In each study summarized in Table 1, the risk of oral cancer was lower among former smokers after the first few years of abstinence than for current smokers. After 3 to 5 years of smoking abstinence, oral cancer risk decreased by 50 percent. In a study in Argentina (Iscovich et al. 1987) and in the large multicenter study conducted by the U.S. National Cancer Institute (NCI) (Blot et al. 1988), the risk of oral cancer among former smokers after 10 years of abstinence was comparable with that among never smokers. This observation has been interpreted as an indication that the greatest effect of smoking on oral cancer risk may be in the later (postinitiation) stages of carcinogenesis (Blot et al. 1988).

Although it is well known that smokeless tobacco (ST) increases the risk of oral cancer (Winn et al. 1981; US DHHS 1986) and that stopping the use of ST reduces the prevalence of premalignant tissue changes in the mouth (Gupta et al. 1986), there is little information on the risk of oral cancer in former users of ST.

Compared with current smokers, former smokers may have different alcohol drinking habits before and after smoking cessation, and thus comparisons of risk between current and former smokers may be confounded by alcohol consumption (Chapter 11). In three investigations, the effect of smoking cessation was examined and past alcohol consumption was controlled by multiple logistic regression (Blot et al. 1988; Kabat and Wynder 1989; Kabat, Hebert, Wynder 1989). In the three studies, estimates of relative risks for both current and former smokers were similar to those observed in studies in which alcohol was not included as an adjustment factor. The stability of the relative risk estimates for smoking with adjustment for alcohol intake suggests that alcohol does not substantially confound the relationship between oral cancer risk and cigarette smoking status and that the lower risk of former smokers cannot be explained by lower levels of alcohol consumption (Chapter 11). One study was sufficiently large to permit detailed stratified analysis of the modification of the smoking effect by alcohol consumption (Blot et al. 1988). In this study, former smokers were observed to have a lower risk than current smokers for both men and women at each of five levels of alcohol consumption.

The U.S. Veterans Study (Kahn 1966) demonstrated that at each of three levels of past cigarette smoking exposure, former smokers had lower risk of oral cancer than did current smokers. Kabat, Hebert, and Wynder (1989) controlled for past cigarette exposure by multiple logistic regression and found that relative risk estimates, which were adjusted for past alcohol and cigarette consumption, did not differ from the crude estimates for former smokers (1.0 vs. 1.0 relative to never smokers).

Second primary cancers of the mouth and pharynx occur commonly in persons with an initial primary cancer in the mouth, pharynx, or larynx. Several studies have addressed the incidence of second primaries of the mouth, pharynx, or larynx in relation to smoking status after diagnosis and treatment of the first primary. The findings of these studies are inconclusive, with some indicating reduced risk of a second primary after cessation (Moore 1965; Moore 1971; Wynder et al. 1969; Silverman, Gorsky, Greenspan 1983) and others showing no clear benefit of cessation (Castigliano 1968; Schottenfeld, Gantt, Wynder 1974; Chapter 5, see section on Multiple Primary Cancers).

The results of two studies indicated that continued smoking after diagnosis of oral cancer may reduce survival, particularly in combination with alcohol consumption (Johnston and Ballantyne 1977; Stevens et al. 1983). These analyses, however, did not adjust for the more advanced stage of cancer among users of alcohol and tobacco at presentation (Johnston and Ballantyne 1977).

The results of studies of oral cancer and cigarette smoking cessation indicate that former smokers experience a lower risk of oral cancer than current smokers and that this lower risk does not appear to be a result of confounding by alcohol or level of cigarette consumption prior to cessation. The risk of oral cancer has been shown to drop substantially within 3 to 5 years of cessation.

Esophageal Cancer

Smoking is a major cause of esophageal cancer (US DHHS 1982, 1989). In the United States, the proportion of esophageal cancer deaths attributable to tobacco has been estimated to be 78 percent for men and 75 percent for women (US DHHS 1989). As for cancer of the oral cavity, cigarette smoking is an independent risk factor for esophageal cancer but can also act in conjunction with alcohol to increase cancer risk.

Table 2 summarizes the studies that have examined the relationship between smoking cessation and esophageal cancer risk. In these studies, the risk of esophageal cancer for current smokers ranges from 1.7 to 6.4 times the risk among never smokers (median of approximately 5). These findings are similar to those for oral cancer as shown in Table 1. The risks for smoking and esophageal cancer were similar among males and females.

Three years after cessation, former smokers showed lower risks than current smokers in each study summarized in Table 2, with the exception of the Swedish prospective study (Cederlof et al. 1975) in which smoking-associated risks were considerably lower than in any other study. However, in followup of this cohort, more dramatic elevations in male mortality from esophageal cancer were observed in current smokers relative to never smokers: standardized mortality ratios were 1.1 for 1 to 7 g tobacco per day, 4.5 for 8 to 15 g tobacco per day, and 5.4 for more than 15 g of tobacco per day (Carstensen, Pershagen, Eklund 1987). For former smokers, the standardized mortality ratio was 1.3. Approximately 3 to 5 years after cessation, risk of esophageal cancer was reduced by approximately 50 percent in the two studies providing information by duration of abstinence (Table 2). Data are very scant about the effects of cessation on the risk of esophageal cancer over long periods of abstinence. The U.S. Veterans Study showed that the risk among former smokers was lower at each of four levels of past numbers of cigarettes smoked per day.

A multivariate analysis in which lifetime alcohol consumption was included as an adjustment factor (La Vecchia, Liati et al. 1986) produced relative risks for current and former smokers that were similar to those observed in other studies. In this study, the crude relative risk for ex-smokers was nearly identical to one that was adjusted for alcohol consumption (2.7 vs. 3.0), suggesting that alcohol was not a confounder in the estimates of the benefits of cessation. A study that was limited to nondrinkers (La Vecchia and Negri 1989) also produced risk estimates for smoking that were very

152

TABLE 2.—Studies of esophageal cancer that have examined the effect of smoking cessation

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
Kahn (1966)	US veterans (1954–62)	Prospective (248,195)	Male	5.3	1.6	NP	Excludes "doctor's orders" quitters Cancer mortality
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,300)	Male	1.7	1.7	NP	Cancer incidence
Wynder and Stellman (1977)	6 US cities (1969–75)	Case:control (159:6,534)	Male	3.6	4.8 1.5 1.4 1.3 1.0	1–3 4–6 7–10 11–15 ≥16	
		(76:6,522)	Female	5.3	3.0 3.1 0 2.2 1.8	1–3 4–6 7–10 11–15 ≥16	
Wigle, Mao, Grace (1980)	Alberta, Canada (1971–73)	Case:control (45:1,002)	Male	5.1	1.1	NP	
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (293,958)	Male	6.4	2.4	NP	Excludes "doctor's orders" quitters Cancer mortality Extension of US Veterans Study

TABLE 2.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
La Vecchia, Liati et al. (1986)	Northern Italy (1984 85)	Case:control (129:426)	Male and female	4.3	3.4 2.5	<5 ≥5	Adjusted for SES, diet, and alcohol
La Vecchia and Negri (1989)	Northern Italy (1984 88)	Case:control (30:189)	Male and female	3.6[a]	1.1	NP	Analysis limited to only nondrinkers

NOTE: NP=not provided; SES=socioeconomic status.

[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.

similar to those derived from other studies, supporting an earlier observation of elevated risk for esophageal cancer in nondrinking smokers (Tuyns 1983).

This review of past research on esophageal cancer and cigarette smoking cessation indicates that former smokers experience a lower risk of esophageal cancer than do current smokers, and that this lower risk is not because of confounding by lower alcohol intake among former smokers.

Pancreatic Cancer

The association, noted for many years, between smoking and cancer of the pancreas is considerably weaker than that between smoking and oral or esophageal cancer (US DHHS 1982). Although the causal mechanisms underlying this association are unclear, smoking has nonetheless been regarded as a contributing factor in cancer of the pancreas (US DHHS 1982, 1989). In the United States in 1985, the proportion of pancreatic cancer deaths attributable to smoking has been estimated to be 29 percent in men and 34 percent in women (US DHHS 1989).

Table 3 summarizes studies of the relationship between pancreatic cancer and smoking cessation. In these studies, current smokers had risks ranging from 1.0 to 5.4 times (median of approximately 2) the risk among never smokers. Risks for pancreatic cancer associated with smoking were similar for males and females.

Former smokers generally had lower risk than current smokers for pancreatic cancer, but the available data do not characterize adequately the change in risk with duration of abstinence. The large case–control study conducted in Los Angeles, CA, (Mack et al. 1986) would suggest that risk is not substantially reduced until after 10 years of abstinence, whereas the smaller English study (Cuzick and Babiker 1989) suggests that substantial risk reduction is more immediate among women than among men; risk reduction may take as long as 20 years among men. This difference in the time course of risk after cessation according to gender has no clear biologic explanation and may be only a chance finding.

The question of potential confounding by differences in cigarette smoking exposure prior to quitting was addressed in the analysis of the U.S. Veterans Study (Kahn 1966). In each of four levels of past cigarette consumption, the risk among former smokers was found to be lower than that among current smokers. In the study conducted by Falk and colleagues (1988), former smokers had a lower risk of pancreatic cancer than current smokers at each of three levels of numbers of cigarettes consumed per day and also at each of four levels of numbers of years smoked.

Because alcohol can cause insult to the pancreas and has been thought to be a possible pancreatic carcinogen (Cubilla and Fitzgerald 1979), two investigators adjusted for lifetime alcohol consumption in multiple logistic regression analyses (Falk et al. 1988; Clavel et al. 1989). These analyses produced relative risk estimates similar to those derived from other studies that did not adjust for alcohol and thus suggested that alcohol consumption is not a confounding factor in the smoking–pancreatic cancer association.

The results of epidemiologic investigations on pancreatic cancer and cigarette smoking cessation indicate that there is a weak, but consistently observed, association between smoking and pancreatic cancer and that former smokers experience a lower

TABLE 3.—Studies of cancer of the pancreas 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)	US veterans (1954–62)	Prospective (248.195)	Male	1.6	1.2	NP	Excludes "doctor's orders" quitters Cancer mortality
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27.300) (27.700)	Male Female	2.5 1.0	1.7 3.5	NP NP	Cancer incidence
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (293.958)	Male	1.8	1.2	NP	Excludes "doctor's orders" quitters Cancer mortality Extension of US Veterans Study
MacMahon et al. (1981)	Boston, MA (1974–79)	Case:control (218:306) (149:337)	Male Female	1.3[a] 1.6[a]	1.4 1.3	NP NP	
Wynder, Hall, Polanski (1983)	6 US cities (1977–81)	Case:control (153:5.461) (121:2.525)	Male Female	2.2[a] 1.7[a]	1.7 1.4	≥1 ≥1	
Gold et al. (1985)	Baltimore, MD (1978–80)	Case:control (201:201)	Male and female	1.8	1.0	NP	

TABLE 3.—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
Mack et al. (1986)	Los Angeles, CA (1976–81)	Case:control (490:490)	Male and female	2.3[a]	3.3 2.3 1.0[a]	<5 5–9 >10	
Norell et al. (1986)	Sweden (1982–84)	Case:control (98:134)	Male and female	1.6[a]	1.1	NP	Data for population controls
La Vecchia et al. (1987)	Northern Italy (1983–86)	Case:control (99:471) (51:134)	Male Female	1.6 1.1	1.4 0.9	NP NP	Crude relative risk computed from data presented
Mills et al. (1988)	California (1976–83)	Prospective (34,000)	Male and female	5.4	1.5	NP	Cancer mortality study
Falk et al. (1988)	Louisiana (1979–83)	Case:control (363:1234)	Male and female	1.8[a]	1.1[a]	>3	Adjusted for diet and alcohol
Clavel et al. (1989)	Paris, France (1982–85)	Case:control (98:161) (63:107)	Male Female	1.6[a] 1.5[a]	1.0 0.9	NP NP	Adjusted for alcohol and coffee

158

TABLE 3.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
Cuzick and Babiker (1989)	England (1983–86)	Case:control (123:150)	Male	2.1[a]	3.6	<10	
					3.6	10–20	
					1.3	>20	
		(93:129)	Female	1.3[a]	0.8	<10	
					1.0	10–20	
					1.1	>20	
Olsen et al. (1989)	Minneapolis St. Paul, MN (1980–83)	Case:control (212:220)	Male	2.5[a]	0.8	NP	
ACS CPS-II (unpublished tabulations)	United States (1982–86)	Prospective (421,663)	Male	2.0	1.2	NP	Cancer mortality
		(605,758)	Female	2.7	1.6		
Farrow and Davis (in press)	Seattle, WA (1982–86)	Case:control (148:188)	Male	3.2	1.0[a]	NP	Adjusted for age, race, and education

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.

risk of pancreatic cancer than current smokers. This diminution of risk with abstinence serves to strengthen the hypothesis that smoking is a contributing cause of pancreatic cancer. Although alcohol does not appear to be a confounder in the assessment of the benefits of smoking cessation, the possibility of confounding by other factors, such as diet or amount of prior cigarette consumption, has not been adequately studied.

Bladder Cancer

As with pancreatic cancer, the relationship between bladder cancer risk and smoking has been noted for many years. However, because relative risks have not been greatly elevated and because of uncertainty about the effects of unidentified confounding factors in this disease, the causality of this association has been considered less certain compared with other diseases in earlier reports of the Surgeon General (US DHHS 1982). Smoking has nonetheless been regarded as a contributing factor in bladder cancer; in 1985, it was estimated that in the United States 47 percent of bladder cancer deaths in males and 37 percent in females are attributable to smoking (US DHHS 1989). A particular problem with causal inference in smoking and bladder cancer arises because of the inconsistent finding of clear exposure–response relationships in all studies, as has been observed between cigarette smoking and respiratory cancers. However, the usual measures of exposure to tobacco smoke may not accurately index the bladder's dose of tobacco-related carcinogens. The International Agency for Research on Cancer (IARC) concluded, based on evidence available through 1985, that smoking of different forms of tobacco is causally related to cancers of the bladder and renal pelvis (IARC 1986).

In addition to the studies reviewed in the 1982 Surgeon General's Report (US DHHS 1982) and in the 1986 report of IARC (1986), more recent data document a consistent association between cigarette smoking and bladder cancer. In an extended followup of a cohort of 25,000 Swedish males, mortality rates for bladder cancer were increased fourfold among ever smokers compared with never smokers (Carstensen, Pershagen, Eklund 1987). In current smokers, the risk of death from bladder cancer was approximately three times greater at all levels of consumption. The excess mortality from bladder cancer among current smokers was comparable in the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) (Table 4).

An extension of a large hospital-based case–control study, originally reported in 1977 (Wynder and Goldsmith 1977), showed similar increases in risk among male and female smokers (Augustine et al. 1988). The study included 1,316 male and 505 female cases and 3,940 male and 1,504 female controls interviewed in 9 U.S. cities between 1969 and 1984. For current smokers, odds ratios increased to approximately 3.5 for male and female smokers of 21 to 30 cigarettes per day. Odds ratios were lower among former smokers, although the risk did not decline as the duration of abstinence lengthened (Table 4).

The findings of a recent population-based case–control study documented similar levels of bladder cancer risk associated with cigarette smoking (Slattery et al. 1988). Slattery and coworkers (1988) assessed cigarette smoking and bladder cancer in 332 white male cases and 686 controls in Utah. The overall crude odds ratio for current

TABLE 4.—Studies of bladder cancer and smoking cessation

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
Kahn (1966)	US veterans (1954-62)	Prospective (248,195)	Male	1.9	1.5	NP	Excludes "doctor's orders" quitters Cancer mortality
Cederlof et al. (1975)	Sweden (1963-72)	Prospective (27,300) (27,700)	Male Female	1.8 1.0	2.1 0	NP NP	Cancer incidence
Wynder and Stellman (1977)	6 US cities (1969-75)	Case:control (541:6,534)	Male	2.7	2.9 1.9 1.4 1.6 1.1	1-3 4-6 7-10 11-15 ≥16	
		(150:6,522)	Female	2.4	3.1 1.5 0 1.5 2.4	1-3 4-6 7-10 11-15 ≥16	
Wigle, Mao, Grace (1980)	Alberta, Canada (1971-73)	Case:control (204:1,002) (51:674)	Male Female	2.8 3.5	2.1 3.1	NP NP	Adjusted for cumulative past dose
Rogot and Murray (1980)	US veterans (1954-69)	Prospective (293,958)	Male	2.2	1.4	NP	Excludes "doctor's order" quitters Cancer mortality Extension of US Veterans Study

TABLE 4.—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
Wynder and Goldsmith (1977)	6 US cities (1969–74)	Case:control (574:568)	Male	2.2	2.6	1–3	Cases are from the same series as reported by Wynder and Stellman (1977)
					2.9	4–6	
					1.5	7–9	
					1.6	10–12	
					1.2	13–15	
					1.1	≥16	
		(155:154)	Female	2.2	2.5	1–6	
					1.2	≥7	
Vineis et al. (1983)	Italy (1978–81)	Case:control (355:276)	Male	6.0	3.7	3–9	
					3.6	10–14	
					2.1	≥15	
Cartwright et al. (1983)	England (1978–81)	Case:control (932:1,402)	Male	1.6	1.0	6–15	
					1.1	16–25	
					0.9	≥26	
		(327:579)	Female	1.4	0.5	6–15	
					0.5	≥16	
Morrison et al. (1984)	Boston, MA (1976–77)	Case:control (427:391)	Male	3.1[a]	1.5	≥1	
		(165:142)	Female	5.6[a]	3.4	≥1	
	Manchester, UK (1976–78)	(398:490)	Male	2.6[a]	1.8	≥1	
		(155:241)	Female	2.1[a]	0.7	≥1	
	Nagoya, Japan (1976–78)	(224:442)	Male	2.0[a]	1.0	≥1	
		(66:146)	Female	4.3[a]	NP	NP	

TABLE 4.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Gender	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
Vineis, Esteve, Terracini (1984)	Italy (1978–83)	Case:control (512:596)	Male	8.0[a,b]	3.1[a] 2.0[a] 2.3[a]	3–9 10–14 ≥15	Adjusted for number of cig/day
Vineis et al. (1985)	Italy (1981–83)	Case:control (55:202)	Female	2.3	1.0	≥3	
Jensen et al. (1987)	Copenhagen, Denmark (1979–81)	Case:control (388:787)	Male and female	3.4	2.0	NP	
Brownson, Chang, Davis (1987)	Missouri (1984–86)	Case:control (823:2,469)	Male	1.9	1.2	NP	Adjusted for alcohol
Hartge et al. (1987)	United States (1977–78)	Case:control (2,982:5,782)	Male and female	2.9	2.2 1.6 1.7 1.4[a]	1–9 10–19 20–29 ≥30	
Iscovich et al. (1987)	Argentina (1983–85)	Case:control (117:234)	Male and female	7.2	4.5 1.8 1.6 1.1	2–4 5–9 10–19 ≥20	
Augustine et al. (1988)	9 US cities (1969–84)	Case:control (1,316:3,940)	Male	2.2[a]	2.4[c] 2.2[c] 2.1[c]	≤6 7–12 ≥13	
		(505:1,504)	Female	0.9[a]	1.7[c] 1.2[c] 1.2[c]	≤6 7–12 ≤13	

TABLE 4.—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
Slattery et al. (1988)	Utah (1977–83)	Case:control (332:686)	Male	3.7	3.7	0.5–7	
					2.7	8–15	
					1.9	16–29	
					1.8	≥30	
Claude, Frenzel-Beyme, Kunze (1988)	Germany (1977–84)	Case:control (531:531)	Male	3.5	1.8	NP	Adjusted for number of cig/day
ACS CPS-II (unpublished tabulations)	United States (1982–86)	Prospective (421,663)	Male	2.9	2.0	NP	Cancer mortality
		(605,758)	Female	2.8	2.0	NP	
Burch et al. (1989)	Canada (1979–82)	Case:control (627:602)	Male	2.7	1.7	NP	
		(199:190)	Female	2.6	1.2	NP	

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

^aComputed 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.

^bIncludes current and former smokers who quit in the past 2 yr.

^cCrude (unadjusted) odds ratio calculated from tables presented in the paper.

163

smoking, compared with never smoking, was 3.69 (95-percent confidence interval (CI), 2.58–5.26). However, an exposure–response relationship was not evident with reported average number of cigarettes smoked daily. The odds ratios for former smokers declined only after 8 years or more of abstinence.

Table 4 summarizes findings from studies that have examined the relationship between cigarette smoking cessation and risk of bladder cancer. Of all the non-respiratory cancer sites, the relationship between bladder cancer risk and cigarette smoking cessation has been most extensively studied. In these studies, the risk among current smokers ranges from 1.0 to 7.2 times the risk among never smokers (median of approximately 3); risks are similar among males and females. More recent studies conducted since the mid-1970s tend to show higher risks for current smokers than do the earlier studies. The higher risks in more recent studies may reflect the earlier age of starting to smoke of more recent cohorts of smokers (US DHHS 1989) or the presence of a long latency period for the smoking effect to become fully manifest after initiation in susceptible persons.

Beyond the first few years of abstinence, former smokers generally have lower risks than current smokers. The study conducted in six U.S. cities (Wynder and Stellman 1977; Wynder and Goldsmith 1977) indicated an approximate 50-percent reduction in risk after 6 years of abstinence, with risk returning to that of nonsmokers among men after 15 years. A similar return to nonsmoker risk was also observed after 6 years of abstinence in an English study (Cartwright et al. 1983) and in an Argentine study after 20 years (Iscovich et al. 1987). However, results from other studies (Howe et al. 1980; Vineis, Esteve, Terracini 1984; Hartge et al. 1987; Burch et al. 1989) indicated that the reduction in risk in the first few years after cessation is followed by little subsequent additional reduction, even beyond 10 or 15 years of abstinence. These observations are in contrast to those for the other cancer sites reviewed in this Chapter.

In some studies, the analyses controlled for the possible confounding effects of lower cigarette consumption among former smokers prior to cessation. The U.S. Veterans Study (Kahn 1966) showed no reduction in risk for former smokers, compared with current smokers, at levels of past cigarette consumption of 1 pack or less per day. There was an approximate 50-percent reduction in risk, however, for those former smokers who had previously smoked more than 1 pack per day. Most studies that included past cigarette smoking exposure as a covariate in multiple logistic regression analyses (Wigle, Mao, Grace 1980; Howe et al. 1980; Vineis, Esteve, Terracini 1984; Claude, Frentzel-Beyme, Kunze 1988; Slattery et al. 1988; Burch et al. 1989) showed relative risks that were similar to those observed in studies in which no such adjustment was made.

A large multicenter study conducted by NCI (Hartge et al. 1987) contained sufficient numbers of subjects for detailed subgroup analyses. Table 5 displays the findings of this study when both average cigarette dose per day and duration of smoking are cross-classified for current and former smokers. In each of these nine categories, bladder cancer risk was lower among former smokers than among current smokers.

As reviewed above, the amount of evidence supporting cigarette smoking as a cause of bladder cancer has become increasingly compelling since the 1982 Report of the Surgeon General (US DHHS 1982), which focused on cancer. Multiple studies of

164

TABLE 5.—Bladder cancer risk according to smoking dose, duration of smoking, and smoking status

| Smoking dose (cig/day) | Duration of smoking (yr) | Risk relative to never smokers | |
		Current smokers	Former smokers
<20	<20	1.7	1.3
	20–39	1.6	1.5
	≥40	2.7	1.9
20–39	<20	2.2	1.4
	20–39	3.8	1.8
	≥40	3.1	2.5
≥40	<20	2.4	1.0
	20–39	4.0	2.1
	≥40	3.8	2.8

SOURCE: Hartge et al. (1987).

varying design conducted throughout the world have shown statistically significant increases in risk of bladder cancer among smokers. Cigarette smoking, determined to be a contributory factor in bladder cancer in past reports of the Surgeon General (US DHHS 1982, 1989), can now be identified as causally associated with bladder cancer. The evidence adequately meets the criteria for causality established in the 1964 Report (US PHS 1964). The decline in risk of bladder cancer with cessation further supports the conclusion that cigarette smoking causes bladder cancer. This diminution in risk cannot be explained by confounding from lower cumulative consumption among former smokers compared with continuing smokers.

Cervical Cancer

Recently, an association has been noted between cancer of the uterine cervix and cigarette smoking (Williams and Horm 1977; Stellman, Austin, Wynder 1980; Lyon et al. 1983; Hellberg, Valentin, Nilsson 1983; Berggren and Sjostedt 1983; Peters et al. 1986; Brock et al. 1988; Nischan, Ebeling, Schindler 1988). However, because of the possibility of confounding by unidentified factors (in particular, a sexually transmitted etiologic agent), this association has not been identified as causal (US DHHS 1982, 1989; IARC 1986). Components of tobacco smoke can be identified in the cervical mucus of smokers (Sasson et al. 1985; Schiffman et al. 1987). These compounds have been found not only to display mutagenic activity in this environment (Holly et al. 1986), but also to have the ability to impair local immunity by reducing the populations of Langerhans' cells within the cervical epithelium (Barton et al. 1988). The reduction in circulating levels of β-carotene caused by cigarette smoking is yet another mechanism whereby cigarettes may increase the risk of cervical cancer (Harris et al. 1986; Brock et al. 1988; Stryker et al. 1988). Thus, the association of cigarette smoking with cervical cancer is biologically plausible.

Table 6 summarizes findings from studies that have examined the relationship between cervical cancer risk and cigarette smoking cessation. In these studies, the risk among current smokers ranges from 1.0 to 5.0 times the risk among never smokers (median of approximately 2). Smoking-associated risks for invasive cancer and for carcinoma in situ are generally similar.

After the first year of abstinence, former smokers have lower cervical cancer risk than current smokers in most studies. Exceptions include the study conducted in Milan (La Vecchia, Franceschi et al. 1986), which showed risk reduction for invasive cancer but not for carcinoma in situ among former smokers, and the study conducted in Central America (Herrero et al. 1989) in which no association with smoking was observed at all, even for current smokers. The effect of time since stopping has not yet been well studied for cervical cancer, but observations from a large multicenter study conducted by NCI (Brinton, Schairer, Haenszel et al. 1986) suggested that risk reduction may occur fairly rapidly after cessation. One study found that smokers tended to have a poorer prognosis for survival after radiation treatment for invasive cervical cancer, but no data were presented regarding smoking cessation (Kucera et al. 1987).

A major concern in studies of smoking and cervical cancer has been the potential for confounding by factors that would predispose a woman to become infected with a sexually transmitted agent that might be causally related to the disease, such as human papilloma virus (Stellman, Austin, Wynder 1980; Winkelstein et al. 1984; IARC 1986). Therefore, it is important to note that those studies that controlled for risk factors for sexually transmitted disease (Trevathan et al. 1983; Greenberg et al. 1985; Herrero et al. 1989; Slattery et al. 1989) produced relative risk estimates for current and former smokers that were quite similar to those from studies that made no such adjustments. The association of smoking and cervical cancer has been considered by some to be a result of residual confounding by inadequately measured indicators of exposure to a sexually transmitted agent. Although factors such as the number of past sexual partners are only surrogates for a hypothetical etiologic infectious agent, they are the very same social correlates of tobacco smoking that would suggest this type of confounding. Therefore, even though such factors as age at first intercourse and the number of sexual partners are imperfect indicators of infection by a possible etiologic agent, their inclusion as covariates in multivariate analyses may be sufficient to control confounding to some extent in the analysis of the effects of smoking on cervical cancer risk.

This review of the evidence on cervical cancer and cigarette smoking cessation indicates that there is a consistently observed association between cervical cancer risk and cigarette smoking and that former smokers experience a lower risk of cervical cancer than current smokers, even after adjusting for the social correlates of smoking and risk of sexually acquired infections. This observed diminution of risk after cessation lends support to the hypothesis that smoking is a contributing cause of cervical cancer. Based on a recent comprehensive review of epidemiologic studies providing data on smoking and cervical cancer, Winkelstein (1990) concluded that smoking is causally associated with cervical cancer.

166

TABLE 6.—Studies of cervical cancer and smoking cessation

Reference	Location (yr of data collection)	Design (number of subjects)	Risk relative to never smokers		Yr since quitting	Comments
			Current smokers	Former smokers		
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,700)	5.0	3.0	NR	Cancer incidence
Clarke, Morgan, Newman (1982)	Toronto, Ontario (1973–76)	Case:control (178:855)	2.3	1.7	NR	Invasive cancer
Marshall et al. (1983)	Buffalo, NY (1957–65)	Case:control (513:490)	1.6	0.8	NR	
Trevathan et al. (1983)	Atlanta, GA (1980–81)	Case:control (99:288)	4.2	2.1	NR	Carcinoma in situ Adjusted for sexual partners, birth control pills, SES
Greenberg et al. (1985)	England (1968–83)	Prospective (17,032)	3.0[d]	0.7	NR	Invasive cancer incidence Adjusted for age at marriage, birth control pills, SES
Brinton, Schairer, Haenszel et al. (1986)	5 US cities (1982–84)	Case:control (480:797)	1.5	3.2 1.1 1.0 1.1	1 2–4 5–9 ≥10	Adjusted for sexual partners, age at first intercourse, SES
La Vecchia, Franceschi et al. (1986)	Milan, Italy (1981–84)	Case:control (183:183) (230:230)	1.4[b] 1.7	2.5 0.8	NR NR	Carcinoma in situ Invasive cancer

TABLE 6.—Continued

Reference	Location (yr of data collection)	Design (number of subjects)	Risk relative to never smokers		Yr since quitting	Comments
			Current smokers	Former smokers		
Brisson et al. (1988)	Quebec (1982–85)	Case:control (247:137)	3.5	1.9	NR	Carcinoma in situ
Herrero et al. (1989)	4 Central American cities (1986–87)	Case:control (666:1,427)	1.0	1.0	NR	Adjusted for sexual partners
Slattery et al. (1989)	Utah (1984–87)	Case:control (266:408)	3.4	1.4	NR	Adjusted for sexual partners and education
ACS CPS-II (unpublished tabulations)	United States (1982–86)	Prospective (605,758)	2.1	1.9	NR	Cancer mortality

NOTE: NR=not reported; SES=socioeconomic status; 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 incident cases within each stratum of smoking.

[b]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.

Breast Cancer

In general, prior research has shown little relation between cigarette smoking and the risk of breast cancer (Baron 1984; Rosenberg et al. 1984; Baron et al. 1986); however, in recent years, several reports have raised the possibility that there might be a weak positive association (Table 7). Because there has been considerable discussion about the possible role of smoking in breast cancer in recent literature, the relationships among cigarette smoking, smoking cessation, and breast cancer risk are reviewed. Cigarette smoking creates a set of physiologic conditions that result in various antiestrogenic effects (Baron 1984; Jensen, Christiansen, Rodbrø 1985; Michnovicz et al. 1986), as well as affecting body mass (Carney and Goldberg 1984; Hofstetter et al. 1986; Chapters 9, 10, 11). The relationship between cigarette smoking and body mass is a particularly important consideration in studies of breast cancer, because body mass has a complex age-dependent association with breast cancer risk, with obesity being protective in premenopausal ages but slightly risk-enhancing later in life (Willett et al. 1985).

Table 7 summarizes findings from studies that have examined the relationship between breast cancer risk and the cessation of cigarette smoking. The risk of breast cancer among current smokers ranges from less than 1.0 to 4.6 times greater than among never smokers (median approximately 1). The relative risks of smoking do not consistently differ in premenopausal and postmenopausal age groups. In addition, there is little consistency regarding the change in risk observed after smoking cessation. Former smokers have lower risks in some studies, but higher risks in others. Adjustment for other breast cancer risk factors does not appear to completely remove the weak association observed in some studies (Schechter, Miller, Howe 1985; Rohan and Baron 1989).

In one study it was found that smokers tended to have a greater prevalence of tumor-positive axillary lymph nodes at the time of diagnosis than did never smokers and former smokers, a finding that could not be explained by patient delay (Daniell 1988). This association was not confirmed, however, in a recent report based on 10-year followup of the Nurses Health Study cohort that included 1,373 cases with information on extent of disease at diagnosis (London et al. 1989).

This review of breast cancer and cigarette smoking suggests that cigarette smoking is not associated with breast cancer. Consistent changes in risk are not observed with smoking cessation.

Endometrial Cancer

The relationship between cigarette smoking and cancer of the endometrium is unique among the associations of smoking with cancers at various sites; of the sites for which smoking has been associated with a change in risk, endometrial cancer is the only cancer for which there is fairly consistent evidence of an inverse (protective) relationship (Baron 1984; Lesko et al. 1985; Stockwell and Lyman 1987), an effect that may be limited to postmenopausal women (Smith, Sowers, Burns 1984; Koumantaki et al. 1989). The reasons for the lower risk among women who smoke are not well under-

TABLE 7.—Studies of breast cancer and smoking cessation

Reference	Location (yr of data collection)	Design (number of subjects)	Menopausal status	Risk relative to never smokers Current smokers	Former smokers	Yr since quitting	Comments
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,700)	Pre and post	0.6	0.4	NR	Cancer incidence
Schechter, Miller, Howe (1985)	Canada (1980–82)	Case:control (49:134) (71:219)	Pre Post	4.6 1.1	1.8 0.8	≥1 ≥1	Adjusted for several breast cancer risk factors
Hiatt and Fireman (1986)	Northern California (1964–80)	Prospective (84,172)	Pre Post	1.2 1.1	1.2 1.3	NR NR	Cancer incidence
Brinton, Schairer, Stanford et al. (1986)	United States (1973–75)	Case:control (447:503) (614:818)	Pre Post	1.1 1.1	1.4 1.0	NR NR	
Stockwell and Lyman (1987)	Florida (1981)	Case:control (4,011:2,952)	Pre Post	1.3^a 1.2^a	0.9 0.9	NR NR	
Brownson et al. (1988)	Missouri (1979–86)	Case:control (114:208) (206:872)	Pre Post	2.3 1.2	1.2 0.7	NR NR	
Adami et al. (1988)	Sweden and Norway (1984–85)	Case:control (422:527)	Pre and post	1.0	0.8		Relative risk calculated from crude data
Rohan and Baron (1989)	Australia (1982–84)	Case:control (146:132) (280:288)	Pre Post	1.3 1.5	2.4 0.9	≥1 ≥1	Adjusted for several breast cancer risk factors

TABLE 7.—Continued

Reference	Location (yr of data collection)	Design (number of subjects)	Menopausal status	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
London et al. (1989)	United States (1976–80)	Prospective (117,557)	Pre	1.0[a]	1.1	NR	
			Post	1.1[a]	1.1	NR	

NOTE: NR=not reported.

[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.

stood, but may be due to smoking effects on estrogen production and metabolism, including increased 2-hydroxylation of estradiol in smokers (Michnovicz et al. 1986), an earlier age at menopause in smokers (Baron 1984), and indirect effects of the body weight differences between smokers and nonsmokers, such as the production of estrogens from precursors within adipose tissue (MacDonald et al. 1978; Chapters 8 and 10).

Table 8 includes a summary of findings from studies of endometrial cancer that have examined cigarette smoking cessation. Although the risk of endometrial cancer among current smokers in these studies is approximately 30 percent lower than that among never smokers, the risk among ex-smokers is similar to, or slightly greater than, that among current smokers.

This review of past research on endometrial cancer risk and cigarette smoking cessation suggests that current smokers are at lower risk of endometrial cancer than never smokers, but it is not clear whether this protective effect of smoking on endometrial cancer risk might be reversed soon after cessation of cigarette smoking. Although further investigation of the mechanisms for the protective effect of smoking on endometrial cancer is of scientific interest to better understand the effects of smoking on hormones and of hormones on endometrial cancer risk, this inverse association with smoking has no public health relevance, as the well-substantiated risks to other organ systems from continued smoking far outweigh any potential benefits to the endometrium.

Other Cancer Sites

The metabolic products of tobacco smoke can be found in ovarian follicular fluid (Hellberg and Nilsson 1988). However, there is little evidence that smoking is associated with cancer of the ovary (Byers et al. 1983; Baron 1984; Baron et al. 1986; Stockwell and Lyman 1987; Whittemore et al. 1988; Mori et al. 1988). The risk of ovarian cancer differs little for either current or former smokers, as indicated in the only two studies that have examined the effect of cigarette smoking cessation on ovarian cancer risk (Table 8).

Tobacco has been regarded as a contributing factor for cancer of the kidney (US DHHS 1982, 1989). The U.S. Veterans Study (Kahn 1966; Rogot and Murray 1980) and ACS CPS-II (ACS, unpublished tabulations) suggest only small differences in mortality from renal cancer between current and former smokers (Table 8). A study of renal pelvis and ureteral cancers in Copenhagen (Jensen et al. 1988), however, showed a pattern of risk diminution with abstinence similar to that observed in bladder cancer, a site with the same histologic type of transitional-cell tumors.

Cancers of the anus and penis are considered possibly to result from infection by a sexually transmitted agent in a way analogous to cancer of the uterine cervix (Daniell 1985; Daling et al. 1987; Hellberg et al. 1987). Smokers have been found to be at increased risk both for cancer of the penis (Hellberg et al. 1987) and anus (Daling et al. 1987; Holmes et al. 1988) in recent studies. Only one study has examined the effect of cessation on the risk of these cancers (Hellberg et al. 1987). This study found that

172

TABLE 8.—Studies of cancer at selected sites that have examined the effect of smoking cessation

Reference	Population (yr of data collection)	Design (number of subjects)	Cancer site	Risk relative to never smokers — Current smokers	Risk relative to never smokers — Former smokers	Yr since quitting	Comments
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,700)	Endometrium	0.5	1.6	NP	Cancer incidence
Lesko et al. (1985)	8 North American cities (1976–83)	Case:control (508:706)	Endometrium	0.8ᵃ	0.9	≥1	Adjusted for obesity and exogenous estrogens
Stockwell and Lyman (1987)	Florida (1981)	Case:control (990:2,952)	Endometrium	0.8ᵃ	0.6	NP	
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,700)	Ovary	0.5	1.6	NP	Cancer incidence
Stockwell and Lyman (1987)	Florida (1981)	Case:control (696:2,952)	Ovary	1.1ᵃ	0.9	NP	
Franks et al. (1987)	United States (1980-82)	Case:control	Ovary	1.1	0.9	≥1	Adjusted for age, parity, and use of oral contraceptives
Kahn (1966)	US veterans (1954–62)	Prospective (248,195)	Kidney	1.4	1.5	NP	Excludes "doctor's orders" quitters Cancer mortality
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (293,958)	Kidney	1.4	1.2	NP	Extension of US Veterans Study
Jensen et al. (1988)	Copenhagen (1979–82)	Case:control (96:288)	Renal pelvis and ureter	3.7	1.9	NP	Crude relative risks computed from data presented

TABLE 8.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Cancer site	Risk relative to never smokers		Yr since quitting	Comments
				Current smokers	Former smokers		
Hellberg et al. (1987)	Sweden (NP)	Case:control (244:232)	Penis	1.6	1.7	NP	
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,300)	Liver	2.4	1.0	NP	Cancer incidence in males
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (248,000)	Liver	2.3	1.8	NP	Cancer mortality
Yu et al. (1983)	Los Angeles, CA (1975–79)	Case:control (76:76)	Liver	1.8[a]	1.1	NP	Abstainers for ≥10 yr were considered never smokers
Kahn (1966)	United States (1954–62)	Prospective (248,195)	Stomach	1.4	1.1	NP	Excludes "doctor's orders" quitters Cancer mortality
Cederlof et al. (1975)	Sweden (1963–72)	Prospective (27,300)	Stomach	1.3	0.7	NP	Cancer incidence in males
Rogot and Murray (1980)	US veterans (1954–69)	Prospective (293,958)	Stomach	1.5	1.1	NP	Extension of US Veterans Study
Nomura et al. (1990)	Japanese men in Hawaii (1965–68)	Prospective (7,990)	Stomach	2.7	1.0	NP	Cohort identified 1965–68 and followed through October 1986
Kahn (1966)	US veterans (1954–62)	Prospective (248,195)	Leukemia	1.4	1.5	NP	Excludes "doctor's orders" quitters Cancer mortality

TABLE 8.—Continued

Reference	Population (yr of data collection)	Design (number of subjects)	Cancer site	Risk relative to never smokers		Y_T since quitting	Comments
				Current smokers	Former smokers		
Cederlof et al.	Sweden	Prospective	Leukemia				
(1975)	(1963–72)	(27,300)	(Males)	1.1	0.8	NP	Cancer incidence
		(27,700)	(Females)	0.4	1.0	NP	
Rogot and Murray	US veterans	Prospective	Leukemia	1.6	1.5	NP	Extension of US Veterans Study
(1980)	(1954–69)	(248,000)					
Trichopoulos et al.	Greece	Case:control	Liver				
(1987)	(1976–84)	(104:454)	HB,Ag	3.3[a]	2.8	NP	
		(89:454)	HB,Ag⁺	1.6[a]	1.3	NP	
ACS CPS-II	United States	Prospective	Kidney				
(unpublished	(1982–86)	(421,623)	(Males)	2.7	2.1	NP	Cancer mortality
tabulations)		(605,758)	(Females)	1.5	1.1	NP	

NOTE: NP=not provided; HB,Ag=hepatitis B surface antigen; 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.