		1–2	22.4 (71)	33.2 (117)	
		3–5	16.5 (82)	20.9 (96)	
		6–10	8.7 (80)	15.0 (106)	
		11–15	6.0 (69)	12.6 (95)	
		≥16	3.1 (144)	5.5 (112)	

TABLE 3.—Continued

Reference	Population	Smoking status and yr since stopped smoking	Mortality ratios (N)[a]		Comments
			1–19 cig/day	≥20 cig/day	
ACS (unpublished tabulations)	ACS CPS-II females				
		Never smokers	1.0 (181)	1.0 (181)	
		Current smokers	7.3 (145)	16.3 (434)	
		Former smokers			
		<1	7.9 (5)	34.3 (31)	
		1–2	9.1 (13)	19.5 (42)	
		3–5	2.9 (7)	14.6 (42)	
		6–10	1.0 (4)	9.1 (32)	
		11–15	1.5 (6)	5.9 (20)	
		≥16	1.4 (23)	2.6 (18)	

NOTE: ACS CPS-I and II=American Cancer Society Cancer Prevention Studies I and II.

[a]Number of observations.

[b]Includes data only for ex-cigarette smokers who stopped for reasons other than physician's order.

TABLE 4.—Relative risks of lung cancer among former smokers, by number of years since stopped smoking, and current smokers, from selected case–control studies

Reference	Population	Definition of former smoker	Smoking status and yr since stopped	Results		Adjustment[a]
Graham and Levin (1971)	New York	At hospital admission		Males		Crude
			Never smokers	1.0		
			Current smokers	8.8		
			Former smokers			
			0–0.5	42.2		
			>0.5–1	23.3		
			>1–3	10.0		
			>3–10	3.3		
			>10	1.3		
Wigle, Mao, Grace (1980)	Alberta, Canada, cancer patients	At interview		Males	Females	Age and cumulative smoking
			Never smokers	0.1	0.2	
			Current smokers	1.0	1.0	
			Former smokers			
			<2	2.4	0.9	
			2–9	0.7	0.5	
			10–14	0.7	0.5	
			≥15	0.2	0.4	
Correa et al. (1984)	Louisiana	NR		Males and females		Sex and age
			Never smokers	1.0		
			Current smokers	12.6		
			Former smokers			
			3–5	7.7		
			6–20	7.0		
			>20	3.9		

TABLE 4.—Continued

Reference	Population	Definition of former smoker	Smoking status and yr since stopped	Results		Adjustment[a]
Alderson, Lee, Wang (1985)	United Kingdom	At hospital admission		Males	Females	Age
			Never smokers	0.1	0.2	
			Current smokers	1.0	1.0	
			Former smokers			
			1–3	1.8	2.1	
			5–10	0.4	0.7	
			>10	0.3	0.3	
Gao et al. (1988)	Shanghai	NR		Males	Females	Age and education
			Never smokers	1.0	1.0	
			Current smokers	3.9	2.9	
			Former smokers			
			1–4	6.9	7.2	
			5–9	3.1	3.9	
			≥10	1.1	2.2	
Higgins, Mahan, Wynder (1988)	6 US cities	At least 1 yr at time of interview		Males		
			Never smokers	1.0		
			Former smokers			
			<10	11.9		
			10–19	6.1		
			20–29	3.7		
			≥30	1.9		
Joly, Lubin, Caraballoso (1983)	Cuba	NR		Males	Females	Duration of smoking
			Current smokers	1.0	1.0	
			Former smokers			
			1–4	1.2	2.0	
			≥5	0.6	0.9	

TABLE 4.—Continued

Reference	Population	Definition of former smoker	Smoking status and yr since stopped	Results		Adjustment[a]
Lubin et al. (1984a)	European case–control study	At interview		Males	Females	Duration of smoking
			Current smokers	1.0	1.0	
			Former smokers			
			1–4	1.1	0.9	
			5–9	0.7	0.7	
			10–14	0.6	0.4	
			15–19	0.4	0.5	
			20–24	0.4	0.5	
			≥25	0.3	0.3	
Pathak et al. (1986)	New Mexico	At least 1 yr before interview		Males		Number of cig/day
				≤65	>65	
			Current smokers	1.0	1.0	
			Former smokers			
			5	0.5	0.7	
			10	0.2	0.5	
			20	0.1	0.3	
Damber and Larsson (1986)	Sweden[b]	NR		Males		Age
			Current smokers	9.5		
			Former smokers			
			1–5	7.5		
			6–10	3.0		
			>10	2.0		

NOTE: NR=not reported.
[a]Factors adjusted for in analysis by yr of smoking abstinence.
[b]Estimated from figure 4 of reference.

Graham and Levin 1971; Pathak et al. 1986), Canada (Wigle, Mao, Grace 1980), Europe (Lubin et al. 1984a; Damber and Larsson 1986), Asia (US DHHS 1982; Gao et al. 1988), and Latin America (Joly, Lubin, Caraballoso 1983). Although only a few studies had information on female former smokers, the pattern of risk reduction was similar to that observed for males. Decrease in risk after smoking cessation also has been reported for each of the major histologic types of lung cancer (Wynder and Stellman 1977; Lubin and Blot 1984; Benhamou et al. 1985; Higgins and Wynder 1988) (Table 5 and Figure 1). Higgins and Wynder (1988) found that the decline in risk after cessation was more consistent for Kreyberg I tumors (primarily squamous cell, small cell, and large cell cancers) than for Kreyberg II tumors (primarily adenocarcinomas and bronchioloalveolar carcinomas) (Figure 1). Smokers of filter and nonfilter cigarettes (Wynder and Stellman 1979; Lubin et al. 1984b) and of other tobacco products (Joly, Lubin, Caraballoso 1983; Lubin et al. 1984b; Damber and Larsson 1986; Higgins, Mahan, Wynder 1988) have reduced lung cancer risk following cessation (Table 6). Although the findings of the reviewed studies uniformly indicate lower risk among former smokers, the magnitude and rapidity of the risk reduction with smoking cessation varies among the studies. This variation has several potential explanations.

First, years of abstinence among those who stopped smoking for the longest time interval varied from 5 to 25 years or more. Second, although former smokers have a risk of lung cancer between those of continuing smokers and never smokers, the pattern of declining risk as duration of abstinence lengthens has not been fully characterized. The small number of former smokers in some studies limits the precision with which the decline in risk can be described, particularly for the longer durations of abstinence. Third, aspects of the active smoking history, including cumulative smoking exposure up to the time of quitting, age at initiation, years of smoking, number of cigarettes smoked per day, inhalation practices, types of cigarettes and other tobacco products smoked, age at smoking cessation, and the reason for stopping, may modify the risk of lung cancer after cessation (Chapter 4, see section on Effect of Antecedent Smoking History). The varying extent to which these factors have been considered in analyzing the effect of cessation may partially explain the differences in risk observed in former smokers among the studies. As discussed below, failure to adjust for previous smoking history may exaggerate the benefit of smoking cessation, but adjustment for cumulative smoking history also may result in overadjustment of the risk estimate (Chapter 2). Fourth, the studies vary in the definition of former or ex-smokers and in the analytic treatment of former smokers who have recently stopped smoking. In the case–control studies, former smokers have been defined as individuals who were abstinent at the time of interview, at the time of cancer diagnosis, or at some other reference point (e.g., 1 year before diagnosis of lung cancer and a comparable time for controls).

To reduce the bias introduced by quitting because of illness, former smokers who stopped smoking after developing symptoms or disease may be excluded from analysis. Information on the reason for cessation was collected only in some studies, and persons with symptoms at cessation have not been handled uniformly in the published literature. Finally, results of the relevant studies are not totally comparable because the risks of former smokers were compared with those of never smokers in some studies and with continuing smokers in others.

TABLE 5.—Relative risks of lung cancer among never, current, and former smokers, by number of years since stopping smoking and histologic type

Reference	Population	Smoking status and yr since stopped	Histologic type			
			Males		Females	
			Kreyberg type		Kreyberg type	
			I	II	I	II
Wynder and Stellman (1979)	6 US cities	Never smokers	1.0	1.0	1.0	1.0
		Current smokers	32.3	10.7	10.5	4.4
		Former smokers				
		1–3	53.8	14.2	13.6	6.7
		4–6	24.9	5.9	6.2	3.6
		7–10	17.2	6.6	5.1	4.1
		11–15	13.7	5.4	8.8	5.6
		≥16	5.0	1.2	--	0.9
			Males			
			Kreyberg type			
			I	II		
Benhamou et al. (1985)	French males, European case–control study	Never smokers	1.0	1.0		
		Former smokers				
		1–3	34.6	6.7		
		4–6	12.2	2.1		
		7–10	10.9	--		
		11–19	6.3	1.0		
		≥20	4.2	--		
			Males		Females	
			SQ	ADENO	SQ	ADENO
Lubin and Blot (1984)	European case–control study	Current smokers	1.0	1.0	1.0	1.0
		Former smokers				
		1–4	1.1	1.0	1.1	0.7
		5–9	0.7	0.8	0.9	1.0
		10–14	0.6	0.6	0.4	0.4
		15–19	0.4	0.6	0.4	1.2
		≥20	0.4	0.5	0.3	0.3

NOTE: SQ=squamous cell carcinoma of the lung; ADENO=adenocarcinoma of the lung.

TABLE 6.—Relative risks of lung cancer among never, former, and current smokers by types of tobacco products smoked

Reference	Population	Tobacco product	Smoking status		
			Never smokers	Former smokers	Current smokers
Higgins, Mahan, Wynder (1988)	6 US cities	Cigarettes only	1.0	6.9	16.0
		Cigars only	1.0	2.5	3.1
		Pipes only	1.0	0.7	1.9
		Cigars and pipes	1.0	2.4	2.5
		Mixed smokers	1.0	5.1	10.5
Lubin, Richter, Blot (1984)	European case–control study			Yr since stopped	
				1–4 / ≥5	
		Cigars only		0.6 / 0.7	1.0
		Mixed cigars and cigarettes		4.4 / 0.9	1.0
		Pipes only		2.0 / 0.9	1.0
		Mixed pipes and cigarettes		1.2 / 0.8	1.0
Damber and Larsson (1986)	Sweden			Yr since stopped	
				1–10 / >10	
		Cigarettes only[a]		5.0 / 1.2	9.5
		Pipes only		5.0 / 4.5	8.0

[a]Estimated from figure 5 of reference; reference group is never smokers.

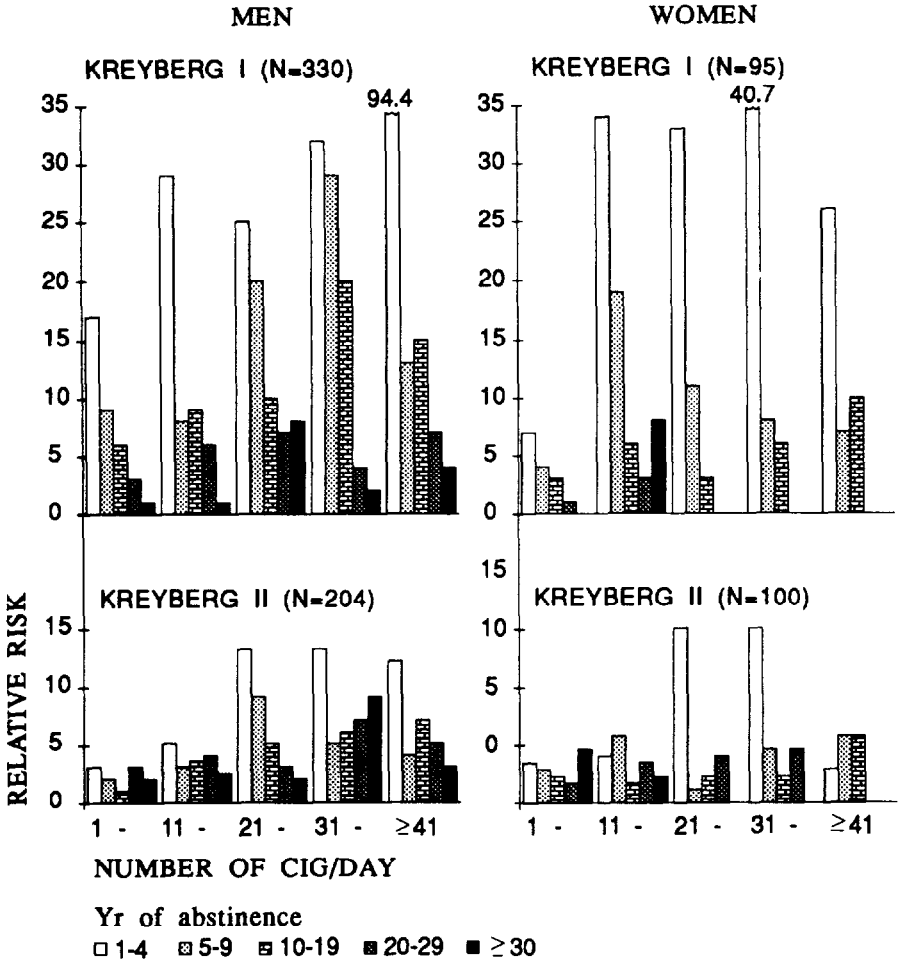

FIGURE 1.—Risk of lung cancer by number of cigarettes smoked per day before quitting, number of years of abstinence, sex, and histologic types

SOURCE: Higgins and Wynder (1988).

Although this review has emphasized the results of cohort and case–control studies, descriptive data on lung cancer mortality in the United States are consistent with a beneficial effect of the declining prevalence of cigarette smoking. Devesa, Blot, and Fraumeni (1989) described declining mortality rates for lung cancer at ages below 45 years. The decreases were greatest among white men but also occurred among white women and blacks of both sexes.

Effect of Antecedent Smoking History

The preceding Section reviewed epidemiologic studies describing the pattern of lung cancer risk following smoking cessation. This Section considers factors related to smoking that plausibly could modify the effect of cessation on lung cancer risk; these factors include the duration of smoking, daily cigarette consumption, inhalation practices, types of tobacco products smoked, and age at cessation.

Duration of Smoking

Duration of smoking prior to cessation is a potentially important modifier of the pattern of risk reduction in ex-smokers. Graham and Levin (1971) examined the risk of lung cancer associated with increasing durations of abstinence and with stratification by duration of smoking (≤30 or ≥31 years and ≤40 or ≥41 years). The decline in risk associated with stopping was greater for those who had smoked for shorter periods than for those who had smoked for longer periods. Similar results were reported by Lubin and colleagues (1984a), who determined the risk of developing lung cancer by time since stopping smoking (0, 1–4, 5–9, and ≥10 years) and total duration of smoking (1–19, 20–39, 40–49, and ≥50 years). In each category of smoking duration, the risk of developing lung cancer decreased as the number of years since stopping smoking increased, but the rate of decline was greater among those who had smoked for a shorter time. Among men who had smoked for 1 to 19 years, the risk of developing lung cancer after 10 years of abstinence dropped to less than one-third of that among current smokers. On the other hand, for men who had smoked 50 years or more and stopped for at least 10 years, the risk was still 90 percent of that for men who continued to smoke. This analysis, which matched for age and controlled for both duration of smoking and length of abstinence, introduces too many variables for the temporal dimensions of cigarette use (Chapter 2). By simultaneously considering attained age, duration of smoking, and length of abstinence, the analytic model incorrectly forces former smokers to have a younger age of starting to smoke than current smokers. In a case–control study in Sweden, Damber and Larsson (1986) also found higher relative risks among former smokers of pipes and cigarettes who had smoked longer.

Brown and Chu (1987) suggested that failure to adjust for previous duration of smoking may result in risk estimates for former smokers that are too low and thus exaggerate the benefits of smoking cessation. Based on reanalysis of data from the large European case–control study, Brown and Chu (1987) reported that the correlation between duration of smoking and time since stopping smoking for ex-smokers was –0.6, indicating that men who had stopped smoking for many years had also smoked for less

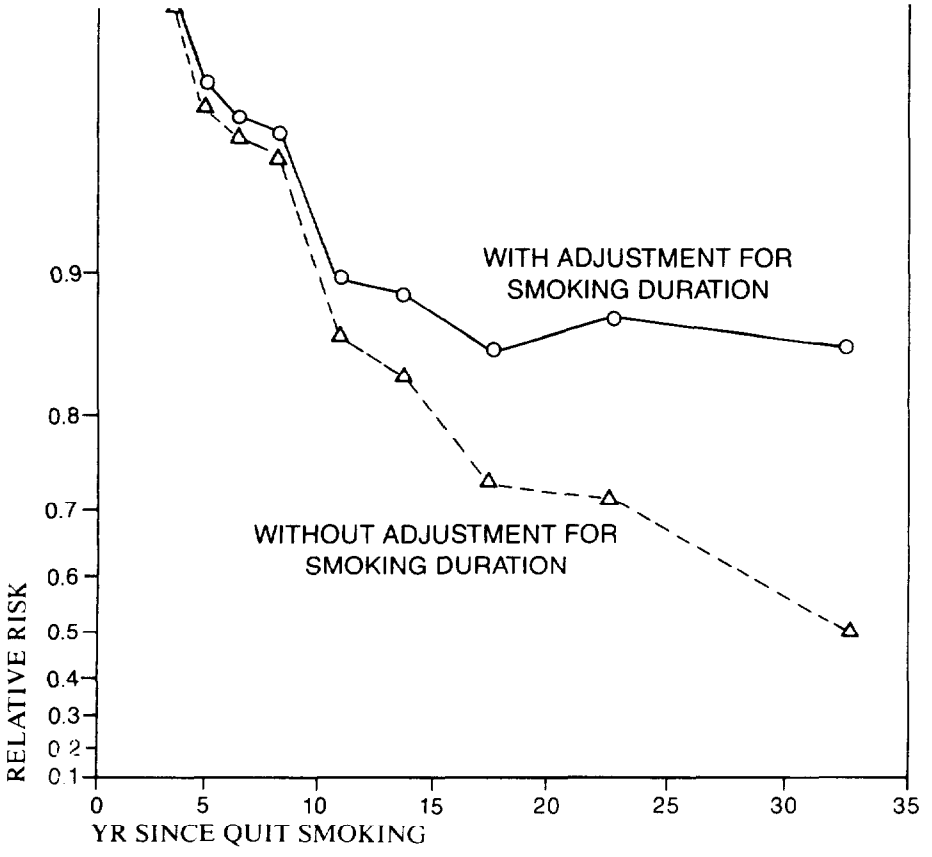

FIGURE 2.—Relative risk of lung cancer among ex-smokers compared with continuing smokers as a function of time since stopped smoking, estimated from logistic regression model, pattern adjusted for smoking duration compared with pattern unadjusted for duration

SOURCE: Brown and Chu (1987).

time than men who had stopped for a shorter time. The relative risk of lung cancer continued to decrease sharply with increasing years of abstinence without adjusting for smoking duration, whereas the decreasing relative risk plateaued when adjusted for duration of smoking (Figure 2). The difference in this pattern was most noticeable for increasing years of smoking abstinence. For those who had stopped smoking for 27 years or more, the relative risk compared with continuing smokers was 0.40 when adjusted for duration, but 0.17 when no adjustment was made. However, control for previous duration of smoking (or cumulative previous smoking history) in determining the risk of lung cancer among former smokers may constitute overadjustment if age and duration of cessation also are included in the model (Chapter 2).

In summary, only limited analyses address the effect of duration of previous smoking on the decline in risk following cessation. The data point to less decline of relative risk following cessation, comparing longer term with shorter term studies, but additional investigation is needed.

Daily Cigarette Consumption

Previous smoking intensity or number of cigarettes smoked per day also affects the pattern of risk reduction after smoking cessation. In the U.S. Veterans Study, the mortality ratios for lung cancer were 1.41, 3.47, 8.34, and 10.05 for ex-smokers who smoked 1 to 9, 10 to 20, 21 to 39, and 40 cigarettes or more per day, respectively (Kahn 1966). The pattern of lung cancer risk reduction by years of smoking abstinence and number of cigarettes smoked has been reported for several studies. In ACS CPS-I and ACS CPS-II (Hammond 1966; Garfinkel and Stellman 1988), the decline in risk with stopping smoking showed a comparable proportional reduction in risk among those who had smoked less (Table 3). In the European case–control study (Lubin et al. 1984a), men who had stopped smoking for 10 years or more, but had previously smoked 30 cigarettes or more per day, had a 40-percent risk of developing lung cancer compared with corresponding current smokers, whereas men who had smoked 1 to 9 cigarettes per day had a 67-percent risk compared with corresponding current smokers. Similar results were observed for female ex-smokers (Lubin et al. 1984a). As previously discussed, duration of smoking was considered in these analyses. Thus, heavier smokers have less reduction of lung cancer risk following cessation than smokers of fewer cigarettes per day.

Inhalation Practices

The pattern of lung cancer risk by years of smoking abstinence and by inhalation practices (i.e., frequency and depth of inhalation) was examined by Lubin and colleagues (1984a). Their analysis indicated a somewhat greater reduction in risk for those ex-smokers who had inhaled less often or less deeply. Among men who had stopped smoking for 10 years or more, relative risk by reported frequency of inhalation compared with current smokers was lowest for those who had rarely or never inhaled (relative risk (RR)=0.39) and for those whose depth of inhalation was reported as only slight or not at all (RR=0.37). In comparison, the relative risk after 10 years or more of abstinence was highest for those who had inhaled all the time (RR=0.50) and for those who had inhaled deeply (RR=0.47). The same pattern was observed among women.

Different Tobacco Products

Differences in the reduction in risk following cessation also have been investigated by types of cigarettes smoked. A lower risk of lung cancer has been observed for smokers of filter cigarettes compared with smokers of nonfilter cigarettes (US DHHS 1982, 1989; Wynder and Kabat 1988), a pattern suggesting that the reduction in risk among former smokers may be more apparent for filter cigarette smokers. However, no significant differences in the trend of risk reduction by years of smoking abstinence (0, 1–4, 5–9, and ≥10) and by type of cigarettes smoked (filter, mixed, nonfilter) were observed by Lubin and coworkers (1984b) in the European case–control study. Among

men, the relative risk for former smokers after stopping smoking for 10 years or more was 0.4 for filter cigarette smokers, 0.3 for nonfilter cigarette smokers, and 0.5 for mixed filter and nonfilter cigarette smokers. These data were collected in five western European countries from 1976 to 1980; the tar yields of the products smoked were relatively high in comparison with cigarettes currently smoked in the United States (Lubin et al. 1984b).

In most studies, cigar and pipe smokers have lower lung cancer risks compared with cigarette smokers (US DHHS 1982). Former smokers of only pipes or cigars also showed an intermediate risk of lung cancer compared with current smokers and never smokers of these tobacco products (Table 6). In the U.S. Veterans Study, the lung cancer mortality ratio, compared with never smokers, was 1.67 among current smokers who used only pipes or cigars and 1.50 among former smokers (Kahn 1966). In a case–control study of smoking-related cancers conducted in the United States, Higgins, Mahan, and Wynder (1988) reported that ex-smokers of cigars only showed a relative risk of 2.5 compared with 3.1 among current smokers of cigars only. The relative risk was 0.7 among ex-smokers of pipes only compared with 1.9 among current pipe smokers only. Analysis of the pattern of risk among ex-smokers of cigars and pipes only by considering the amount and duration smoked prior to smoking cessation revealed similar patterns of risk reduction among light and heavy smokers.

Lubin, Richter, and Blot (1984) also examined the pattern of risk reduction by years of smoking abstinence (0, 1–4, ≥5 years) and types of tobacco smoked (cigars only, mixed cigar and cigarette smokers, pipes only, and mixed pipe and cigarette smokers). No apparent differences were observed in the estimated risks, when analyzed by tobacco products, among those who had stopped smoking for at least 5 years, but the numbers of cases who smoked cigars only and pipes only were quite small. On the other hand, Damber and Larsson (1986) reported that the decrease in relative risk among ex-smokers was less pronounced in smokers of pipes compared with cigarette smokers only in a case–control study conducted in Sweden. However, in this population, the risk of lung cancer for pipe smokers (RR=6.9) was similar to that of cigarette smokers (RR=7.0).

In summary, these analyses, limited by the sample sizes within strata of types of products smoked, do not characterize precisely the changing lung cancer risk following cessation for smokers of various tobacco products.

Effect of Age at Cessation

Several researchers have suggested that the reduction in risk after smoking cessation may differ by age at cessation. Wynder and Stellman (1979) reported that the reduction in risk after cessation was appreciably greater for people aged 50 to 69 than for those 70 or older. However, only data for those aged 50 to 69 were presented in this publication. Pathak and associates (1986) also reported a strong interaction between age and duration of cigarette smoking. Risk of lung cancer among ex-smokers was compared with that of current smokers with adjustment for the amount smoked. For ex-smokers less than 65 years of age, the estimated relative risks compared with current smokers declined to 0.49, 0.24, and 0.06 for 5, 10, and 20 years of smoking abstinence,