Chapter 3. Health Consequences of Tobacco Use Among Women

Introduction

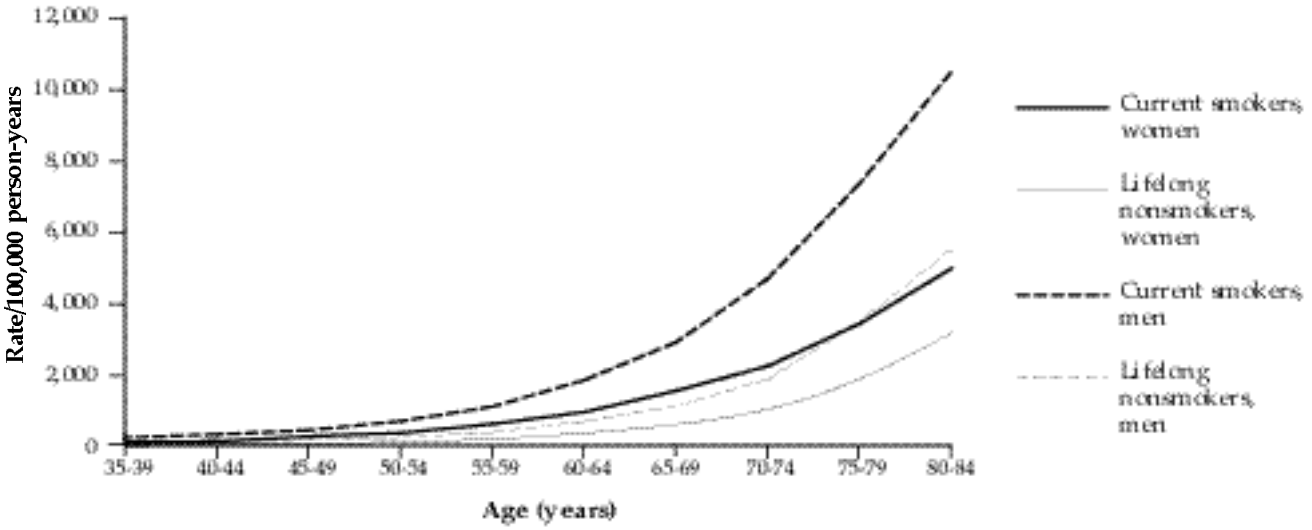
This chapter reviews the evidence for a relationship between smoking, as well as exposure to environmental tobacco smoke (ETS), and a wide range of diseases and health-related conditions among women. It begins with a section on the impact of smoking on mortality from all causes combined among women who smoke compared with women who have never smoked. Most of the remainder of the chapter is devoted to the effects of active smoking on specific health outcomes among women, ranging from cancer to bone density. Lung cancer is discussed first because of the strength of its association with smoking and because smoking is responsible for lung cancer becoming the leading cause of cancer death among U.S. women by the late 1980s, a position it continues to hold. Female-specific cancers are discussed next, followed by other cancers. Because coronary heart disease constitutes the major overall cause of death among women and because of the well-established association of smoking with heart disease and stroke, a section devoted to cardiovascular disease appears next. After that, another important cause of smoking-related morbidity and mortality, chronic obstructive pulmonary disease, is discussed. A brief section on sex hormones, thyroid disorders, and diabetes follows. Next reviewed are areas of unique concern among women, namely the effects of smoking on menstrual function and menopause and on reproductive hormones. Other sections review a variety of diseases (e.g., eye disease, gastrointestinal disease) or physiologic effects (e.g., bone density, nicotine addiction) that have been examined in relation to smoking among women. The chapter concludes with sections on the effect of ETS on female lung cancer, heart disease, and reproductive outcomes. Our knowledge base regarding the effects of smoking on women's health has grown enormously since the Surgeon General's first report on women and smoking was published in 1980 (U.S. Department of Health and Human Services [USDHHS] 1980). The physiologic effects of smoking are broad ranging and, in addition to the health risks shared with men who smoke, women smokers experience unique risks such as those related to reproduction and menopause. Since 1980, approximately three million U.S. women have died prematurely as a result of a smoking-related disease. In 1997 alone, an estimated 165,000 U.S. women died prematurely of a smoking-related disease.

Because numerous experts contributed to this report, with varying preferences for use of terms to report outcome measures and statistical significance, the editors chose certain simplifying conventions in reporting research results. In particular, the term "relative risk" generally was adopted throughout this chapter for ratio measures of association—whether original study results were reported as relative risks, estimated relative risks, odds ratios, rate ratios, risk ratios, or other terms that express risk for one group of individuals (e.g., smokers) as a ratio of another (e.g., nonsmokers). Moreover, relative risks and confidence intervals were generally rounded to one decimal place, except when rounding could change a marginally statistically significant finding to an insignificant finding; thus, only when the original confidence limit was within 0.95 to 0.99 or within 1.01 to 1.04 were two decimal places retained in the reporting of results.

Total Mortality

Women in the United States began regular cigarette smoking in large numbers decades before women in most other countries did; among women born before 1960, adolescent girls took up regular smoking at progressively earlier ages (Burns et al. 1997a) (see Chapter 2). Thus, U.S. women have been at the forefront of an emerging worldwide epidemic of deaths from smoking, and their experience underscores the need to curtail tobacco marketing worldwide. Women in the United States make up approximately 20 percent of women in the developed world. In 1990, they accounted for more than 40 percent of all deaths attributable to smoking among women in developed countries (Peto et al. 1994).

Figure 3.1. All-cause death rates for current smokers and lifelong nonsmokers, by age and gender, Cancer Prevention Study II, 1982–1988



Sources: Thun et al. 1997a,c.

In this section of Chapter 3, the death rate from all causes combined among women who continue to smoke (current smokers) is compared with the rate in those who have never smoked regularly. The risk from smoking depends on the duration of smoking, the number of cigarettes smoked per day, the age of the smoker, and the epidemiologic measure used to assess risk. By all measures, however, risk increased dramatically among U.S. women from the 1950s through the late 1980s. This finding is clearly demonstrated by the results of at least eight large prospective studies from North America.

Age-Specific and Smoking-Specific Death Rates

The largest contemporary study of smoking and mortality in the United States is the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II)—a prospective, epidemiologic study of more than one million adults that was begun by ACS in 1982 (Garfinkel 1985; Stellman and Garfinkel 1986; Garfinkel and Stellman 1988; Thun et al. 1995, 1997a). Descriptions of CPS-II and of other epidemiologic studies discussed in this section are provided in the Appendix to this chapter.

As illustrated in Figure 3.1 and Table 3.1, overall death rates in CPS-II were substantially higher among women who currently smoked cigarettes when enrolled than among those who had never smoked regularly (lifelong nonsmokers). The death rate (per 100,000 person-years at risk) among women who smoked was approximately twice that among women who had never smoked in every age group from 45 through 74 years (Table 3.1). Although death rates were lower among women than among men (Figure 3.1), the relationship of smoking to all-cause death rates was similar among women and men. The large size of CPS-II allows death rates to be estimated fairly precisely by gender and smoking status and within five-year intervals of age at the time of follow-up.

CPS-II data on the relationship of smoking and the risk for death from all causes combined are shown in Table 3.1. This relationship was measured in three ways. (1) The death rate, defined as deaths per 100,000 person-years at risk, reflects the absolute probability (risk) of death per year (also see Figure 3.1). (2) Relative risk (RR), defined as the death rate among smokers divided by the rate among those who had never smoked, expresses the risk among smokers as a multiple of the annual risk among those who had never smoked. (3) Rate difference, defined as the death rate among smokers minus the rate among those who had never smoked, reflects the absolute excess risk for death per year among smokers compared with those who had never smoked. The CPS-II results illustrate that the impact of smoking on deaths

Table 3.1. All-cause mortality among women for lifelong nonsmokers and current smokers, by age, Cancer Prevention Study II, 1982–1988

Age specific

Age (years)	Lifelong nonsmokers		Current smokers		Relative risk	Rate difference*
	Number of deaths	Death rate*	Number of deaths	Death rate*		
35–39	40	80.6	22	88.8	1.1	8.2
40–44	93	109.3	50	110.9	1.0	1.6
45–49	255	122.4	256	252.6	2.1	130.2
50–54	564	182.1	501	348.5	1.9	166.4
55–59	927	268.2	874	598.8	2.2	330.6
60–64	1,401	411.4	1,140	936.3	2.3	525.0
65–69	1,871	666.5	1,243	1,533.7	2.3	867.2
70–74	2,216	1,073.9	1,020	2,227.0	2.1	1,153.1
75–79	2,487	1,838.7	658	3,417.9	1.9	1,579.1
80–84	2,245	3,154.2	285	4,959.2	1.6	1,805.0
Total	12,099		6,049			

Age standardized to age distribution in 1980 U.S. population

	Lifelong nonsmokers	Current smokers
Death rate*	475.0	913.5
95% CI[†]	465.6–484.3	885.2–941.8
Relative risk	1.0	1.9
95% CI	NA[‡]	1.9–2.0
Rate difference*	0	438.5
95% CI	NA	408.7–468.3

Note: Analyses restricted to women aged 35–84 years to maximize stability and validity of results.
*Death rate and rate difference, for all causes, per 100,000 person-years.
[†]CI = Confidence interval.
[‡]NA= Not applicable.
Sources: Thun et al. 1997a,c.

from all causes varies at different ages for each of the three measures of risk (Thun et al. 1997c). Beginning at approximately age 45 years, the death rate from all causes was progressively higher among women who smoked than among those who had never smoked (Figure 3.1). The absolute increase in risk associated with smoking became greater with age, as measured by the increase in the rate difference from ages 45 through 84 years (Table 3.1). In contrast, the value for RR associated with any current smoking increased from approximately 1.0 among women younger than 45 years to a maximum of 2.3 at ages 60 through 69 years, then decreased to 1.6 at ages 80 through 84 years (Table 3.1).

Measured in absolute terms, smoking becomes more, rather than less, hazardous with increasing age. Older smokers incur a larger individual risk for dying prematurely from their smoking than do younger smokers, and the total number of smoking attributable deaths is greater among older smokers than among younger smokers. On the other hand, trends in RR reflect first the increase and later the decrease, with age, of the proportionate contribution of smoking to deaths among smokers. In the CPS-II data, the RR associated with smoking among women peaked at 2.3 at ages 60 through 69 years (Table 3.1). The corresponding RR among British male physicians and men in CPS-II who continued to smoke cigarettes was

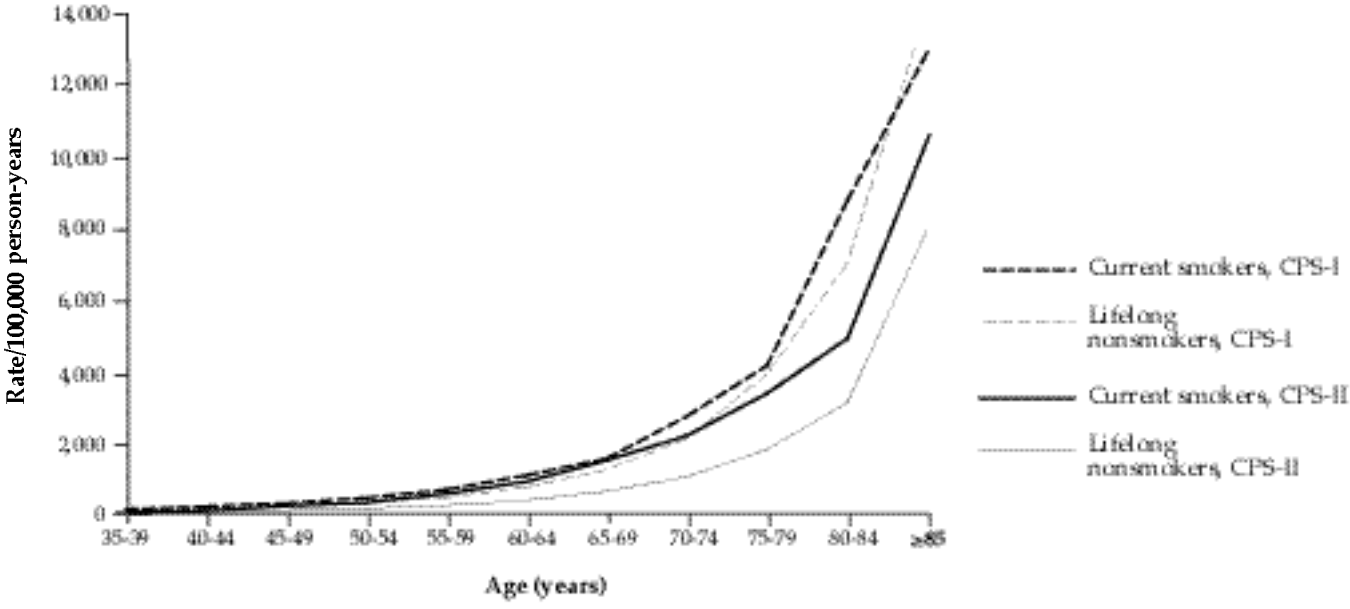
approximately 3.0 at approximately 40 through 60 years of age (Doll et al. 1994; Thun et al. 1997c). The proportionately smaller contribution of smoking to death among older smokers indicated that death rates from factors unrelated to smoking increase even faster at older ages than do the increasing hazards from smoking.

Changes over Time in the Association Between Smoking and All-Cause Death Rates

Changes in women's smoking behavior, particularly the trend up to 1960 among adolescent girls to start smoking at progressively earlier ages, underlie the gradual increase in smoking-associated RR for death among women smokers in the last half-century. A unique longitudinal perspective on how smoking behavior and smoking-specific death rates changed among U.S. women from the late 1950s through the 1980s may be seen by comparing the results of CPS-II with its predecessor, the Cancer Prevention Study I (CPS-I), which was conducted by ACS in 1959–1965 (USDHHS 1989b; Thun et al. 1995, 1997a). In CPS-I, methods of recruitment and follow-up were similar to those in CPS-II (see Appendix to this chapter). In general, women in CPS-I who smoked began to smoke regularly just before, during, or after World War II, and relatively few had smoked for more than 20 years. In contrast, many women enrolled in CPS-II had smoked regularly for 30 to 40 years. Women in CPS-II started smoking in larger numbers at younger ages and, in every age group, the mean number of cigarettes smoked daily at baseline was greater (Thun et al. 1997a,c).

Two major temporal trends are evident in the comparison of age-specific and smoking-specific all-cause death rates in CPS-I and CPS-II. The first trend (Figure 3.2) is that the difference in female age-specific, all-cause death rates (rate difference) between current smokers and women who had never smoked (as reported at enrollment) was much greater in CPS-II than in CPS-I at age 45 years and older. Tables 3.1 (CPS-II) and 3.2 (CPS-I) present age-specific, all-cause death rates among women for the two studies directly standardized to the age distribution of the U.S. population in 1980. The rate difference between women who were current smokers and those who had never smoked almost doubled, from 238.4 in CPS-I (Table 3.2) to 438.5 in CPS-II (Table 3.1). Similarly, the RR associated with current

Figure 3.2. All-cause death rates among women for current smokers and lifelong nonsmokers, by age, Cancer Prevention Study I (CPS-I), 1959–1965, and Cancer Prevention Study II (CPS-II), 1982–1988



Source: Thun et al. 1997a.

smoking increased from 1.3 (Table 3.2) to 1.9 (Table 3.1). These large increases during the two decades between the two ACS studies in both the rate difference and the RR for U.S. women who smoked reflect the emergence of the full effect of smoking-related deaths among women who were long-term smokers.

The second important difference between CPS-I and CPS-II is the decline in background rates of all-cause mortality in the time period between the two studies. This mortality rate difference was largely due to the decline over the past several decades in death rates for cardiovascular diseases—the leading cause of death in the United States among women and men. Table 3.2 (CPS-I) and Table 3.1 (CPS-II) show the age-adjusted, all-cause death rates among smokers and among persons who had never smoked. The all-cause death rate among women who had never smoked was approximately 50 percent lower for those in CPS-II than for those in CPS-I, but only 22 percent lower among current smokers in CPS-II than among current smokers in CPS-I. This difference largely reflects the decline in death rates for cardiovascular disease over these two decades, and the decline in cardiovascular disease death rates between the two studies was smaller among women who smoked than among women who had never smoked.

Table 3.2. All-cause mortality among women for lifelong nonsmokers and current smokers, by age, Cancer Prevention Study I, 1959–1965

Age specific

	Lifelong nonsmokers		Current smokers			
Age (years)	**Number of deaths**	**Death rate***	**Number of deaths**	**Death rate***	**Relative risk**	**Rate difference***
35–39	73	100.1	67	111.4	1.1	11.3
40–44	230	150.7	230	199.2	1.3	48.5
45–49	638	211.4	600	291.6	1.4	80.2
50–54	1,247	320.9	932	442.0	1.4	121.1
55–59	1,696	454.2	906	673.1	1.5	218.9
60–64	2,371	749.5	756	1,076.6	1.4	327.1
65–69	3,140	1,234.7	545	1,545.4	1.3	310.7
70–74	3,700	2,101.1	425	2,739.9	1.3	638.8
75–79	3,933	3,925.1	241	4,162.7	1.1	237.6
80–84	3,406	7,031.6	147	8,802.4	1.3	1,770.8
Total	20,434		4,849			

Age standardized to age distribution in 1980 U.S. population

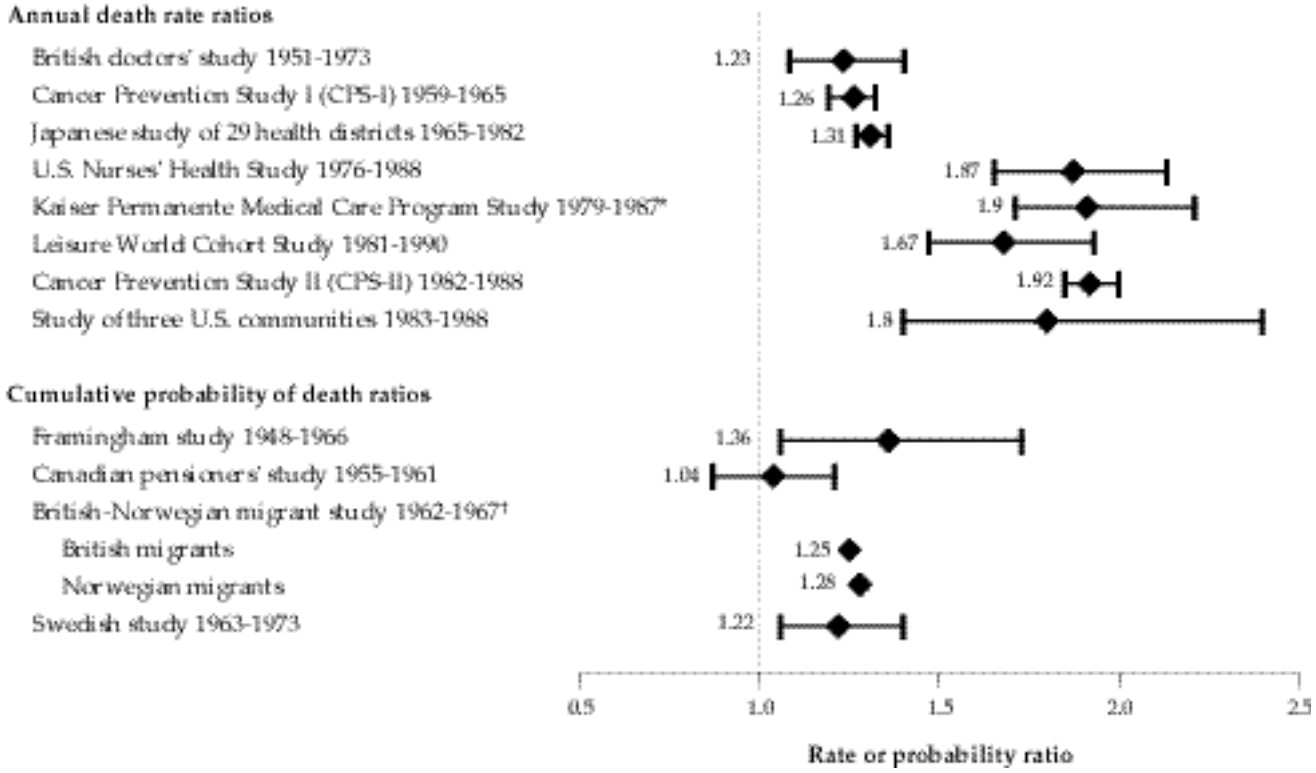
	Lifelong nonsmokers	Current smokers
Death rate*	927.6	1,166.0
95% CI†	914.2–941.0	1,107.9–1,224.1
Relative risk	1.0	1.3
95% CI	NA‡	1.2–1.3
Rate difference*	0	238.4
95% CI	NA	178.8–298.1

Note: Analyses restricted to women aged 35–84 years to maximize stability and validity of results.
*Death rate and rate of difference, for all causes, per 100,000 person-years.
†CI = Confidence interval.
‡NA= Not applicable.
Sources: Thun et al. 1997a,c.

Consistency of Temporal Trends Across Studies

Beside the results of CPS-I and CPS-II, other prospective studies since the late 1940s suggested a temporal trend of increasing RR for death from all causes among female smokers and an increasing proportion of deaths attributable to smoking (Figure 3.3). None of these cohort studies (see Appendix to this chapter) was designed specifically to assess a temporal trend in risk. Collectively, however, their results suggested that the all-cause RR associated with current smoking for women was similar across studies and that the RR increased from approximately 1.2 in the 1950s and early 1960s to a range of 1.8 to 1.9 by the 1980s. In the earlier studies, including the British doctors' study (Doll et al. 1980), a large census-based study in Japan (Hirayama 1990), and CPS-I (Thun et al. 1997a), women who smoked had usually begun to smoke regularly less than 20 years before the start of the study. In the more recent studies, including the U.S. Nurses' Health Study (Kawachi et al. 1993a), the Kaiser Permanente Medical Care Program cohort study (Friedman et al. 1997), a study of three U.S.

Figure 3.3. Age-adjusted total mortality ratios among women (and 95% confidence interval) for current smokers compared with lifelong nonsmokers, prospective studies



Note: All confidence intervals shown represent 95% except the study in Japan (90%). Age standardized to 1980 U.S. population.

*Data for white women.

†Data not available to compute 95% confidence intervals.

Sources: **British doctors' study:** Doll et al. 1980. **CPS-I and CPS-II:** Thun et al. 1995. **Japanese study of 29 health districts:** Hirayama 1990. **U.S. Nurses' Health Study:** Kawachi et al. 1993a, 1997b. **Kaiser Permanente Medical Care Program Study:** Friedman et al. 1997. **Leisure World Cohort Study:** Paganini-Hill and Hsu 1994. **Study of three U.S. communities:** LaCroix et al. 1991. **Framingham study:** Shurtleff 1974; Cupples and D'Agostino 1987; Freund et al. 1993. **Canadian pensioners' study:** Best et al. 1961; Canadian Department of National Health and Welfare 1966. **British-Norwegian migrant study:** Pearl et al. 1966; U.S. Department of Health and Human Services 1980. **Swedish study:** Cederlöf et al. 1975.

communities (LaCroix et al. 1991), and CPS-II (Thun et al. 1997a), women who reported current smoking had smoked for longer periods of time than they did in the earlier studies. In a recent cohort study, the estimated RR for death from all causes combined was slightly lower (1.7; 95 percent confidence interval [CI], 1.5 to 1.9) than in the other studies (Paganini-Hill and Hsu 1994). Participants in that study, however, were members of the Leisure World retirement community of southern California and were substantially older at the time of enrollment (median age, 73 years) than were the participants in most of the other studies.

The investigators of four studies (Canadian Department of National Health and Welfare 1966; Shurtleff 1974; Cederlöf et al. 1975; USDHHS 1980) measured the excess risk among smokers by calculating the cumulative probability of death ratio, which was defined as the probability of death among smokers divided by the probability among those who had never smoked, over a specified period (Kleinbaum et al. 1982). In studies with prolonged follow-ups and a common end point, the use of this ratio results in a slight underestimation of the RR (Rothman 1986). Thus, these studies are presented separately from the eight studies, including CPS-I and CPS-II, that reported annual death rate ratios (Figure 3.3 and Appendix to this chapter).

The findings in CPS-I, CPS-II, and the other studies generally support the observation that the risk for death from smoking among U.S. women has increased over time. Total mortality by amount smoked also has been reported based on pooled data from three prospective studies conducted in Copenhagen, with initial exams between 1964 and 1992 and follow-up until 1994 (Prescott et al. 1998a). RRs for all-cause mortality increased with amount smoked: compared with persons who had never smoked, the RR was 2.2 (95 percent CI, 2.0 to 2.5) among women who smoked less than 15 g of tobacco per day, 2.7 (95 percent CI, 2.4 to 3.1) among women who smoked 15 to 24 g per day, and 3.6 (95 percent CI, 2.9 to 4.5) among those who smoked 25 g or more per day.

Adjustment for Risk Factors Other than Smoking

Although factors such as the duration of smoking, the number of cigarettes smoked per day, and the age of the smoker strongly influence the association between smoking and all-cause mortality, other demographic and behavioral factors associated with smoking also appear to affect the risks associated with smoking.

In most studies, risk estimates were not adjusted for potential confounders other than age. However, studies in which adjustment was made for other factors found little evidence that the estimates of risk associated with smoking were substantially different after adjustment. Data from the 12-year follow-up of the U.S. Nurses' Health Study showed no real difference between the estimates of RR for death from all causes combined that were adjusted for age alone and the estimates that were adjusted for age, hypertension, cholesterol, menopausal status, postmenopausal estrogen therapy, and other factors (Kawachi et al. 1993a, 1997b) (Table 3.3).

Among women in CPS-II, values for the RR for death from all causes combined were negligibly different among current smokers aged 30 years or older

Table 3.3. Age-adjusted and multivariate relative risks (RRs) for all-cause mortality, by smoking status and number of cigarettes smoked per day, U.S. Nurses' Health Study, 1976–1988

	Lifelong nonsmokers	Former smokers	Current smokers	Number of cigarettes/day for current smokers			
				1–14	15–24	25–34	≥ 35
Number of deaths	933	799	1,115	234	480	215	153
RR*	1.0	1.3	1.9	1.4	1.99	2.1	2.6
RR†	1.0	1.3	1.9	1.5	2.0	2.1	2.6
95% CI‡		1.1–1.5	1.7–2.1	1.3–1.8	1.7–2.4	1.7–2.6	2.1–3.3

*Adjusted for age only.

†Adjusted for age; follow-up period; body mass index (weight / height^2); history of hypertension, high cholesterol, or diabetes; parental history of myocardial infarction before age 60 years; postmenopausal estrogen therapy; menopausal status; previous use of oral contraceptives; and age at start of smoking.

‡CI = Confidence interval.

Sources: Kawachi et al. 1993a, 1997b.

after adjustment for age, dietary fat and vegetable consumption, physical activity, and aspirin use (ACS, unpublished data) (Table 3.4). Small changes in the RR after multivariate adjustment (Table 3.4) would result in even smaller change in the attributable fraction among persons exposed, assuming that the estimates of RR accurately reflect a causal relationship with smoking. Adjustment for covariates decreased the attributable fraction from 50 to 47 percent of all deaths among current smokers and increased it from 23 to 29 percent among former smokers (Table 3.4). Thus, when adjusted only for age, nearly one-half of all deaths among women who currently smoked and about one-fourth of deaths in former smokers were attributable to smoking. In comparison, the percentage of deaths that would be attributable to smoking among women current smokers in the earlier period of CPS-I was only 21 percent (Table 3.2 and Figure 3.3).

Smoking Attributable Deaths Among U.S. Women

Two approaches have been used to estimate the number of deaths attributable to smoking among U.S. women and to assess how this burden has changed over time. Estimates for the U.S. Public Health Service are produced by the Centers for Disease Control and Prevention (CDC), Office on Smoking and Health, using a computer program—Smoking Attributable Mortality, Morbidity, and Economic Costs (SAMMEC 3.0), which incorporates an epidemiologic measure of risk known as the population attributable risk (USDHHS 1997). These estimates for women take three factors into account: (1) the prevalence of current and former smoking among U.S. women in a particular year, (2) the RR estimates among women in CPS-II during the initial four years of follow-up for selected conditions having a firmly established relationship to smoking, and (3) the total number of deaths coded to these conditions among U.S. women. The SAMMEC estimate has increased from 30,000 in 1965 to 106,000 in 1985 (USDHHS 1989b) and to 152,000 annually during 1990–1994 (CDC 1997). For 1995–1997, the annual SAMMEC estimates for U.S. women averaged 163,000 (CDC, unpublished data). On the basis of recent trends in these estimates, it can be projected that SAMMEC estimates among U.S. women during the years 1998–2000 will average about 170,000 (CDC, unpublished data). Thus, since the last report on the health consequences of smoking among women in 1980, it can be estimated that approximately 3 million deaths among U.S. women have been attributable to smoking (CDC, unpublished data).

An alternate technique was developed by Peto and associates (1994) to provide estimates of deaths from smoking in developed countries, even where reliable data on smoking prevalence are not available. By using the national death rate for lung cancer to index past smoking habits, Peto and associates estimated that smoking caused approximately 14,100 deaths among U.S. women in 1965 and 131,000 in 1985. Although not expected to be exact, the estimates of smoking attributable mortality generated for different countries by use of this method showed that women in the United States and the United Kingdom who have smoked longer than women in other countries are at the forefront of the emerging global epidemic of deaths from tobacco smoking (Peto et al. 1994).

Years of Potential Life Lost

Another measure of the impact of smoking on survival is years of potential life lost (YPLL). Although less commonly used, YPLL takes into account the age at which people die, as well as the total number of deaths. Using the SAMMEC software program

Table 3.4. Relative risks among women for death from all causes, and smoking attributable fraction of deaths among smokers (AF_{exp}), with adjustment for age and multiple potential risk factors, Cancer Prevention Study II, 1982–1988

		Current smokers (n = 6,416)		Former smokers (n = 4,812)	
Adjustment for:	Lifelong nonsmokers (n = 15,929)	Relative risk (95% CI)*	AF_{exp} (%)	Relative risk (95% CI)	AF_{exp} (%)
Age	1.0	2.0 (2.0–2.1)	50	1.3 (1.3–1.4)	23
Multiple risk factors†	1.0	1.9 (1.9–2.0)	47	1.4 (1.3–1.4)	29

*CI = Confidence interval.
†Age, dietary fat and vegetable consumption, physical activity, and aspirin use.
Source: American Cancer Society, unpublished data.

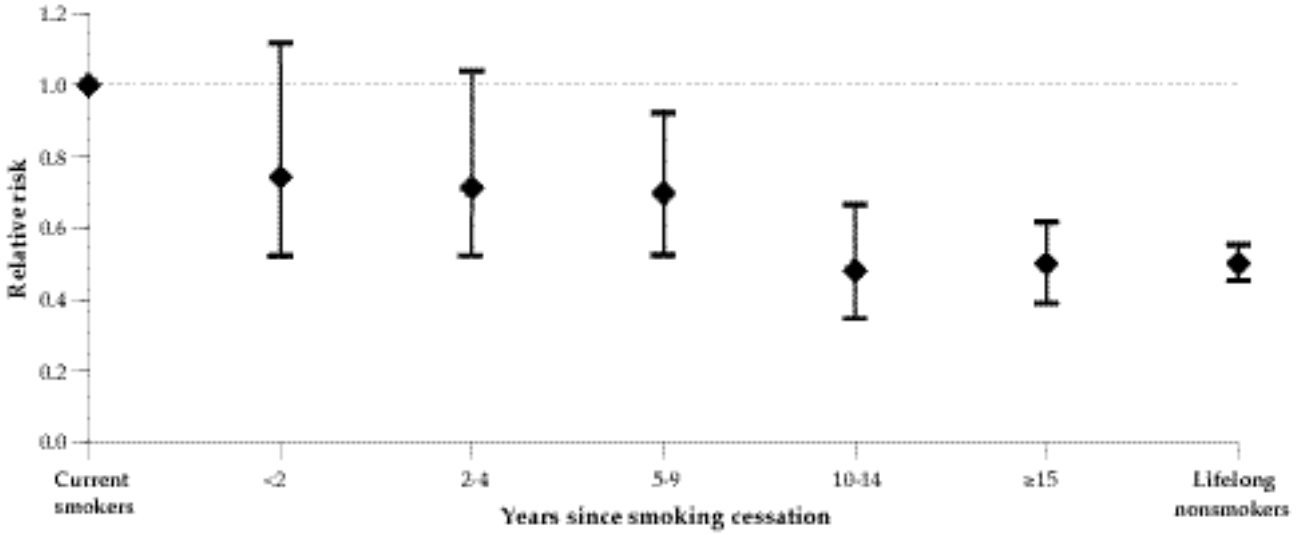
(USDHHS 1997), CDC's Office on Smoking and Health estimated YPLL from smoking among U.S. women each year during 1990–1994 on the basis of disease-specific RRs among women smokers from CPS-II for 1982–1986, mortality data among U.S. women for 1990, and prevalence of current and former women smokers in the United States in 1990–1994 (CDC 1997). Based on survival to life expectancy, the average annual YPLL due to smoking-related deaths from neoplastic, cardiovascular, respiratory, and pediatric diseases was 2,148,000, or about 14 years for each smoking attributable death (CDC, unpublished data). This estimate did not include YPLL due to exposure to ETS. Other investigators estimated that U.S. white women who were current smokers had a life expectancy in 1986 that was three to seven years less than that of women the same age who had never smoked (Rogers and Powell-Griner 1991). A multisite, population-based, prospective study of persons aged 65 years or older found that even when level of physical activity was controlled for, women who had ever smoked lived an average of four to five years less than women who had never smoked (Ferrucci et al. 1999). On the basis of these YPLL estimates and the estimated number of deaths among U.S. women attributable to smoking, it can be estimated that since the last report on the health consequences of smoking among women in 1980, from 9 to 41 million years of potential life have been lost by U.S. women because of smoking (CDC, unpublished data).

Effects of Smoking Cessation

Several studies examined the reduction in all-cause death rates among women that is related to smoking cessation (USDHHS 1990). In the U.S. Nurses' Health Study, to better estimate the effect of cessation, women with nonfatal coronary heart disease, stroke, or cancer (except nonmelanoma skin cancer) were excluded at baseline and at the beginning of each 2-year follow-up period. The RR for death from all causes combined during the 12-year follow-up was 1.15 (95 percent CI, 1.01 to 1.29) among women who had stopped smoking (Kawachi et al. 1993a, 1997b). This RR was substantially lower than that of 2.04 (95 percent CI, 1.85 to 2.27) among women who continued to smoke (Kawachi et al. 1993a, 1997b). The RR among former smokers decreased progressively with time since smoking cessation; 10 through 14 years after smoking cessation, the RR approached the risk among those who had never smoked (Figure 3.4).

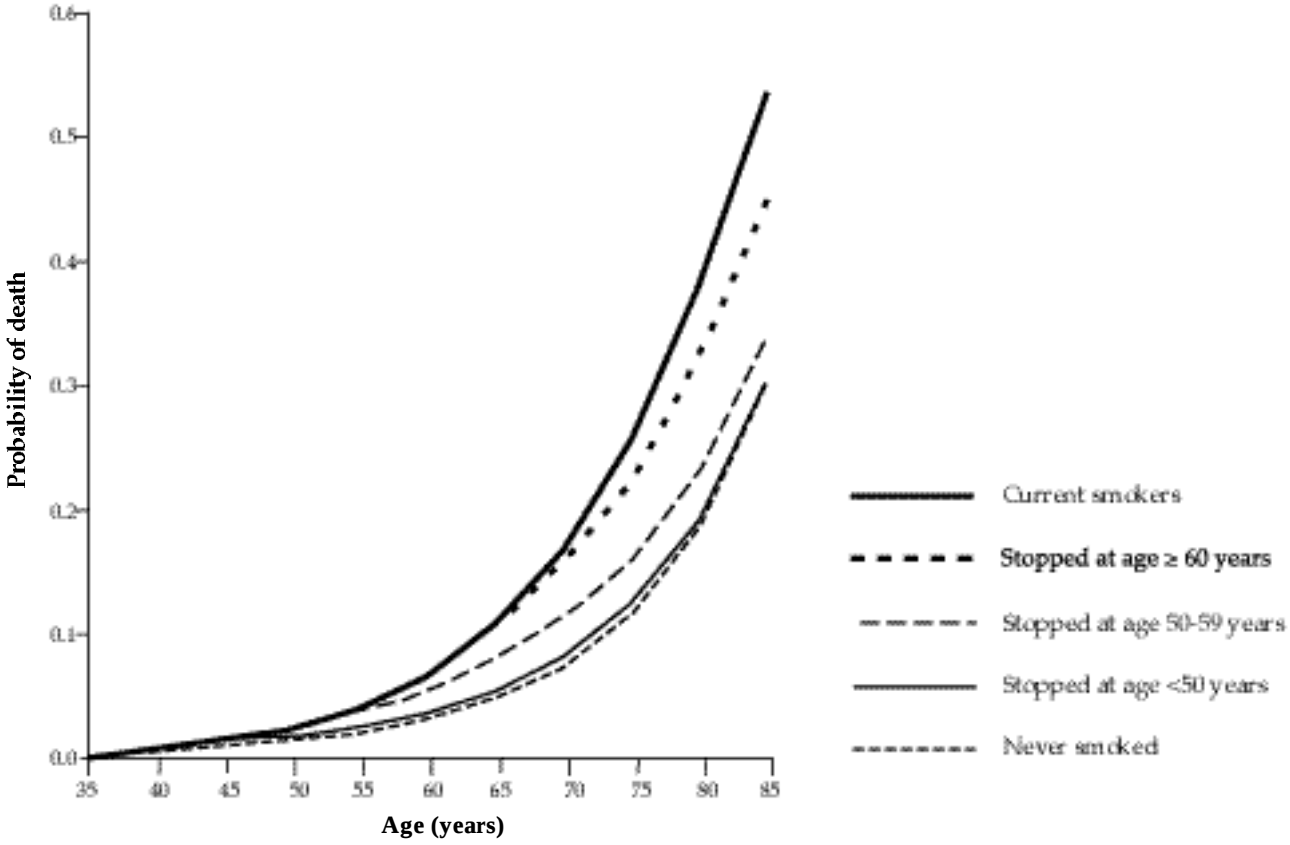
An alternate method of expressing the benefits of smoking cessation is to present the absolute risk for death at various ages during follow-up by grouping

Figure 3.4. Relative risks of death from all causes (and 95% confidence interval) for current smokers compared with lifelong nonsmokers, by years since smoking cessation, U.S. Nurses' Health Study, 1976–1988



Note: Multivariate relative risks were adjusted for age, follow-up period, body mass index, history of hypertension, diabetes, high cholesterol level, postmenopausal estrogen therapy, menopausal status, previous use of oral contraceptives, parental history of myocardial infarction before age 60 years, and daily number of cigarettes smoked during the period prior to smoking cessation. Persons with nonfatal coronary heart disease, stroke, and cancer (except nonmelanoma skin cancer) were excluded at baseline and at the beginning of each two-year follow-up period.
Source: Kawachi et al. 1997b.

Figure 3.5. Cumulative probability of death from all causes among women who stopped smoking, by smoking status and age at smoking cessation, Cancer Prevention Study II, 1984–1991



Note: Study excludes data from first 2 years of follow-up; persons with a history of cancer, heart disease, or stroke at enrollment; and those who stopped smoking <2 years before entering study.
Source: American Cancer Society, unpublished data.

women according to age at cessation of smoking. Figure 3.5 shows the cumulative probability that a woman in CPS-II would die during follow-up in 1984–1991 according to smoking status at study entry and, for former smokers, according to age at the time of smoking cessation (ACS, unpublished data). To minimize bias from smoking cessation due to illness, this analysis excluded data from the first two years of follow-up; persons with a history of cancer, heart disease, or stroke at study entry; and persons who had stopped smoking less than two years before enrollment. During the seven-year period, women who were current smokers at baseline had the highest cumulative probability of death during follow-up; those who had stopped smoking, particularly at younger ages, had intermediate risk; and those who had never smoked had the lowest risk. The risk among women who had stopped smoking before age 50 years was only slightly higher than that among women who had never smoked and, over time, the risk became indistinguishable from that among those who had never smoked. However, it should be stressed that the probabilities shown in Figure 3.5 are underestimates of the true cumulative risk for death at any age in the general population because the calculations are based on data from a cohort that included only women who survived and could therefore enter the study and excluded women with cancer, heart disease, or stroke at the time of enrollment, thereby making the study population healthier than the general U.S. population. Nevertheless, Figure 3.5 illustrates the substantial benefits of smoking cessation, the additional benefit for women who stop smoking at a younger age, and the optimal situation of never having started to smoke.

Conclusions

1. Cigarette smoking plays a major role in the mortality of U.S. women.
2. The excess risk for death from all causes among current smokers compared with persons who have never smoked increases with both the number of years of smoking and the number of cigarettes smoked per day.
3. Among women who smoke, the percentage of deaths attributable to smoking has increased over the past several decades, largely because of increases in the quantity of cigarettes smoked and the duration of smoking.
4. Cohort studies with follow-up data analyzed in the 1980s show that the annual risk for death from all causes is 80 to 90 percent greater among women who smoke cigarettes than among women who have never smoked. A woman's annual risk for death more than doubles among continuing smokers compared with persons who have never smoked in every age group from 45 through 74 years.
5. In 1997, approximately 165,000 U.S. women died prematurely from a smoking-related disease. Since 1980, approximately three million U.S. women have died prematurely from a smoking-related disease.
6. U.S. females lost an estimated 2.1 million years of life each year during the 1990s as a result of smoking-related deaths due to neoplastic, cardiovascular, respiratory, and pediatric diseases as well as from burns caused by cigarettes. For every smoking attributable death, an average of 14 years of life was lost.
7. Women who stop smoking greatly reduce their risk for dying prematurely. The relative benefits of smoking cessation are greater when women stop smoking at younger ages, but smoking cessation is beneficial at all ages.

Cancer

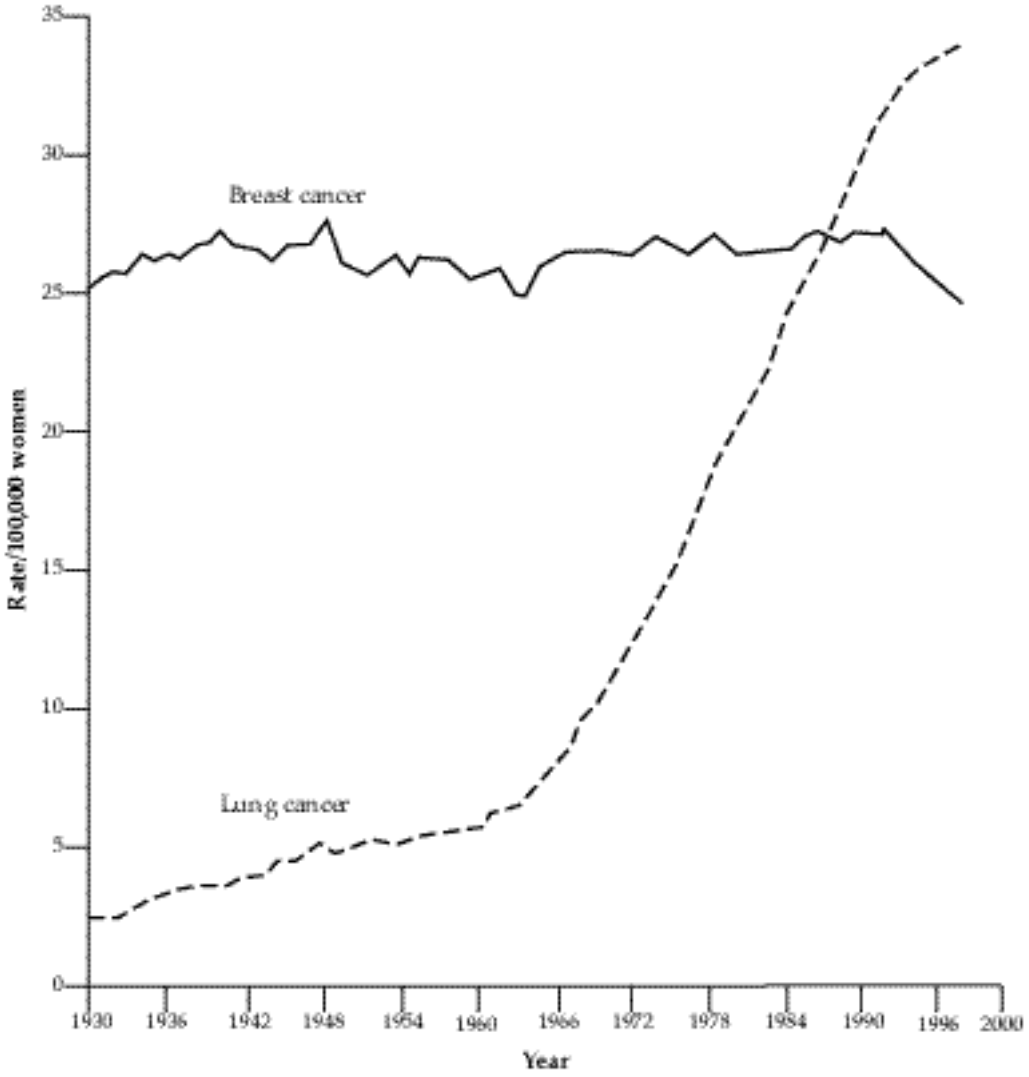
Lung Cancer

When the report to the Surgeon General on smoking and health was published in 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), lung cancer mortality among women was low (approximately 7 deaths per 100,000 women). The 1964 report concluded that evidence suggested a causal association between smoking and lung cancer among women but did not conclude that smoking was a cause of lung cancer among women. Subsequent reports of the Surgeon General reviewed data published after 1964, including both cohort and case-control studies of lung cancer among women, and strongly affirmed a causal relationship (USDHHS 1980, 1982, 1989b, 1990) between smoking and lung cancer among women.

Women started smoking in the 1930s and 1940s, about 20 to 30 years later than men. Thus, the sharp rise in lung cancer mortality that was so apparent among men before 1964 (from 5 deaths per 100,000 in 1930 to 45 deaths per 100,000 in 1964) did not occur until the 1970s among women (USDHHS 1989b). By 1980, when the first Surgeon General's report on women and smoking was released, lung cancer had become the second-leading cause of cancer deaths among women (USDHHS 1980). The lung cancer death rate among white women rose by over 600 percent from 1950 through 1997. This rise was equivalent to an average annual increase of 5.3 percent (Ries et al. 2000). During the 1973–1997 period, the lung cancer death rate among women increased 149 percent, but only 6.5 percent among men (Ries et al. 2000). In 1987, lung cancer surpassed breast cancer as the leading cause of cancer death among women (Figure 3.6), and in 2000, lung cancer accounted for an estimated 1 of every 4 cancer deaths and nearly 1 of every 8 newly diagnosed cancers among women (Greenlee et al. 2000). The estimates for 2000 also indicated that about 74,600 new cases of lung cancer would be diagnosed and that 67,600 deaths from the disease would occur among women (Greenlee et al. 2000).

Lung cancer incidence among women increased by 127 percent from 1973, when ongoing collection of population-based cancer incidence data by the National Cancer Institute (NCI) began, through 1997, when the annual age-adjusted incidence was 43.1 cases

Figure 3.6. Age-adjusted death rates for lung cancer and breast cancer among women, United States, 1930–1997

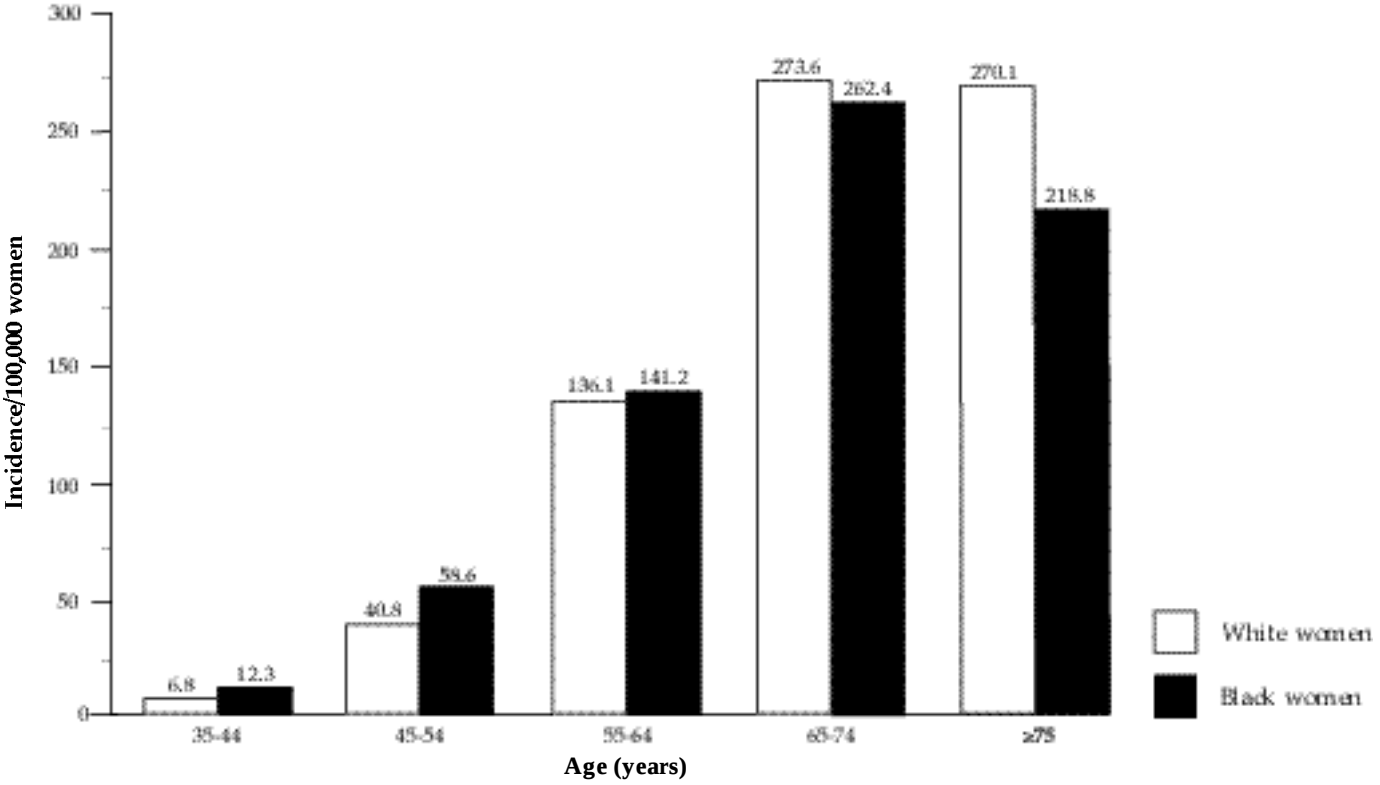


Note: Death rates are age-adjusted to the 1970 population.
Sources: Parker et al. 1996; National Center for Health Statistics 1999; Ries et al. 2000; American Cancer Society, unpublished data.

per 100,000 women (Ries et al. 2000). In recent years, the rate of increase has slowed—from 9.1 percent per year for 1973–1976 to 0.0 percent per year for 1991–1997. Incidence rates among women may have peaked in the 1990s (Wingo et al. 1999; Ries et al. 2000). Rates among women aged 40 through 49 years and among women aged 50 through 59 years reached a peak in the mid-1970s and late 1980s, respectively, whereas rates remained stable among women aged 60 through 69 years (Wingo et al. 1999). The overall age-adjusted incidence among men has declined steadily since 1987 (Ries et al. 2000). By 1997, the male-to-female ratio for incidence of lung cancer was 1.6:1, a change from 3:1 in 1980. In 1995–1997, the lifetime risk for developing lung cancer was 1 in 17.3 among women.

The overall incidence of lung cancer among black women resembles that among white women. In 1997, the age-adjusted incidence per 100,000 women was 42.6 among blacks and 45.0 among whites (Ries et al. 2000). In contrast, the incidence among black men was more than 50 percent higher than that among white men. In 1996–1997, lung cancer incidence rates

Figure 3.7. Lung cancer incidence rates among white women and black women, Surveillance, Epidemiology, and End Results (SEER) Program, 1996–1997



Source: Ries et al. 2000.

among women younger than age 65 years were higher among blacks than among whites (Figure 3.7). This finding suggested that differences between incidence among black women and white women may increase in the future.

In the United States, the incidence rate for 1990–1997 among Hispanic white women (20.3 per 100,000 women) was one-half that among non-Hispanic white women (45.9) (Ries et al. 2000). The rate among Asian or Pacific Islander women (22.5 per 100,000 women) was also lower than that among white women. Variation exists among subgroups of Asian women. Based on data for 1988–1992, rates were lowest among Japanese women and highest among Vietnamese women: 15.2 per 100,000 among Japanese, 16.0 among Korean, 17.5 among Filipino, 25.3 among Chinese, and 31.2 among Vietnamese women (NCI 1996b). Hawaiian women, however, developed lung cancer at approximately the same rate as did white women (43.1) (NCI 1996b). Incidence rates from California for 1991–1995 were comparable among non-Hispanic black women (48.2) and non-Hispanic white women (50.4), whereas rates among Hispanic women (19.7) and Asian women (21.7) were about 50 percent lower (Perkins et al. 1998). These differences in the incidence rate of lung cancer are likely the result of lower rates of cigarette smoking among Hispanic women and Asian women.

Because of the poor survival associated with lung cancer, mortality parallels incidence for all age and ethnic groups. The 5-year relative survival rates among black women and white women diagnosed with lung cancer in 1989–1996 were 13.5 and 16.6 percent, respectively (Ries et al. 2000). Survival was higher among women with localized disease (52.5 percent), but only 16 percent of cases among women were diagnosed at this early stage. Survival rates declined with age at diagnosis and advanced stage of disease but were higher among women than among men at all ages and stages and for all cell types. Survival rates have changed little in the past 20 years (Ries et al. 2000).

Table 3.5. Relative risks of death from lung cancer for women and men, by quantity smoked, major prospective studies

	Women		Men	
Study	**Smoking status**	**Relative risk**	**Smoking status**	**Relative risk**
British doctors' study	Nonsmokers	1.0	Nonsmokers	1.0
1951–1973	Current smokers	5.0	Current smokers	14.0
	1–14 cigarettes / day	1.3	1–14 cigarettes / day	7.8
	15–24 cigarettes / day	6.4	15–24 cigarettes / day	12.7
	≥ 25 cigarettes / day	29.7	≥ 25 cigarettes / day	25.1
Cancer Prevention	Never smoked	1.0	Never smoked	1.0
Study I (CPS-I)	Current smokers	3.6	Current smokers	8.5
1959–1972	1–9 cigarettes / day	1.3	1–9 cigarettes / day	4.6
	10–19 cigarettes / day	2.4	10–19 cigarettes / day	8.6
	20–39 cigarettes / day	4.9	20–39 cigarettes / day	14.7
	≥ 40 cigarettes / day	7.5	≥ 40 cigarettes / day	18.7
Swedish study	Nonsmokers	1.0	Nonsmokers	1.0
1963–1979	Current smokers	4.5	Current smokers	7.0
	1–7 cigarettes / day	1.8	1–7 cigarettes / day	2.3
	8–15 cigarettes / day	11.3	8–15 cigarettes / day	8.8
			≥ 16 cigarettes / day	13.7
Japanese study of	Nonsmokers	1.0	Nonsmokers	1.0
29 health districts	Current smokers	2.0	Current smokers	3.8
1966–1982	<20 cigarettes / day	1.9	<20 cigarettes / day	3.5
	20–29 cigarettes / day	4.2	20–39 cigarettes / day	5.7
			≥ 40 cigarettes / day	6.5
Kaiser Permanente	Nonsmokers	1.0	Nonsmokers	1.0
Medical Care	Current smokers	15.1	Current smokers	8.1
Program Study	1–19 cigarettes / day	8.5	1–19 cigarettes / day	4.7
1979–1987	≥ 20 cigarettes / day	21.7	≥ 20 cigarettes / day	10.4
Cancer Prevention	Never smoked	1.0	Never smoked	1.0
Study II (CPS-II)	Former smokers	4.7	Former smokers	9.4
1982–1988	Current smokers	11.9	Current smokers	20.3
	1–9 cigarettes / day	3.9	1–9 cigarettes / day	12.2
	10–19 cigarettes / day	8.3	10–19 cigarettes / day	14.6
	20 cigarettes / day	14.2	20 cigarettes / day	21.7
	21–39 cigarettes / day	21.4	21–39 cigarettes / day	22.8
	40 cigarettes / day	19.3	40 cigarettes / day	24.2
	≥ 41 cigarettes / day	18.2	≥ 41 cigarettes / day	45.7

Sources: U.S. Department of Health and Human Services 1982 for British doctors' study, CPS-I, Swedish study, and Japanese study of 29 health districts; Friedman et al. 1997 for Kaiser Permanente Medical Care Program Study; Thun et al. 1997a for CPS-II.

Smoking-Associated Risks

Evidence from Cohort Studies

Six prospective studies, which included more than one million women from four countries, provided data on smoking and risk for lung cancer among women. Many of the results from these studies were described previously (USDHHS 1982, 1989b). All showed significantly higher lung cancer mortality among smokers than among nonsmokers (Table 3.5). Together with case-control studies, these studies demonstrated that lung cancer mortality among

Table 3.6. Age-adjusted death rates, relative risks, and rate differences for lung cancer, among women and men who were current smokers and never smokers, Cancer Prevention Study I (CPS-I), 1959–1965, and Cancer Prevention Study II (CPS-II), 1982–1988

	CPS–I		CPS-II	
	Women	**Men**	**Women**	**Men**
Death rate*				
Never smoked	9.6	15.7	12.0	14.7
Current smokers	26.1	187.1	154.6	341.3
Relative risk (95% CI)†	2.7 (2.1–3.5)	11.9 (9.5–14.9)	12.8 (11.3–14.7)	23.2 (19.3–27.9)
Rate difference (95% CI)	16.5 (11–22)	171.4 (157–186)	142.6 (132–153)	326.6 (309–344)

*Per 100,000 person-years.
†CI = Confidence interval.
Source: Thun et al. 1997a.

women increases with increasing exposure to cigarette smoking, as measured by the number of cigarettes smoked daily, duration of smoking, depth of inhalation, age at smoking initiation, and tar content of the cigarettes smoked (USDHHS 1980, 1982, 1989b). The lower RRs observed among women than among men reflect differences in smoking habits across birth cohorts. Historically, women adopted the smoking habit at a later age than did men, smoked fewer cigarettes per day for fewer years, were less likely to inhale deeply, and were more likely to smoke filter-tipped or low-tar cigarettes (USDHHS 1980).

CPS-I, which was begun in 1959, and CPS-II, which was begun in 1982, enabled examination of changes over time in smoking-associated risk for death from lung cancer. Data from CPS-I and CPS-II confirmed that the epidemic of lung cancer among women was confined largely to smokers. The age-adjusted lung cancer death rate among women who had never smoked was about the same during the two study periods, but among current smokers, it increased nearly sixfold (Table 3.6). In CPS-I, lung cancer mortality was 2 to 3 times higher among women smokers than among women who had never smoked; 20 years later, in CPS-II, mortality was more than 12 times higher. (During this same period, the rate among men increased by a factor of 2.) Women in CPS-II began smoking earlier in life, smoked for more years, and reported inhaling moderately or deeply more often than did women in CPS-I. These findings probably largely explain the higher RR among smokers in CPS-II than in CPS-I, the corresponding greater differences in absolute risk among women smokers and nonsmokers, and the narrowing of the gender gap for these measures over time (Thun et al. 1997a) (Table 3.6).

The risk for lung cancer mortality increases with the number of cigarettes smoked (USDHHS 1989b) (Table 3.5). In CPS-II, the RR for lung cancer death increased from 3.9 among women who smoked 1 to 9 cigarettes per day to 21.4 among women who smoked one to two packs of cigarettes (21 to 39 cigarettes) per day (Thun et al. 1997a). Analyses from a cohort study of subscribers of a large health maintenance organization (HMO) (Kaiser Permanente Medical Health Care Program Study) also showed a RR of 21.7 among women who smoked 20 or more cigarettes per day (Table 3.5). The risk increased 12.0 times among women who smoked for 20 to 39 years and 27.5 times for women who smoked 40 or more years (data not shown) (Friedman et al. 1997).

The age-adjusted RR among current smokers and among persons who had never smoked varies with race and ethnicity. The RR was lower among Asian women (3.2) than among black women (23.5) or white women (18.6) in an HMO cohort study (Friedman et al. 1997). These differences may reflect racial or ethnic differences in dose, duration, and intensity of smoking (Shopland 1995). Cohort studies have not included enough minority women to allow comparison of the dose-response effect of smoking and lung cancer among racial and ethnic groups.

In CPS-II, RRs decreased after cessation of cigarette smoking. The RR for death from lung cancer among women former smokers was about 50 percent lower than that among women current smokers, but it

was still higher than that among women who had never smoked (Table 3.5). The RR for lung cancer in both the HMO study and CPS-II decreased with increased duration of smoking cessation (Table 3.7). CPS-II data showed marked reductions in RR within 3 to 5 years after smoking cessation, especially among lighter smokers. However, lung cancer mortality remained higher among women former smokers than among those who had never smoked, even after more than 15 years of smoking cessation (USDHHS 1990).

Evidence from Case-Control Studies

More than 20 case-control studies of smoking and lung cancer that included women have been reviewed (USDHEW 1971, 1979; USDHHS 1982). Table 3.8 presents estimated RRs from 11 studies reported during 1985–1993 from the United States, Canada, and northern Europe. Each of these studies included approximately 100 or more cases of lung cancer among women. Consistent with findings in cohort studies and temporal trends in women's smoking, results of case-control investigations showed an increase in smoking-associated risk for lung cancer during the 1950s through 1970s (USDHHS 1982). A steep upward gradient in risk with the number of cigarettes smoked per day was reported from almost all case-control studies of smoking and lung cancer among women conducted during the 1980s (USDHHS 1989b). The estimated risk for lung cancer among women who smoked 20 or more cigarettes per day relative to nonsmokers (10- to 20-fold excess risk) was remarkably consistent in both hospital- and population-based studies in Europe and North America.

Lung cancer risk increased with the number of years of smoking, and this increase was independent of the number of cigarettes smoked per day (Schoenberg et al. 1989; Osann 1991). The RRs were 2 to 3 among women who smoked for shorter durations (<20 years [Osann 1991], <20 pack-years [pack-years is the number of packs of cigarettes smoked per day multiplied by the number of years of cigarette smoking] [Sellers et al. 1991], or <35 years and <20 cigarettes per day [Schoenberg et al. 1989]) and 8 to 24 among those who smoked for longer durations. The risk for lung cancer was two to four times higher among women who inhaled tobacco smoke frequently and deeply than among those who did not inhale (Potter et al. 1985; Osann 1991) (data not shown).

Age at initiation of smoking is closely associated with the number of years of smoking. Because women who smoked for the longest duration usually began to smoke at younger ages, it is difficult to separate the independent effect of each factor related to lung cancer risk (Thun et al. 1997c). Although a

Table 3.7. Age-adjusted relative risks for lung cancer associated with smoking status and smoking cessation among women, cohort studies

Study	Smoking status	Number of years of cessation	Relative risk	
Kaiser Permanente Medical Care Program Study 1979–1987	Never smoked	NA*	1.0	
	Former smokers	2–10	8.4	
		11–20	3.8	
		>20	4.4	
Cancer Prevention Study II 1982–1988	Never smoked	NA	1.0	
			Number of cigarettes / day	
			1–19	≥ 20
	Former smokers	<1	7.9	34.3
		1–2	9.1	19.5
		3–5	2.9	14.6
		6–10	1.0	9.1
		11–15	1.5	5.9
		≥ 16	1.4	2.6

*NA= Not applicable.
Sources: U.S. Department of Health and Human Services 1990; Friedman et al. 1997.

Table 3.8. Relative risks for lung cancer among women smokers compared with nonsmokers, by smoking status and quantity smoked, case-control studies

Study	Number of cases/controls	Source	Relative risk (95% confidence interval) by smoking status			Relative risk (95% confidence interval) by quantity/duration of smoking		
			Ever smoked	Current smokers	Former smokers			
Humble et al. 1985	173 / 272	Registry	—*	—	6.5 (2.8–15.4)	<20 cigarettes / day ≥ 20 cigarettes / day	19.2 16.0	(6.5–60.8) (6.7–36.3)
Benhamou et al. 1987	96† / 192	Hospital	6.6 (3.0–14.4)	—	—	<10 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.2‡ 2.9 20.0	 (1.2–7.2) (6.0–66.9)
Schoenberg et al. 1989	994 / 995	Population	8.5 (6.7–10.8)	—	—	<20 cigarettes / day <35 years ≥ 35 years ≥ 20 cigarettes / day <35 years ≥ 35 years	 3.2 8.4 6.5 16.0	 (2.3–4.4) (6.2–11.2) (4.5–9.4) (11.9–21.7)
Svensson et al. 1989	210 / 209	Population	6.4 (4.0–10.5)	—	2.6 (1.4–5.1)	<10 cigarettes / day 11–20 cigarettes / day ≥ 20 cigarettes / day	4.6 12.6 59.0	(2.5–9.3) (6.5–25.2) (7.6–)§
Katsouyanni et al. 1991	101 / 89	Hospital	—	3.4 (1.8–6.6)	—	≥ 30 cigarettes / day	7.5	(2.4–23.2)
Osann 1991	217 / 217	Registry	6.7 (3.7–12.0)	9.1 (4.8–17.3)	2.5 (1.1–5.9)	<20 cigarettes / day ≥ 20 cigarettes / day ≤ 20 years >20 years	2.5 12.6 1.6 11.6	(1.2–5.2) (6.2–25.6) (0.7–3.5) (5.8–23.3)
Sellers et al. 1991	152 / 1,900	Registry	—	18.3 (11.1–30.3)	5.3 (3.7–11.2)	0–19 pack-years 20-39 pack-years ≥ 40 pack-years	3.4 12.7 23.9	(1.7–6.8) (7.3–21.9) (14.1–40.1)
Brownson et al. 1992b	5,212 / >10,000Δ	Registry	12.7 (11.5–13.9)	13.6 (12.3–15.1)	11.6 (10.4–13.0)	<20 cigarettes / day ≥ 20 cigarettes / day	8.4 17.1	(7.2–9.7) (15.3–19.1)
Hegmann et al. 1993	100 / 1,087	Registry	—	—	—	Age at smoking initiation ≤ 25 years >25 years	 26.8 4.8	 (15.4–46.8) (1.0–22.1)
Osann et al. 1993	833 / 1,656	Registry	15.0 (11.8–19.1)	19.6 (15.2–25.2)	8.1 (6.0–11.0)	<40 cigarettes / day ≥ 40 cigarettes / day	14.4 40.9	(11.0–18.9) (29.3–57.1)
Risch et al. 1993	442 / 410	Registry	9.2 (5.95–15.1)	16.8 (9.9–30.6)	8.0¶ (4.3–15.9)	<30 pack-years 30–59 pack-years ≥ 60 pack-years	7.3 26.7 81.9	(4.1–13.0) (14.0–50.6) (25.2–267)

*Dash = Data not available.
†Kreyberg I cases (squamous cell, small cell, and large cell carcinoma).
‡Not statistically significant.
§Upper confidence limit is not provided because of the small numbers in this category.
ΔThe exact number of controls is not specified, but authors state that the ratio of controls to cases was approximately 2.5.
¶Former smokers who had stopped smoking 2–10 years previously.

significant increase in risk with early age at smoking initiation was noted in one study of women (Hegmann et al. 1993), other studies showed no such increase after adjustment for duration of smoking (Svensson et al. 1989; Benhamou and Benhamou 1994). A differential effect for age at initiation, independent of the quantity of cigarettes smoked and the duration of smoking, would imply that the lung is more susceptible to the carcinogenic effects of cigarette smoke at a younger age.

Data from case-control studies generally support the association between tar level of cigarettes and lung cancer risk observed in some cohort studies (Stellman and Garfinkel 1986; Garfinkel and Stellman 1988; Sidney et al. 1993; Stellman et al. 1997). Women who smoked nonfiltered cigarettes had higher risk than did women who smoked filter-tipped brands (Pathak et al. 1986; Wynder and Kabat 1988; Lubin et al. 1984; Stellman et al. 1997). Several researchers attempted to account for variation in tar yield over time and by brand of cigarettes. Kaufman and colleagues (1989) examined dose-response relationships by using the average tar content of cigarettes smoked over a specified period. Zang and Wynder (1992) constructed an index of cumulative tar exposure. Both methods showed an increase in lung cancer risk among women with increased exposure to tar. Limitations of studies of tar exposure include use of surrogate measures for tar in some studies (e.g., presence or absence of a filter), use of a machine-derived tar yield of specific brands at a certain time or during a short interval, and failure to account for compensatory changes in smoking habits (e.g., increased depth of inhalation or number of puffs). Underestimation of actual exposure to tar levels in human-based or machine-derived results of Federal Trade Commission (FTC) testing methods to date has long been a concern (National Cancer Institute 1996a; Djordjevic et al. 2000).

Few case-control studies reported data on variation in smoking-associated risk by race or ethnicity. In a hospital-based study, the odds for lung cancer were higher among black women than among white women at each level of tar exposure (Harris et al. 1993). Although RRs were generally higher among black women across all histologic types of lung cancer, the differences were greater for the types most strongly associated with smoking. Humble and coworkers (1985) found no significant differences between non-Hispanic white women and Hispanic women in dose-response relationships. A case-control study examined risk for lung cancer by race and ethnicity among women in Hawaii who had ever smoked (Le Marchand et al. 1992). Relative to Japanese women, RRs were higher among Hawaiian (1.7), Caucasian (2.7), and Filipino (3.7) women and lower among Chinese women (0.4), after adjustment for pack-years of smoking and age. However, these results were not statistically significant. Differences across ethnic groups in the reporting of smoking habits or the intensity of smoking may be responsible for some of the observed differences in lung cancer risk.

Case-control studies of lung cancer risk among women former smokers were described previously (USDHHS 1990). Retrospective investigations reported since 1985 all showed lower risk among former smokers than among current smokers (Table 3.8). Risk declined within 5 years of smoking cessation, varied with the level of previous exposure, but remained higher than the risk among those who had never smoked, even after 20 years of abstinence. The rate of decline in risk with years of abstinence is not well characterized because of the small number of former smokers, particularly long-term former smokers, in most case-control studies.

Differences by Gender

Although the RR for death from lung cancer among women current smokers increased over time (Thun et al. 1997a), all but one of the six major cohort studies (Table 3.5) showed lower RRs among women than among men (Kaiser Permanente Medical Care Program Study). The difference is believed to result from the time lag in smoking initiation among women and thus the lower cumulative exposure to smoking among birth cohorts of women (Burns et al. 1997b). In CPS-I, the RRs among women smokers were approximately one-fifth as high as those among men (Thun et al. 1997a). Among women smokers in CPS-II, death rates and RRs were about one-half those among men smokers in CPS-II and were equal to those among men 20 years earlier in CPS-I (Thun et al. 1997a). Differences in RR may be due to differences between women and men in duration and intensity of smoking within each age- and quantity-specific stratum or to residual confounding within these large strata (Thun et al. 1997c). Cohort studies generally have not been large enough to allow comparison of RR for subgroups of women and men of exactly comparable age and smoking exposure. However, within categories defined by age, number of cigarettes smoked, and duration of smoking in years that were examined using CPS-II data, men generally had higher lung cancer death rates than did women (Thun et al. 1997a) and the rate ratios associated with smoking

were generally higher among men than among women (Thun et al. 1997b). A pooled analysis of data from three prospective population-based studies conducted in the area of Copenhagen, Denmark (13,444 women and 17,430 men), examined risk for lung cancer by pack-years of smoking and gender. After adjustment for pack-years of smoking, the ratio of female to male smokers' RRs for developing lung cancer was 0.8 (95 percent CI, 0.3 to 2.1) (Prescott et al. 1998b). On the other hand, results from the HMO study found that risk was higher among female heavy smokers than among male heavy smokers in every age group (Friedman et al. 1997).

Some case-control studies have found RRs among women that were nearly equal to (Schoenberg et al. 1989; Osann et al. 1993) or higher than those among men (Brownson et al. 1992b; Risch et al. 1993; Zang and Wynder 1996). A lower baseline risk for lung cancer or higher cigarette consumption among women smokers could explain the higher RR associated with ever smoking cigarettes among women (Hoover 1994; Wilcox 1994). In cohort studies, however, the death rates for lung cancer have been similar among women and men who had never smoked (Burns et al. 1997a; Thun et al. 1997a), and U.S. national survey data showed that the proportion of heavy smokers has consistently been higher over the years among men, not women (see Chapter 2). Several possible reasons may explain the higher smoking-associated RRs for lung cancer among women than among men reported from some case-control studies. The smoking patterns of women and men may differ in ways that have not been entirely accounted for in the study design and analysis. Women may underreport daily consumption of cigarettes and may, therefore, appear to have a higher risk than men for a given quantity smoked. Because smoking prevalence has always been higher among men than women (even though the gender gap has narrowed over time), women who smoke may also be more likely than men to be exposed to spousal smoking, which is itself associated with an increased risk for lung cancer (see "Environmental Tobacco Smoke" later in this chapter). Even when women smoke the same number of cigarettes as men do, exposure to cigarette smoke may be greater among women than among men because of differences in puff volume, puff frequency, or depth of inhalation. Alternately, women may be more biologically susceptible to the effects of cigarette smoke (Risch et al. 1993). McDuffie and colleagues (1991) observed that women with lung cancer developed disease at a younger age than did men and had a similar level of pulmonary dysfunction, but after less exposure to cigarette smoking. It is also likely that some of the observed gender differences represent chance findings. Thus, no conclusion regarding differential gender susceptibility to smoking-related lung cancer can be made at present.

Differences by gender in the proportion of lung cancer deaths directly attributable to current smoking are small. In CPS-II, the proportion of lung cancer deaths attributable to current smoking was 92 percent among women and 95 percent among men (Thun et al. 1997c). Smoking attributable fractions of deaths among women current smokers decreased with age, from 95 percent among women aged 45 through 49 years to 86 percent among women aged 80 years or older. This decrease among older women smokers likely is a result of differences in the smoking histories of older women, including later ages of initiation and lower cumulative exposures to smoking (Burns et al. 1997b). Nearly the same proportion of lung cancer deaths among women and men could be prevented by eliminating cigarette smoking.

Histologic Types

Lung cancers are classified into four main categories: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma (Churg 1994). Differences in histologic type have been observed between smokers and nonsmokers, and among smokers, gender-specific differences may be seen in the distribution of lung cancers by histologic type (Muscat and Wynder 1995b) (Table 3.9). In 1962, Kreyberg hypothesized that smoking causes squamous cell, small cell, and large cell carcinomas (Kreyberg type I), but that other factors cause adenocarcinoma and bronchioloalveolar carcinoma (Kreyberg type II) (Kreyberg 1962). Squamous cell carcinoma has long been the predominant type of lung cancer found among men, and adenocarcinoma has been predominant among women. Kreyberg (1962) based his hypothesis on this difference and on differences in the smoking habits of women and men at the time.

Although some early studies suggested that smoking might not be responsible for some histologic types of lung cancer, the association between smoking and all the major histologic types has been recognized since the 1980 Surgeon General's report (USDHHS 1980). Studies conducted since that report have confirmed that smoking strongly increases the risk for the four major types of lung cancer among women (Table 3.10). The risk was significantly higher among smokers than among women who had never smoked and, in

Table 3.9. Percent distribution of lung cancer cases, by gender, histologic type, and smoking status

	Women (n = 2,098)			Men (n = 3,756)		
Histologic type	Current smokers	Former smokers	Never smoked	Current smokers	Former smokers	Never smoked
Adenocarcinoma	42	44	59	32	34	58
Squamous cell carcinoma	20	20	12	35	37	19
Small cell carcinoma	19	12	3	15	11	0
Other	19	24	26	18	18	23

Source: Compiled from Muscat and Wynder 1995b.

general, increased as the quantity of cigarettes smoked increased (Lubin and Blot 1984; Wu et al. 1985; Schoenberg et al. 1989; Svensson et al. 1989; Katsouyanni et al. 1991; Morabia and Wynder 1991; Osann 1991; Brownson et al. 1992b; Osann et al. 1993; Zang and Wynder 1996) (Table 3.10). Risk also increased with duration of smoking (Schoenberg et al. 1989; Osann 1991; Risch et al. 1993) and depth of inhalation (Osann 1991) (data not shown). In one study, after adjustment for duration, risk did not increase with early age at smoking initiation for any histologic type of lung cancer (Svensson et al. 1989) (data not shown). Risk was generally lower among former smokers than among current smokers for each type of lung cancer (Wu et al. 1985; Svensson et al. 1989; Morabia and Wynder 1991; Osann 1991; Brownson et al. 1992b; Osann et al. 1993) (Table 3.10). Risk also decreased with duration of smoking cessation (Svensson et al. 1989; Morabia and Wynder 1991; Risch et al. 1993) (data not shown).

Among women, the RRs among smokers compared with those who had never smoked were consistently highest for small cell carcinoma (range, 37.6 to 86.0), followed by squamous cell carcinoma (range, 10.6 to 26.4), and then adenocarcinoma (range, 3.5 to 9.5) (Potter et al. 1985; Schoenberg et al. 1989; Brownson et al. 1992b; Osann et al. 1993; Risch et al. 1993) (Table 3.11). At each dose level of smoking, the RR was higher for small cell carcinoma than for squamous cell carcinoma and lowest for adenocarcinoma (Schoenberg et al. 1989; Brownson et al. 1992b; Osann et al. 1993; Zang and Wynder 1996) (data not shown). With the exception of the study by Risch and associates (1993), several investigators found that the risk among men was equally high for small cell and squamous cell carcinoma but lower for adenocarcinoma (Table 3.11). The RR among women and men who had ever smoked differed by less than a factor of 2 for adenocarcinoma (generally higher among men) and squamous cell carcinoma (higher among women in one-half of the studies), but the RR for small cell carcinoma among women consistently exceeded that among men by at least two to three times. In one study, dose-response RRs associated with specific levels of cumulative exposure to cigarette smoke (in kilograms of tar) were significantly higher by 1.5 to 1.7 times among women than among men for all three major histologic types (Zang and Wynder 1996).

Comparisons among histologic types and between women and men are subject to limitations because of diagnostic uncertainties, unstable estimates, and difficulties in assessment of cumulative exposure. Accurate classification of lung cancers into the four main histologic categories is compromised by interobserver variability and intrinsic tumor heterogeneity (Churg 1994). Comparisons of smoking-associated RR among histologic types and between genders are also limited by the small numbers of study participants who had never smoked. This limitation results in unstable risk estimates with wide, overlapping CIs. The lower smoking-associated risk for adenocarcinoma could be explained by a higher baseline risk for adenocarcinoma among women who had never smoked—a risk that is possibly due to exposure to ETS or other factors. Consistent with this explanation, adenocarcinoma does constitute a greater proportion of lung cancers among nonsmokers than among current or former smokers (Brownson et al. 1995; Muscat and Wynder 1995b). The subjective assessment of exposure to cigarette smoke may also differ between women and men.

Temporal Trends

Over time, the smoking habits of women have changed to more closely resemble those of men (Burns et al. 1997a). Differences between women and

men in histologic patterns of lung cancer have lessened but have not disappeared (Wynder and Hoffman 1994).

The incidence of each of the main histologic types of lung cancer has increased among women since 1973, but adenocarcinoma had the greatest percent increase (206 percent during 1973–1992) (Surveillance, Epidemiology, and End Results Program, unpublished data) (Figure 3.8). Among men, the overall lung cancer rate has begun to decline, but adenocarcinoma increased by 84 percent during 1973–1992. The increasing incidence of adenocarcinoma among both women and men may reflect the increase over time in the use of filter-tipped and low-tar cigarettes, which may result in greater deposition of smoke particles in the small airways of the lung periphery (Zheng et al. 1994). Yang and colleagues (1989) observed that smoke from filter-tipped and low-tar cigarettes contains fewer large particles and more small particles and may preferentially predispose smokers to peripheral tumors such as adenocarcinoma. Case-control results support an increased risk for adenocarcinoma among smokers of low-tar cigarettes (Stellman et al. 1997).

Analyses of gender-specific lung cancer trends by histologic type from data from the United States, Switzerland, and elsewhere showed that changes over time represent birth cohort effects reflecting gender-specific and generational changes in smoking and the types of cigarettes consumed (Levi et al. 1997; Thun et al. 1997b). For example, smoking among women was on the increase when filter-tipped and lower yield cigarettes were introduced. Such products are more likely to be inhaled than high-tar, unfiltered cigarettes because they are less irritating and because smokers compensate for the lower yield by smoking more intensely (greater number and depth of puffs). Thus, carcinogens may be more likely to travel beyond the central bronchi, where squamous cell carcinomas often occur, and to reach the bronchioloalveolar regions and smaller bronchi, where adenocarcinomas typically develop. Among women, the incidence of small cell carcinoma has increased steeply since 1973 and smaller increases have been seen in squamous cell carcinoma (Dodds et al. 1986; Wu et al. 1986; Butler et al. 1987; el-Torky et al. 1990; Devesa et al. 1991; Travis et al. 1995). An increase in bronchioloalveolar carcinoma found in hospital-based studies (Auerbach and Garfinkel 1991; Barsky et al. 1994) was not confirmed in population-based studies (Zheng et al. 1994). Analysis of more recent trends showed that rates for squamous cell carcinoma among women have remained fairly stable since the mid-1980s, rates for large cell carcinoma have decreased since the late 1980s, and rates for small cell carcinoma declined between 1991 and 1996. Incidence rates for adenocarcinoma, however, continued to increase, but the rate of increase appeared to be slowing (Wingo et al. 1999). Examination of trends by birth cohort revealed a decrease in the incidence of squamous cell carcinoma among birth cohorts of women and men born since 1935 and a reduction in the rate of increase in small cell carcinoma and adenocarcinoma among birth cohorts of women born since 1940 (Zheng et al. 1994).

Changes over time in the overall age-adjusted incidence of lung cancer can be primarily attributed to changes in smoking prevalence (Burns et al. 1997a). The steep rise in the incidence among women began in the 1960s and trailed the increase among men by about 20 years—a finding that reflects the later adoption of smoking by women. The recent decline in rates for squamous and small cell carcinomas and the slower rate of increase for adenocarcinoma among younger birth cohorts (Zheng et al. 1994) may be related to the decrease in smoking prevalence among these groups. Changes in smoking prevalence, however, may not explain all of the observed male-female differences in incidence patterns by histologic type. Additional risks related to use of low-tar, low-nicotine cigarettes and increasing exposure to tobacco-specific nitrosamines (TSNAs) may partially explain the increase in adenocarcinoma among women and men beginning in the 1970s (Wynder and Hoffman 1994).

Tobacco-Specific Nitrosamines

Wynder and Hoffman (1994) raised concerns about the level of TSNA carcinogens in brands of cigarettes smoked by women. The level of TSNA carcinogens in tobacco products is known to vary according to blend (Fischer et al. 1989), processing (Burton et al. 1989), and storage (Andersen et al. 1982c); this variation is a concern within the tobacco industry (Fisher 2000). As part of the validation of an analytical chemistry method to measure TSNAs in cigarette tobacco, the 10 best selling brands in the United States in 1996 were tested (Song and Ashley 1999). Two cigarettes from one pack of each brand were tested for this analysis. In this report, the 10 cigarette brands were ranked in the order of increasing *N*'-nitrosonornicotine (NNN) level, and Virginia Slims cigarettes (reported as Brand J in Table 5 in the report) (David Ashley, CDC, e-mail to Patricia Richter, CDC, August 31, 2000) were found to have the highest levels of

Table 3.10. Relative risks for lung cancer among women, by smoking status and histologic type, case-control studies

Study	Years	Smoking status	Relative risk (95% confidence interval)			
			Squamous cell carcinoma	Kreyberg I*	Small cell carcinoma	Adeno-carcinoma
Lubin and Blot 1984	1976–1980	Never smoked	1.0		1.0	1.0
		Ever smoked				
		1–9 cigarettes / day	2.8†		2.3†	1.0†
		10–19 cigarettes / day	2.4†		2.4†	2.0†
		20–29 cigarettes / day	5.3†		6.2†	1.1†
		≥ 30 cigarettes / day	4.2†		5.6†	2.3†
Potter et al. 1985	1976–1980	Nonsmokers	1.0		1.0	1.0
		Smokers	8.3†		52.3†	4.0†
Wu et al. 1985	1981–1982	Nonsmokers	1.0			1.0
		Former smokers	7.7 (0.8–70.3)			1.2 (0.6–2.3)
		Current smokers	35.3 (4.7–267.3)			4.1 (2.3–7.5)
		1–20 cigarettes / day	17.7 (2.3–138.2)			2.7 (1.4–5.4)
		≥ 21 cigarettes / day	94.4 (9.9–904.6)			6.5 (3.1–13.9)
Benhamou et al. 1987	1976–1980	Nonsmokers		1.0		1.0
		Smokers		6.6 (3.0–14.4)		2.1 (0.7–6.4)
Schoenberg et al. 1989	1982–1983	Nonsmokers	1.0		1.0	1.0
		All smokers				
		<20 cigarettes / day				
		<35 years	2.7 (1.4–5.1)		19.0 (6.4–56.5)	2.0 (1.3–3.2)
		≥ 35 years	12.0 (7.4–19.6)		62.5 (22.3–176.0)	3.9 (2.6–5.9)
		≥ 20 cigarettes / day				
		<35 years	7.7 (4.1–14.3)		40.6 (13.5–122.0)	3.4 (2.0–5.6)
		≥ 35 years	21.4 (13.1–34.9)		140.0 (49.8–391.0)	6.8 (4.5–10.1)
Svensson et al. 1989	1983–1986	Never smoked	1.0		1.0	1.0
		Former smokers	4.0 (1.0–16.9)		9.1 (1.4–69.7)	1.8 (0.8–4.3)
		Current smokers				
		≤ 10 cigarettes / day	9.7 (2.9–45.9)		33.7 (6.9–265.3)	2.2 (1.0–5.8)
		11–20 cigarettes / day	36.2 (12.0–168.9)		72.1 (11.9–452.6)	5.4 (2.4–13.2)
		>20 cigarettes / day	96.0 (6.9–)‡		215.8 (18.3–)‡	19.7 (1.7–)‡
Katsouyanni et al. 1991	1987–1989	Nonsmokers		1.0		1.0
		Former smokers		4.7 (1.05–21.1)		1.8 (0.4–8.7)
		Current smokers				
		≤ 20 cigarettes / day		3.2 (1.1–8.9)		1.4 (0.52–3.49)
		>20 cigarettes / day		19.5 (5.4–71.1)		3.0 (0.76–11.41)

*Kreyberg I includes squamous cell, small cell, and large cell carcinoma.
†95% confidence interval was not reported.
‡Upper confidence limit is not given; estimates are imprecise because of the small number of persons in the high-exposure category.

NNN: 5.60 micrograms per gram (µg / g) of tobacco with a relative standard deviation of 1.4 percent, versus 1.89 µg / g with a relative standard deviation of 11 percent for Brand A. Of the TSNAs, NNN and *N*'-nitrosoanatabine (NAT) levels correlated more closely; however, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*'-nitrosoanabasine (NAB) levels did not correlate with NNN or NAT levels across

Table 3.10. Continued

Study	Years	Smoking status	Relative risk (95% confidence interval)			
			Squamous cell carcinoma	Kreyberg I*	Small cell carcinoma	Adeno-carcinoma
Morabia and Wynder 1991	1985–1990	Former smokers				
		<20 cigarettes / day	0.4 (0.1–1.2)		0.5 (0.1–2.0)	0.7 (0.4–1.3)
		≥ 20 cigarettes / day	2.0 (1.0–4.3)		1.8 (0.7–4.9)	0.9 (0.5–1.5)
		Current smokers				
		1–19 cigarettes / day§	1.0		1.0	1.0
		20–29 cigarettes / day	1.5 (0.7–3.3)		1.8 (0.7–4.9)	1.3 (0.8–2.2)
		≥ 30 cigarettes / day	2.7 (1.3–5.7)		3.2 (1.2–8.1)	1.5 (0.9–2.6)
Osann 1991	1969–1977	Never smoked		1.0		1.0
		Former smokers		12.6 (1.4–113.0)		1.7 (0.5–5.3)
		Current smokers				
		<20 cigarettes / day		12.1 (1.5–96.3)		0.9 (0.3–2.7)
		≥ 20 cigarettes / day		71.2 (8.3–609.0)		3.8 (1.6–8.8)
Brownson et al. 1992b	1984–1990	Never smoked	1.0		1.0	1.0
		Former smokers	19.2 (15.2–24.2)		29.8 (22.0–40.3)	7.2 (6.2–8.5)
		Current smokers	20.6 (16.6–25.6)		42.5 (32.1–56.6)	7.2 (6.2–8.3)
		<20 cigarettes / day	11.7 (8.7–15.8)		25.6 (18.1–36.3)	5.8 (4.7–7.1)
		≥ 20 cigarettes / day	26.1 (20.7–32.8)		53.1 (39.5–71.3)	8.6 (7.3–10.1)
Osann et al. 1993	1984–1986	Never smoked	1.0		1.0	1.0
		Former smokers	13.5 (6.8–27.0)		43.3 (15.1–124.0)	5.8 (3.8–9.0)
		Ever smoked				
		<40 cigarettes / day	24.0 (12.7–45.5)		76.7 (27.5–215.0)	8.8 (6.1–12.8)
		≥ 40 cigarettes / day	72.3 (36.8–142.0)		316.1 (111.0–900.0)	24.2 (15.8–37.2)
Risch et al. 1993	1981–1985	Never smoked	1.0		1.0	1.0
		Smoked ≥ 40 pack-years	101.0 (15.3–660.0)		87.3 (26.7–286.0)	8.8 (3.7–20.8)
Zang and Wynder 1996	1981–1994	Never smoked	1.0			1.0
		Current smokers				
		1–10 cigarettes / day	9.3 (3.9–22.1)			4.5 (2.7–7.7)
		11–20 cigarettes / day	33.0 (16.3–66.6)			14.2 (9.6–20.9)
		21–40 cigarettes / day	74.9 (37.0–151.5)			27.2 (17.8–41.6)
		≥ 41 cigarettes / day	85.3 (29.5–247.1)			34.3 (16.2–72.5)

*Kreyberg I includes squamous cell, small cell, and large cell carcinoma.
§Referent group.

the 10 brands. Nevertheless, Virginia Slims had the highest levels of both NAB and NAT and the second-highest level of NNK. As alleged by a former Philip Morris chemist, internal industry testing of Virginia Slims cigarettes "found levels of nitrosamines 10 times higher than other cigarettes, including Marlboros" (Geyelin 1997). Although preliminary, these findings call for the rigorous testing of Virginia Slims and other cigarette brands popular among women who smoke.

Family History and Genetic Susceptibility Markers

Although approximately 90 percent of lung cancers are attributed to tobacco exposure, only a fraction of smokers (<20 percent) will develop lung cancer in their lifetime. Familial aggregation of lung cancer provides indirect evidence for a role of genetic predisposition to carcinogenesis from exposure to tobacco.

Table 3.11. Relative risks for lung cancer associated with ever smoking for women and men, by histologic type

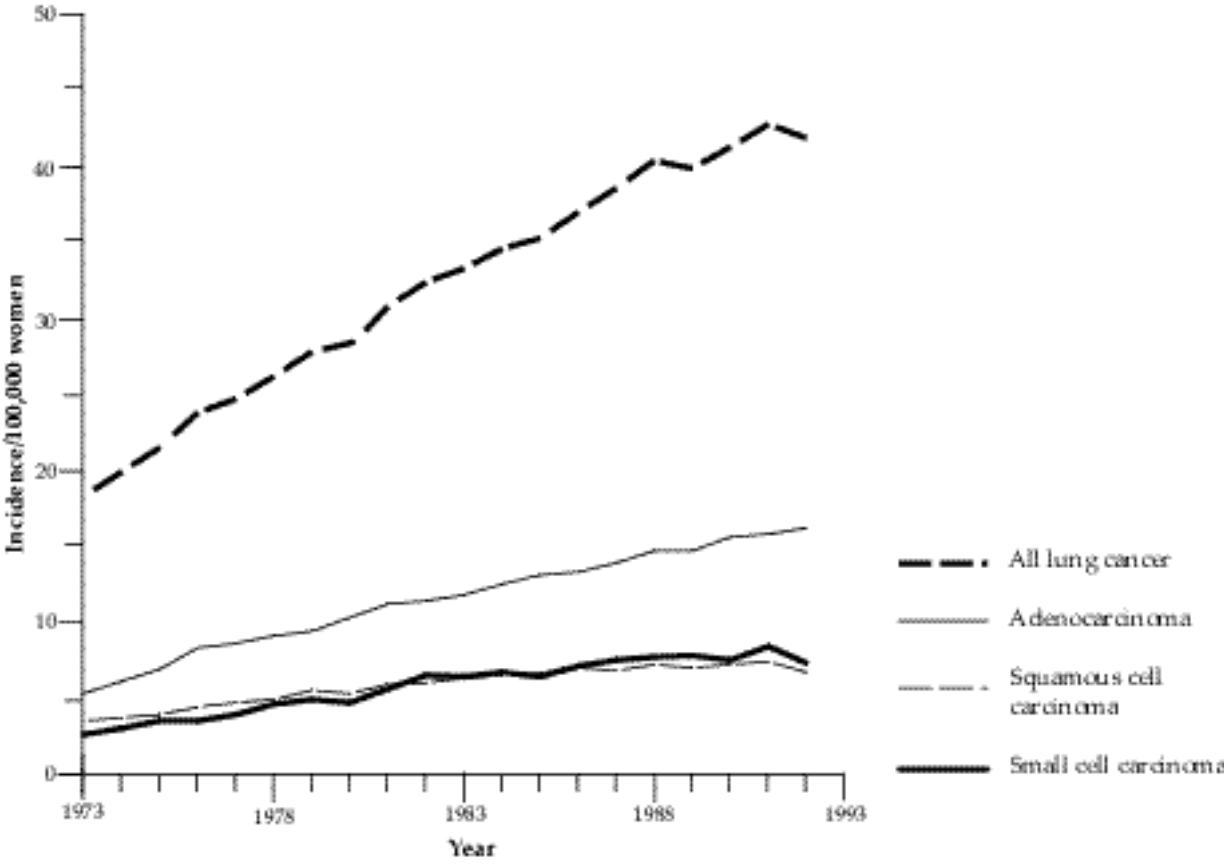
Study	Gender	Relative risk (95% confidence interval) Squamous cell carcinoma	Small cell carcinoma	Adenocarcinoma
Potter et al. 1985	Women	8.3*	52.3*	4.0*
Schoenberg et al. 1989	Women	10.6 (6.8–16.6)	59.0 (21.6–161)	3.6 (2.6–5.0)
	Men	18.9 (7.0–51.3)	22.9 (3.2–166)	4.8 (1.9–12.0)
Brownson et al. 1992b	Women	20.1 (16.4–24.8)	37.6 (28.5–49.3)	6.9 (6.1–7.8)
	Men	11.1 (9.5–12.9)	11.4 (9.1–14.2)	8.2 (6.9–9.7)
Osann et al. 1993	Women	26.4 (14.5–48.1)	86.0 (31.6–234)	9.5 (6.8–13.8)
	Men	36.1 (17.8–73.3)	37.5 (13.9–102)	17.9 (10.4–31.0)
Risch et al. 1993	Women	25.5 (7.9–156)	48.0 (10.5–849)	3.5 (1.8–7.1)
	Men	18.0 (5.5–111)	6.3 (2.2–27.0)	8.0 (2.3–50.6)

*95% confidence interval was not reported.

Lung cancer is prevalent in certain families (Lynch et al. 1978; Paul et al. 1987). In case-control studies, patients with lung cancer were more likely than control subjects to report having relatives with lung cancer (Lynch et al. 1986; Ooi et al. 1986; Samet et al. 1986; Sellers et al. 1987; Horwitz et al. 1988; Wu et al. 1988; Osann 1991; Shaw et al. 1991), and risk appears to increase with the number of first-degree relatives affected (Shaw et al. 1991). A study in Germany examined the effects of smoking and family history of lung cancer among case patients older than age 45 years and among those aged 55 through 69 years, and among control subjects of comparable age. After adjustment for pack-years of smoking, a first-degree family history of lung cancer was associated with a significantly increased risk for lung cancer among those in the younger age group (RR, 2.6; 95 percent CI, 1.1 to 6.0) but not the older age group (RR, 1.2; 95 percent CI, 0.9 to 1.6) (Kreuzer et al. 1998). Gender-specific results were not reported in that study, but the finding of a stronger association of family history with early onset of disease is consistent with an inherited predisposition. Another German case-control study, in which 83 percent of subjects were men, also found increased smoking-adjusted RRs associated with lung cancer in a parent or sibling, again with greater elevations in RR for cases diagnosed at younger (<51 years) relative to older ages (Bromen et al. 2000). Paternal but not maternal history of lung cancer was associated with increased risk. Elsewhere, smoking was found to interact synergistically with a family history of lung cancer and to increase lung cancer risk by 30 to 47 times the risk for nonsmokers with no family history of lung cancer (Tokuhata 1963; Horwitz et al. 1988; Osann 1991). In two studies, risk was greatest among female relatives (Ooi et al. 1986) and sisters of probands (McDuffie 1991). Findings from segregation analysis were compatible with Mendelian codominant inheritance of a rare major autosomal gene for predisposition to lung cancer. These findings also supported a model in which 62 percent of the population was susceptible and women were both more susceptible and affected at an earlier age than were men (Sellers et al. 1990).

These studies on patterns of inheritance suggested that a small proportion of lung cancer resulting from cigarette smoking is due to "lung cancer genes" that are likely to be of low frequency but high penetrance. The discovery of high-penetrance/low-frequency genes for lung cancer, however, is not likely to explain the vast majority of lung cancers. Instead, there may be low-penetrance genes of relatively high frequency that interact with smoking to increase the odds of developing lung cancer and for which attributable risks may be high. This field of investigation is burgeoning (Amos et al. 1992), but few definitive conclusions can be drawn as to which specific low-penetrance genes affect lung cancer risk or whether there are differential gender-specific effects.

Figure 3.8. Trends in lung cancer incidence among women, by histologic type, Surveillance, Epidemiology, and End Results (SEER) Program, 1973–1992



Source: SEER Program, unpublished data.

Mutations in the p53 tumor-suppressor gene are more common in lung cancers among smokers than among nonsmokers, and the p53 mutational spectra differ between smokers and nonsmokers with lung cancer (Bennett et al. 1999; Gealy et al. 1999). The frequency of mutations correlates positively with lifetime exposure to cigarette smoking, and good evidence indicated that benzo[*a*]pyrene, a chemical carcinogen in cigarettes, causes specific p53 mutations (Bennett et al. 1999).

Future research in this area may identify smokers who, by virtue of their genetic profile, are at particularly high risk and may determine whether gender-specific differences exist in the effects of genetic susceptibility markers on the risk for lung cancer associated with smoking. It is unlikely that one marker alone will be completely predictive of lung cancer risk; it is more likely that multiple susceptibility factors must be accounted for to represent the true dimensions of interactions between genes and exposure to tobacco.

Other Risk Factors

Cigarette smoking is overwhelmingly the most important cause of lung cancer. However, other risk factors that influence susceptibility to the effects of smoking have been identified (Kabat 1993; Ernster 1994); these include exposure to carcinogens such as radon and asbestos that act synergistically with cigarette smoking to increase lung cancer risk (Reif and Heeren 1999). Selected environmental exposures and host characteristics that may alter lung cancer risk in combination with cigarette smoking are discussed here.

Diet

The role of diet in the etiology of lung cancer has been reviewed and is supported by a large body of experimental and epidemiologic evidence (Goodman 1984; Colditz et al. 1987; Fontham 1990; Willett 1990). Both prospective studies (Hirayama 1984b; Steinmetz et al. 1993) and retrospective studies (Fontham et al. 1988; Koo 1988; Le Marchand et al. 1989; Jain et al. 1990) of women reported a 50-percent reduction in risk for lung cancer associated with high intake of fruits and vegetables containing beta-carotene. Although three studies found a significant protective effect of these dietary factors among women nonsmokers (Koo 1988; Kalandidi et al. 1990; Mayne et al. 1994), most studies included few nonsmokers and noted a protective effect primarily among smokers. This finding suggested a possible interaction of diet with smoking (Fontham 1990). No consensus has emerged about which group of smokers may enjoy the greatest protection—current smokers (Dorgan et al. 1993), heavy smokers (Dorgan et al. 1993), light smokers (Fontham et al. 1988; Le Marchand et al. 1989), or former smokers (Samet et al. 1985; Humble et al. 1987b; Steinmetz et al. 1993). Research has shown a reduced risk for squamous and small cell carcinomas, which occur predominantly among smokers, but has not shown a reduced risk for adenocarcinoma. These findings provided additional support for a possible interaction between smoking and consumption of carotenoids (Byers et al. 1987; Fontham et al. 1988). However, other studies reported significant inverse associations between carotenoids and adenocarcinoma (Wu et al. 1985, 1988; Koo 1988), large cell carcinoma (Steinmetz et al. 1993), and lung cancers of all cell types (Dorgan et al. 1993; Wu et al. 1994).

Despite the protective effects associated with fruits and vegetables in observational studies, large-scale, randomized intervention trials showed either no benefit or a possibly harmful effect, at pharmacologic doses, of beta-carotene supplementation on lung cancer mortality, and no effect was found for alpha-tocopherol (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994; Omenn et al. 1996). Only one of the trials included women (Omenn et al. 1996).

Protective effects of preformed vitamin A (retinol) (Pastorino et al. 1987; Fontham et al. 1988; Koo 1988), vitamin C (Fontham et al. 1988; Koo 1988), vitamin E (Comstock et al. 1991; Mayne et al. 1994), and selenium (van den Brandt et al. 1993) were reported in some studies, but others reported no effect (Hinds et al. 1984; Samet et al. 1985; Wu et al. 1985, 1988; Byers et al. 1987; Humble et al. 1987b; Le Marchand et al. 1989). Epidemiologic studies of a possible increase in lung cancer risk with increased consumption of fat and cholesterol yielded conflicting results (Jain et al. 1990; Goodman et al. 1992; Alavanja et al. 1993; Wu et al. 1994). The ability to examine both independent associations and interactions of dietary factors with smoking is limited by small sample sizes and by inadequate estimation and analytic control for exposure to smoking.

Occupation

Few studies have examined specific occupational risks for lung cancer among women. Hazardous occupational exposures may explain 5 percent of lung cancers among women and 15 percent among men (Doll and Peto 1981). Occupational studies are often subject to limitations because of an inadequate number of women and insufficient adjustment for the effects of cigarette smoking.

Regardless of limitations of studies, investigators have identified several occupational exposures that interact synergistically with smoking to increase risk beyond that observed for smoking alone (Ives et al. 1988; Saracci and Boffetta 1994). Results of combined analysis for Japanese women and men exposed to arsenic-contaminated drinking water supported a previously observed synergistic effect for smoking and arsenic exposure (Hertz-Picciotto et al. 1992; Tsuda et al. 1995).

Air Pollution

Although most cohort studies conducted in the 1950s through the 1970s that considered the effects of air pollution included only men, more recent case-control studies have included women and have attempted to control for smoking and other confounders. A case-control study in New Mexico found that living in urban areas was associated with increased smoking among non-Hispanic, white female controls; however, in multivariate analyses, living in urban areas was not associated with increased risk for lung cancer (Samet et al. 1987). Researchers also noted a significant association between smoking and duration of urban residence among women in the Niagara region of Ontario (Holowaty et al. 1991). However, even after adjustment for smoking, women in Shenyang, China, had a twofold increase in risk for lung cancer that was associated with living in a smoky environment, residing near industrial

factories, and using coal-burning stoves (Xu et al. 1989). In Poland, researchers found interaction between the effects of smoking and air pollution among men but not among women (Jedrychowski et al. 1990). Among women in Athens, a nonsignificant interaction between the effects of smoking duration and air pollution was reported (Katsouyanni et al. 1991). Although data are potentially consistent with a small role for air pollution in lung cancer risk, the limitations of inadequate control of confounding from smoking and occupational exposures and the difficulties in measuring cumulative exposure preclude definite conclusions.

Radon and Ionizing Radiation

Radon gas is released from the decay of radium in rock, soil, and water, and it accumulates in mines, caves, and buildings. Findings in studies of uranium miners indicated that radon is a cause of lung cancer and suggested a synergistic effect with cigarette smoking (Samet 1989b; Samet et al. 1989; Lubin 1994; National Research Council 1999). Because women have traditionally spent more time in the home, they have a higher risk from exposure to residential radon than do men.

Results from studies of atomic bomb survivors, who are at increased risk for lung cancer, were consistent with either a multiplicative or additive relationship among radiation, smoking, and risk (Prentice et al. 1983). Elsewhere, an excess risk for developing lung cancer 10 or more years following radiotherapy for breast cancer was observed among women smokers (Neugut et al. 1994). Compared with nonsmokers who were not exposed to radiotherapy, study participants who were exposed to radiation alone had a RR of 3, those who smoked but were not exposed to radiation had a RR of 14, and those who both smoked and were exposed to radiation had a RR of nearly 33. Because no increased risk was found for the first 10 years after radiotherapy, some doubt exists about the causal nature of the association. Current radiotherapy practices deliver substantially less radiation to the lungs than previously and reduce any potential hazard.

Conclusions

1. Cigarette smoking is the major cause of lung cancer among women. About 90 percent of all lung cancer deaths among U.S. women smokers are attributable to smoking.
2. The risk for lung cancer increases with quantity, duration, and intensity of smoking. The risk for dying of lung cancer is 20 times higher among women who smoke two or more packs of cigarettes per day than among women who do not smoke.
3. Lung cancer mortality rates among U.S. women have increased about 600 percent since 1950. In 1987, lung cancer surpassed breast cancer to become the leading cause of cancer death among U.S. women. Overall age-adjusted incidence rates for lung cancer among women appear to have peaked in the mid-1990s.
4. In the past, men who smoked appeared to have a higher relative risk for lung cancer than did women who smoked, but recent data suggest that such differences have narrowed considerably. Earlier findings largely reflect past gender-specific differences in duration and amount of cigarette smoking.
5. Former smokers have a lower risk for lung cancer than do current smokers, and risk declines with the number of years of smoking cessation.

International Trends in Lung Cancer Among Women

In 1990, cancers of the trachea, bronchus, and lung accounted for about 10 percent of all cancer deaths among women worldwide. The proportion of cancers varied widely among countries, which reflects the historical differences across countries in smoking initiation by women. Among women in Canada, the United Kingdom, and the United States, 20 percent or more of all cancer deaths were due to lung cancer; among women in France, Portugal, and Spain, the proportion was less than 5 percent. The estimated number of lung cancer deaths among women worldwide increased 23 percent between 1985 and 1990 (Pisani et al. 1999).

Since the early 1950s, lung cancer mortality for women in many industrialized countries has risen, on average, by more than 300 percent (Peto et al. 1994). Meanwhile, death rates among women for all other cancers combined have fallen by about 6 to 8 percent (Lopez 1995). Large prospective studies in the United Kingdom, the United States, and other industrialized countries showed that lung cancer death rates among nonsmokers have remained low, constant, and comparable among women and men (USDHHS 1989b; NCI 1997). These rates, about 5 cases per 100,000 persons (standardized to the European age structure of

the World Health Organization [WHO]), are similar to the rates found for women in Southern Europe, where smoking prevalence among women has been low until recently.

Breast cancer has been the leading cause of cancer death among women in the industrialized world as a whole for about the last four decades. However, in some countries, notably Canada, Denmark, Scotland, and the United States, lung cancer now exceeds breast cancer as the principal cause of cancer death. Because lung cancer mortality is increasing among women in many countries, this crossover of death rates for the two cancer sites will probably occur in other countries as well. For women in the United States, the death rate for lung cancer also overtook the rate for colorectal cancer around 1980.

Trends in Developed Countries

The predominant determinant of the lung cancer trends among both women and men is cigarette smoking (Peto et al. 1994). Several decades elapse between the initiation of regular smoking by a particular generation and the manifestation of smoking-related lung cancer risk in that cohort (Doll and Peto 1981; Harris 1983; Brown and Kessler 1988). In the United States, for example, cigarette consumption among women did not substantially take hold until the 1930s and 1940s (USDHHS 1980) (see "Historical Trends in Smoking" in Chapter 2), and until the early 1960s, lung cancer death rates were low.

Data from the early 1990s indicated that Denmark (35.6 per 100,000 women) and the United States (36.9 per 100,000 women) had the highest lung cancer death rates. Australia, Canada, Hungary, New Zealand, England, Wales, and Ireland had rates around 20 to 30 deaths per 100,000 women (Table 3.12). These are some of the countries in which women first began cigarette smoking and in which the prevalence of smoking among women remained at a fairly high level. Among developed countries, the lung cancer rates among women were lowest (about 10 cases or fewer per 100,000 women) in countries of Eastern and Southern Europe as well as in Finland and France.

The rate at which mortality from lung cancer has increased among women in different countries between 1985 and 1990–1993 is a public health concern (Table 3.12). Death rates rose most rapidly (about 5 percent per year) in Hungary, the Netherlands, and Switzerland; the percent increase was almost as high (3.3 to 3.7 percent per year) in several other countries, including Germany, Norway, and Sweden. Much more modest increases (about 0.5 percent per year) occurred in Bulgaria, Finland, Greece, Ireland, and Spain. In Ireland, the epidemic of lung cancer appears to have reached a plateau (Peto et al. 1994), but in Bulgaria, Finland, Greece, and Spain, low rates of increase suggested that the epidemic has yet to occur.

The range of lung cancer death rates in the early 1990s confirms that the lung cancer epidemic is heterogeneous even among women in industrialized countries (Peto et al. 1994). Countries for which data

Table 3.12. Age-standardized average annual death rate for lung cancer among women, 1990–1993, and average annual percent increase between 1985 and 1990–1993, selected industrialized countries

Country	Death rate*	% increase	Country	Death rate*	% increase
United States	36.9	3.3	Austria	13.6	1.8
Denmark	35.6	2.9	Germany†	12.8	3.5
Canada	31.5	3.1	Japan	12.6	0.9
England and Wales	30.8	0.8	Switzerland	12.0	5.1
Ireland	26.3	0.4	Italy	10.9	1.2
New Zealand	25.9	2.9	Greece	10.2	0.4
Hungary	23.9	5.2	Finland	10.2	0.6
Australia	19.2	2.0	Bulgaria	9.2	0.2
The Netherlands	15.5	4.6	Romania	9.0	0.9
Norway	15.4	3.4	France	7.7	2.9
Sweden	15.2	3.7	Portugal	6.8	3.1
Poland	14.5	3.1	Spain	5.4	0.6

*Per 100,000 women.
†Former Federal Republic of Germany.
Source: Calculated from unpublished data provided to the World Health Organization by respective countries.

are available can be grouped into three broad categories describing trends of about the last four decades.

- Group 1: Countries where death rates are already high (about 20 deaths or more per 100,000 women) and, in most cases, are still rising or have peaked. These countries include Australia, Canada, Denmark, Hungary, Ireland, New Zealand, the United Kingdom, and the United States.
- Group 2: Countries where death rates are still moderately low (10 to 15 deaths per 100,000 women) but are rising. These countries include Austria, Germany, Italy, Japan, the Netherlands, Norway, Poland, Sweden, and Switzerland.
- Group 3: Countries where death rates are low (about 5 to 10 deaths per 100,000 women) and roughly stable and where the lung cancer epidemic generally has not yet become apparent among women. These countries include Bulgaria, Finland, France, Greece, Portugal, Romania, and Spain.

Although the countries in each group may have similar death rates at a given time, trends in rates over time may differ. For example, unlike some countries in Group 3, which has low rates, France and Portugal have rates that are low but have been rising since about 1980. A trend of rising rates is evident in France, but it is not clear whether the increase in rates in Portugal is the beginning of an upward trend or a random fluctuation (Peto et al. 1994).

In the United Kingdom, the age-standardized lung cancer death rate among women has remained at around 31 deaths per 100,000 women since 1988. This rate, which is based on a large number of lung cancer deaths among women annually (about 12,500), suggested that the lung cancer epidemic has peaked among women in the United Kingdom. As noted earlier in this section, it also appears to have peaked in the United States (Wingo et al. 1999). The epidemic may have peaked in Australia, Ireland, and New Zealand, but because the number of lung cancer deaths in these countries is much smaller, the evidence is less conclusive.

Evidence that lung cancer rates among women in some areas may soon begin to rise was provided by trends in age-standardized death rates among women aged 35 through 54 years and among women aged 55 through 74 years. Lung cancer death rates among women aged 35 through 54 years have been declining since the late 1970s in the United Kingdom. Rates in this age group also appear to have reached their maximum level in Denmark and the United States more than a decade ago and more recently in Canada. On the other hand, rates among women aged 35 through 54 years were still rising in several countries in the early 1990s, for example in Hungary. The death rates among older women (aged 55 through 74 years) have generally continued to rise, as the cohorts most exposed to smoking have aged. However, death rates have already peaked and begun to decline among women in Ireland and the United Kingdom for this age group as well. The data for Australia and New Zealand also suggested that lung cancer mortality has peaked there among older women, but the trend is less conclusive in those two countries (Lopez 1995).

In several countries, including Austria, Germany, the Netherlands, Poland, Sweden, and Switzerland, and especially Hungary, the lung cancer death rate among women aged 35 through 54 years is relatively high compared with that among women aged 55 through 74 years. The ratios of these rates suggested that the epidemic of lung cancer is beginning among younger middle-aged women who have now been smoking long enough to incur an increased risk for developing the disease. As these cohorts of women at high risk for disease grow older, the lung cancer epidemic among women is likely to continue to develop in those countries.

If the epidemic of lung cancer among women has peaked or will soon peak in those countries where it first began, then it will have been less severe than the epidemic among men (Peto et al. 1994). In the United Kingdom, the age-standardized lung cancer death rates among men peaked at 110 deaths per 100,000 men in the early 1970s. In the United States, the peak among men was lower—about 85 deaths per 100,000 men. If the circumstances in the United Kingdom and the United States are replicated in other countries, the lung cancer death rate among women may rise to only about one-third to one-half that found among men at the height of the epidemic of lung cancer among men.

Trends in Developing Countries

Mortality trends for lung cancer are not known for most developing countries, because data collection systems that would yield comparable, reliable estimates of mortality over time generally have not existed. However, current available data suggest that lung cancer death rates are generally low (Pisani et al. 1999), as would be expected for populations without a long history of smoking. An exception to the general pattern is the relatively high lung cancer rate among Chinese women in Asia (Parkin et al. 1999), despite

the fact that relatively few Chinese women smoke. Factors other than smoking appear to be responsible for the high lung cancer death rates among women in China, possibly factors related to indoor air pollution created by certain cooking and heating sources. Despite the low prevalence of smoking, however, case-control studies have shown that smoking is also a strong risk factor for lung cancer among Chinese women (Wu-Williams et al. 1990).

Conclusion

1. International lung cancer death rates among women vary dramatically. This variation reflects historical differences in the adoption of cigarette smoking by women in different countries. In 1990, lung cancer accounted for about 10 percent of all cancer deaths among women worldwide and more than 20 percent of cancer deaths among women in some developed countries.

Female Cancers

Various factors associated with smoking, such as decreased fertility, age at menopause, and low body weight, are predictors of risk for many female cancers. The recognition that smoking can affect estrogen-related diseases and events (Baron et al. 1990) provided further reason to examine the relationship between smoking and cancers influenced by endogenous hormones. Studies have also shown that smoking can influence the metabolism of exogenous hormones (Jensen et al. 1985; Cassidenti et al. 1990). These findings have prompted evaluation of combined effects of smoking and use of oral contraceptives (OCs) or menopausal estrogens, exposures that have been repeatedly examined with respect to various female cancers.

Breast Cancer

Indirect evidence suggests the biological possibility that smoking may reduce the risk for breast cancer. It is recognized that high levels of estrogens, particularly estrone and estradiol, contribute to an increased risk for breast cancer (Bernstein and Ross 1993), and smoking is thought to have an antiestrogenic effect (see "Sex Hormones" later in this chapter). The occurrence of menopause at an earlier age among smokers than among nonsmokers is also well established, and late age at menopause has been consistently related to an increased risk for breast cancer (Alexander and Roberts 1987). Thus, smoking could reduce the risk for breast cancer. On the other hand, cigarette smoke contains numerous carcinogens that could plausibly affect the breast. Also, nicotine has been detected in the breast fluid of nonlactating women (Petrakis et al. 1978).

Multiple case-control studies and several cohort studies assessed the relationship between smoking and breast cancer risk (Palmer and Rosenberg 1993). The results of some studies, particularly hospital-based, case-control studies, must be interpreted cautiously. Smoking prevalence may be higher among hospital control subjects than among women in the general population and may result in an underestimation of the effects of smoking. Furthermore, questions have been raised about the results of some studies of women in breast cancer screening programs (Schechter et al. 1985; Meara et al. 1989) because the extent to which early detection methods are used may be correlated with smoking behaviors. Population-based studies are generally believed to provide the most valid results.

Many studies have reported no significant differences in breast cancer risk by whether participants had ever smoked (Rosenberg et al. 1984; Smith et al. 1984; Baron et al. 1986b, 1996b; Adami et al. 1988; Kato et al. 1989; London et al. 1989; Schechter et al. 1989; Ewertz 1990; Vatten and Kvinnsland 1990; Field et al. 1992; Braga et al. 1996; Engeland et al. 1996; Gammon et al. 1998; Millikan et al. 1998). (See Table 3.13 for results from case-control studies.) One study reported a lower but nonsignificant risk for breast cancer among current smokers but not among former smokers (O'Connell et al. 1987). Other studies reported a slightly to moderately higher risk among smokers (Schechter et al. 1985; Brinton et al. 1986b; Hiatt and Fireman 1986; Stockwell and Lyman 1987; Meara et al. 1989; Rohan and Baron 1989; Chu et al. 1990; Palmer et al. 1991; Bennicke et al. 1995; Morabia et al. 1996). Most elevations in RRs have been modest. Increased risk for breast cancer associated with smoking has been reported from at least two studies that used as the referent group women who were nonsmokers and who had not been exposed to ETS (Lash and Aschengrau 1999; Johnson et al. 2000).

Most studies showed that RRs were generally similar for current and former smokers (Rosenberg et al. 1984; Lund 1985; Brinton et al. 1986b; Hiatt and Fireman 1986; London et al. 1989; Rohan and Baron 1989; Chu et al. 1990; Ewertz 1990; Baron et al. 1996b; Braga et al. 1996). (See Table 3.13 for results from case-control studies.) In the few studies in which risk differed, the direction of the difference was inconsistent; some studies showed a higher risk among

current smokers (Schechter et al. 1985; Stockwell and Lyman 1987; Brownson et al. 1988; Palmer et al. 1991), and other studies showed a higher risk among former smokers (Hiatt and Fireman 1986; O'Connell et al. 1987). Meara and colleagues (1989) showed a higher risk among current smokers aged 45 through 69 years in a screening program study and a decreased risk among current smokers aged 45 through 59 in a hospital-based study. One study showed an elevated risk among recent smokers that was restricted to postmenopausal women (Millikan et al. 1998). Similarly, studies that examined risk by years since smoking cessation or by age at cessation showed no substantive relationships (Chu et al. 1990; Field et al. 1992; Baron et al. 1996b).

The majority of studies have indicated no differences in risk from either long-term or high-intensity smoking. Age at initiation of smoking also seems unrelated to breast cancer risk (Brinton et al. 1986b; Adami et al. 1988; Ewertz 1990; Palmer et al. 1991; Field et al. 1992; Baron et al. 1996b; Braga et al. 1996). Furthermore, the few studies that examined risk by years since initiation of smoking showed no significant relationship (Adami et al. 1988; Braga et al. 1996). One study examined whether many years of smoking before a first-term pregnancy affected risk and found no adverse effect (Adami et al. 1988).

Some studies reported an increased risk for premenopausal breast cancer associated with ever smoking (Schechter et al. 1985), cigarette-years of smoking (Schechter et al. 1985), current but not former smoking (Brownson et al. 1988), or former smoking (Brinton et al. 1986b). Johnson and colleagues (2000) used never active smokers who had also not been exposed to ETS as the referent group and found that premenopausal women had an increased risk for breast cancer associated with active smoking and higher RRs than did postmenopausal women. In one study that focused on women whose breast cancers were detected before age 45 years, current smoking was related to reduced risk among women who began smoking before 16 years of age (Gammon et al. 1998). However, in another study, which included women with a diagnosis of breast cancer before age 36 years, smoking was not related to risk (Smith et al. 1994). Most well-conducted studies have not confirmed an association between current or former smoking and premenopausal breast cancer (Hiatt and Fireman 1986; London et al. 1989; Rohan and Baron 1989; Schechter et al. 1989; Ewertz 1990; Field et al. 1992; Baron et al. 1996b). In the large Cancer and Steroid Hormone (CASH) study in which only women younger than 55 years of age were included, Chu and associates (1990) found that smoking-associated risk for breast cancer was somewhat higher among women diagnosed before menopause; the differences by menopausal status at diagnosis were not statistically significant.

Smoking-associated risk was also examined by age at diagnosis of breast cancer, but again no definitive relationships were found. In the CASH study (Chu et al. 1990), risk was somewhat higher among women who had a diagnosis of breast cancer before age 45 years, but the interaction with age was not statistically significant. Stockwell and Lyman (1987) similarly found the highest risk when cancer was diagnosed before age 50 years, but Vatten and Kvinnsland (1990) reported no difference in the effects of smoking before and after age 51 years. In another study, women with a diagnosis of breast cancer at 65 years of age or older (Brinton et al. 1986b) had a smoking-associated RR less than 1.0. However, the data showed no trends in risk among current smokers with long duration or high intensity of smoking. Other investigators reported no substantial difference in risk for breast cancer among women by age at diagnosis (before or after age 50 years) (Palmer et al. 1991).

Although most studies did not find a significant relationship between smoking and breast cancer, the biological rationale for such a relationship has been compelling enough to motivate investigators to assess relationships within subgroups defined by hormonally related risk factors (e.g., use of exogenous hormones), hormone receptor status, and most recently, genetic polymorphisms.

Because evidence suggested that smoking might enhance the clearance of exogenous hormones, several studies evaluated whether any effects of smoking were modified by use of OCs or menopausal estrogens. In one study, cigarette smoking was strongly associated with breast cancer risk among women who had used either OCs or menopausal estrogens (Brinton et al. 1986b), but other studies failed to confirm this result (Adami et al. 1988; Chu et al. 1990; Ewertz 1990; Palmer et al. 1991; Gammon et al. 1998).

Most studies did not find the effects of smoking to be modified by additional risk factors, including parity, family history of breast cancer, body mass, alcohol consumption, dietary factors, and educational status (Rosenberg et al. 1984; Smith et al. 1984; Brinton et al. 1986b; Chu et al. 1990; Ewertz 1990; Palmer et al. 1991).

Data are conflicting on whether a different relationship might exist for smoking among estrogen

Table 3.13. Relative risks for breast cancer for smokers compared with nonsmokers, case-control studies

Study	Number of cases	Number of controls	Source of controls	Relative risk (95% confidence interval)		
				Ever smoked	Current smokers	Former smokers
Rosenberg et al. 1984	2,160	717	Other cancers		1.1 (0.8–1.7)*	1.1 (0.8–1.3)
Smith et al. 1984	429	612	Population	1.2 (0.9–1.6)†		
Schechter et al. 1985	123	369	Screening program	1.4 (0.9–2.1)	1.9 (1.2–3.1)	1.0 (0.6–1.7)
Brinton et al. 1986b	1,547	1,930	Screening program	1.2 (1.0–1.4)	1.2 (0.9–1.4)	1.2 (1.0–1.5)
O'Connell et al. 1987	276	1,519	Community		0.6 (0.3–1.1)‡	1.2 (0.8–1.7)
Stockwell and Lyman 1987	5,246	3,921	Other cancers		1.3 (1.0–1.8)§	1.0 (0.8–1.1)
Adami et al. 1988	422	527	Population	1.0 (0.8–1.3)	1.1 (0.7–1.8)Δ	
Brownson et al. 1988	456	1,693	Screening program	1.1 (0.9–1.4)	1.4 (1.0–1.9)	0.9 (0.6–1.2)
Kato et al. 1989	1,740	8,920	Other cancers	0.9 (0.7–1.0)		
Meara et al. 1989	998	998	Hospital			
			Ages 25–44 years		1.2 (0.7–1.8)¶	0.9 (0.6–1.5)
			Ages 45–59 years		0.8 (0.6–1.1)¶	0.9 (0.7–1.3)
	118	118	Screening program			
			Ages 45–69 years		2.9 (1.2–7.2)¶	1.0 (0.4–2.3)
Rohan and Baron 1989	451	451	Population	1.2 (0.9–1.5)	1.4 (0.9–2.0)	1.0 (0.7–1.5)
Schechter et al. 1989	254	762	Screening program			
			Prevalent	1.1 (0.9–1.5)		
			Incident	1.2 (0.9–1.6)		
Chu et al. 1990	4,720	4,682	Population	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.1 (1.0–1.3)

*≥ 25 cigarettes / day.
†Continuous smokers.
‡>20 cigarettes / day.
§ >40 cigarettes / day.
Δ≥ 20 cigarettes / day.
¶≥ 5 cigarettes / day.

receptor (ER)-positive tumors and among ER-negative tumors. In one population-based, case-control study, smoking was associated with a 63-percent higher risk for ER-negative tumors, a risk that was significantly different from the null association observed for ER-positive tumors (Cooper et al. 1989). This association of smoking with ER-negative tumors was confined to women with premenopausal cancer—an effect consistent with that found in a clinical study that included only women with breast cancer (Ranocchia et al. 1991). However, a second study reported the opposite relationship—a fairly weak association with smoking for women with ER-positive tumors (London et al. 1989). A third study found that the risks for both ER-positive and ER-negative breast cancer increased with both active and passive smoking (Morabia et al. 1998). Other studies have not shown cigarette smoking to vary by the ER status of tumors (McTiernan et al. 1986; Stanford et al. 1987b; Yoo et al. 1997).

Table 3.13. Continued

Study	Number of cases	Number of controls	Source of controls	Relative risk (95% confidence interval)		
				Ever smoked	Current smokers	Former smokers
Ewertz 1990	1,480	1,332	Population		0.9 (0.8–1.1)	1.0 (0.8–1.2)
Palmer et al. 1991						
Canada	607	1,214	Neighborhood	1.0 (0.8–1.3)	1.1 (0.9–1.4)	1.0 (0.7–1.3)
United States	1,955	805	Other cancers	1.2 (1.0–1.5)	1.3 (1.1–1.6)	1.1 (0.9–1.4)
Field et al. 1992	1,617	1,617	Driver's license	1.0 (0.9–1.2)		
Smith et al. 1994	755	755	Population	1.0 (0.8–1.3)		
Baron et al. 1996b	6,888	9,529	Driver's license and Medicare		1.0 (0.9–1.1)	1.1 (1.0–1.2)
Braga et al. 1996	2,569	2,588	Hospital	0.9 (0.8–1.1)	0.8 (0.7–1.0)	1.1 (0.9–1.4)
Morabia et al. 1996	244	1,032	Population		5.1 (2.1–12.6)**	
Gammon et al. 1998[††]	1,645	1,497	Population	0.9 (0.8–1.1)	0.8 (0.7–1.0)	1.0 (0.8–1.2)
Millikan et al. 1998	498	473	HCFA[‡‡] and state Division of Motor Vehicles		1.0 (0.7–1.4)	1.3 (0.9–1.8)
Lash and Aschengrau 1999	265	765	HCFA and next of kin	2.0 (1.1–3.6)[§§]	2.3 (0.8-6.8)[ΔΔ]	
Johnson et al. 2000	2,317	2,438	Population	Premenopausal women: 2.3 (1.2–4.5)[§§] Postmenopausal women: 1.5 (1.0–2.3)[§§]	Premenopausal women: 1.9 (0.9–3.8)[§§] Postmenopausal women: 1.6 (1.0–2.5)[§§]	Premenopausal women: 2.6 (1.3–5.3)[§§] Postmenopausal women: 1.4 (0.9–2.1)[§§]

**≥ 20 cigarettes / day; reference group comprised of subjects not exposed to active or passive smoking.
[††]Women <45 years of age.
[‡‡]HCFA = Health Care Financing Administration.
[§§]Compared with subjects not exposed to active or passive smoking.
[ΔΔ]Persons smoking within 5 years before diagnosis.

ACS's CPS-II prospective study reported a significant increase in breast cancer mortality among current smokers (RR, 1.3); the risk from smoking for a long duration or at high intensity was even higher (RR, 1.7 for >40 cigarettes per day) (Calle et al. 1994). The investigators hypothesized that these findings could be due to delayed diagnosis of breast cancer among smokers or to a poorer prognosis among patients with breast cancer who smoke. Consistent with a poorer prognosis are results that showed a shorter average interval to recurrence of breast cancer among smokers than among nonsmokers (Daniell 1984) and poorer survival among patients with breast cancer who smoked than among nonsmokers (Yu et al. 1997). In another study, however, diagnosis of local breast cancer, as opposed to regional or distant breast cancer, was more likely among smokers than among nonsmokers (Smith et al. 1984). Thus, additional studies are necessary to address how breast cancers are detected among smokers and how smoking affects the prognosis of the disease.

More recent studies focused on whether smoking may have unusual effects on breast cancer risk among genetically susceptible subgroups. These studies examined whether risk varied in the presence or absence of certain genetic polymorphisms involved in the activation or detoxification of carcinogens, including polymorphisms in *GSTM1*, *CYP1A1*, and *N*-acetyltransferase 2 (*NAT2*) genotypes. Although two studies did not find that the *GSTM1* genotype modified the effect of smoking on overall breast cancer risk (Ambrosone et al. 1996; Kelsey et al. 1997), one of the studies did find an increased risk for breast cancer among heavy smokers with specific polymorphisms in either the *CYP1A1* (Ambrosone et al. 1995) or *NAT2* genes (Ambrosone et al. 1996). Other studies have also identified some interaction of smoking with either the *NAT1* gene (Zheng et al. 1999), the *NAT2* gene (Morabia et al. 2000), or both genes (Millikan et al. 1998), but in the study of both genes, the effect was restricted to postmenopausal women who had smoked recently. Later data from the large prospective U.S. Nurses' Health Study did not find that the *NAT2* polymorphism increased the risk for breast cancer among smokers (Hunter et al. 1997), but did find some support for an interaction of smoking with the *CYP1A1* gene among women who began smoking early in life (Ishibe et al. 1998). Additional studies are examining potential interactions with these as well as other genetic polymorphisms. A recent study also suggested that cigarette smoking may reduce the risk for breast cancer among carriers of the highly penetrant genes *BRCA1* and *BRCA2* (Brunet et al. 1998). Studies are also beginning to assess the relationships between smoking and breast cancer within groups defined by tumor-suppressor genes; one recent investigation showed a higher risk associated with current cigarette smoking among patients with p53-positive tumors (Gammon et al. 1999). These various preliminary findings require further verification.

Correlations between the incidence of lung cancer among men and breast cancer among women in various countries and parts of the United States supported the hypothesis that ambient tobacco smoke may be related to breast cancer (Horton 1988). In a case-control study, exposure to ETS was associated with breast cancer among premenopausal women but not among postmenopausal women (Sandler et al. 1985, 1986), but the number of cases was small and the analysis was controlled only for age and level of education. In a large Japanese cohort study, Hirayama (1990) observed a significant dose-response relationship between the number of cigarettes smoked by husbands and their wives' risk for breast cancer at ages 50 through 59 years. In a case-control study of women younger than age 36 years, those exposed to ETS had an elevated risk for developing breast cancer, but the investigators noted little evidence of significant trends with increasing exposure (Smith et al. 1994).

Wells (1991, 1998) recommended further study of the effects of ETS exposure on breast cancer risk, because any risk associated with active smoking might be underestimated if the possibly confounding effect of ETS exposure is not considered. Indeed, the first study to examine this issue found a RR of 3.2 among nonsmoking women exposed to ETS compared with nonsmoking women who had not been exposed to ETS (Morabia et al. 1996). The plausibility of this finding was questionable because the RR associated with active smoking, using never active smokers as the referent group, was much higher (RR, 1.9 for smokers of >20 cigarettes per day) than that observed in other investigations. However, subsequent case-control studies that used persons who had never smoked or who had never been exposed to ETS as the referent group also found evidence of increased risk associated with ETS exposure (Lash and Aschengrau 1999; Johnson et al. 2000). In the study by Lash and Aschengrau (1999), the RRs associated with active smoking and with exposure to ETS were each 2.0, with evidence of higher risks among active smokers who smoked only before the first pregnancy and among subjects exposed to ETS before age 12 years. Similarly, in a large, population-based case-control study in Canada with adjustment for multiple potentially confounding variables, Johnson and colleagues (2000) found both ever active smoking and ETS exposure to be associated with increased risks for premenopausal and postmenopausal breast cancer after adjustment for multiple confounding variables. The referent group was women who were neither active smokers nor exposed to ETS. Millikan and associates (1998) reported positive associations between ETS exposure and breast cancer among never active smokers (RRs, 1.2 to 1.5), but the associations were weak and the findings were not statistically significant. In contrast, Wartenberg and colleagues (2000) found no association between ETS exposure and breast cancer mortality in the CPS-II cohort study. They noted that after 12 years of follow-up, the risk was similar among women who were lifelong never smokers whose spouse was a current smoker at baseline and among women whose spouse had never smoked (multivariate RR, 1.0; 95 percent CI, 0.8 to 1.2), and no dose-response relationship was found. Biologically it is implausible that ETS exposure could impart a risk

that is the same as that of active smoking, but whether ETS is related to breast cancer risk remains an open question and one that is receiving attention in other investigations.

The relationship of breast cancer risk to in utero exposure to tobacco smoke is also of interest because smoking may be associated with lower estrogen levels during pregnancy (Petridou et al. 1990). Although reduced estrogen levels might be expected to lower the risk for breast cancer, Sanderson and associates (1996), in a study that evaluated effects of maternal smoking and the risk for breast cancer, reported no significant effect overall and only a slight increase in risk among women diagnosed with breast cancer at age 30 years or younger whose mothers had smoked during pregnancy. This association persisted after the investigators considered the effects of birth weight.

Thus, active smoking does not appear to appreciably affect breast cancer risk overall. However, several issues are not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS exposure affects risk.

Benign Breast Disease

Studies provided mixed evidence as to whether smoking affects the risk for developing various benign breast conditions (Nomura et al. 1977; Berkowitz et al. 1985; Pastides et al. 1987; Rohan et al. 1989; Parazzini et al. 1991b; Yu et al. 1992). To compare the results of these studies is difficult because they differ by the types of conditions examined (fibroadenoma, fibrocystic disease, or proliferative disorders of varying degrees of severity), by how smoking status was defined (ever, current, or former smoking), and by whether data were analyzed by menopausal status.

Endometrial Cancer

Some researchers proposed that exposure to tobacco may reduce the risk for endometrial cancer by reducing estrogen production (MacMahon et al. 1982), a hypothesis that received some support from findings that estriol excretion is reduced among postmenopausal smokers (Key et al. 1996). Another theory is that smoking affects endometrial cancer risk by altering the metabolism, absorption, or distribution of hormones. Research has shown that smokers have higher rates of conversion of estradiol to 2-hydroxyestrones, which have low estrogenic activity (Michnovicz et al. 1986). Furthermore, antiestrogenic effects of smoking may be mediated by inducing microsomal, mixed-function oxidase systems that metabolize sex hormones (Lu et al. 1972). Both mechanisms are consistent with findings that women smokers who take oral estradiol have lower levels of unbound estradiol and higher serum hormone-binding capacity than do women nonsmokers who take estradiol (Jensen et al. 1985; Cassidenti et al. 1990). However, other mechanisms should not be dismissed. For example, several investigators believe that the effects of smoking on androgen, progestogen, or cortisol may reduce the risk for endometrial cancer among smokers (Seyler et al. 1986; Khaw et al. 1988; Baron et al. 1990; Berta et al. 1991).

Multiple case-control studies showed a reduced risk for endometrial cancer among cigarette smokers (Baron et al. 1986b; Franks et al. 1987a; Levi et al. 1987; Stockwell and Lyman 1987; Kato et al. 1989; Koumantaki et al. 1989; Dahlgren et al. 1991; Brinton et al. 1993; Parazzini et al. 1995) (Table 3.14). Several other studies found reduced risks among smokers that were not statistically significant (Smith et al. 1984; Lesko et al. 1985; Tyler et al. 1985; Lawrence et al. 1987; Weir et al. 1994). Some of these studies examined results by menopausal status and showed that the reduced risk among smokers was restricted to women with endometrial cancer diagnosed after menopause (Lesko et al. 1985; Stockwell and Lyman 1987; Koumantaki et al. 1989; Parazzini et al. 1995). Among postmenopausal women, the magnitude of the risk reduction associated with ever smoking was about 50 percent. One study found a significantly elevated risk for premenopausal endometrial cancer associated with ever smoking (Smith et al. 1984). In most studies that showed a reduced risk associated with smoking, the effect was greater among current smokers than among former smokers or was confined to current smokers.

The factors that are known to increase the risk for endometrial cancer and that are potential confounders of the association between smoking and the disease include obesity, late onset of menopause, menstrual disorders, infertility, and use of menopausal estrogens; reduced risk has been associated with use of OCs. Despite careful control for these variables, the magnitude of observed reductions in risk associated with smoking has not been substantially affected.

Beside considering confounding effects, several investigators assessed whether the presence of selected risk factors could modify the relationship between smoking and endometrial cancer risk. Three studies noted a greater reduction in smoking-associated risk

Table 3.14. Relative risks for endometrial cancer for smokers compared with nonsmokers, case-control studies

Study	Number of cases	Number of controls	Source of controls	Relative risk (95% confidence interval)		
				Ever smoked	Current smokers	Former smokers
Smith et al. 1984	70	612	Population		0.8 (0.4–1.5)*	
Lesko et al. 1985	510	727	Other cancers		0.7 (0.5–1.0)	0.9 (0.6–1.2)
Tyler et al. 1985	437†	3,200†	Population	0.9 (0.7–1.1)	0.8 (0.7–1.1)	1.0 (0.7–1.4)
Franks et al. 1987a	79‡	416‡	Population	0.5 (0.3–0.8)		
Lawrence et al. 1987	200§	200	Driver's license		0.5Δ	0.6Δ
Levi et al. 1987	357	1,122	Hospital		0.4 (0.3–0.7)	0.9 (0.5–1.5)
Stockwell and Lyman 1987	1,374	3,921	Other cancers		0.5 (0.3–0.9)¶	0.6 (0.5–0.8)
Kato et al. 1989	239	8,920	Other cancers	0.4 (0.3–0.8)		
Lawrence et al. 1989a	844**	168	Driver's license		0.9Δ	1.0Δ
Brinton et al. 1993	405	297	Population	0.8 (0.5–1.1)	0.4 (0.2–0.7)	1.1 (0.7–1.6)
Weir et al. 1994	73††	399††	Neighbor	0.8 (0.5–1.4)	0.8 (0.4–1.5)	0.8 (0.3–2.1)‡‡
Parazzini et al. 1995	726	1,452	Hospital		0.8 (0.7–1.1)	0.6 (0.4–0.9)

*Continuous smokers.
†Women 20–54 years of age.
‡Postmenopausal women >40 years of age.
§Women with early-stage tumors.
Δ>1 pack of cigarettes / day. 95% confidence interval was not reported, but the results of Lawrence et al. 1987 were reported to be statistically significant and results of Lawrence et al. 1989a were not.
¶>40 cigarettes / day.
**Women with late-stage tumors.
††Postmenopausal women.
‡‡Women who had stopped smoking ≥ 10 years before.

among obese women (Lawrence et al. 1987; Brinton et al. 1993; Parazzini et al. 1995). Other research indicated that obesity enhances the capacity to produce estrogens through extraovarian sources and is associated with higher levels of sex hormone-binding globulin (Siiteri 1987). Several studies reported a greater reduction in risk for smokers than nonsmokers among women taking estrogen replacement therapy (Weiss et al. 1980; Franks et al. 1987a), but not all study results supported such an effect (Brinton et al. 1993; Parazzini et al. 1995). One study found the greatest reduction in risk associated with smoking among multiparous women (Brinton et al. 1993).

Endometrial hyperplasia is generally recognized as a precursor of endometrial cancer (Kurman et al. 1985). Weir and colleagues (1994) examined the association between smoking and endometrial hyperplasia and showed a lower RR among both premenopausal and postmenopausal women smokers. The results of this study, however, were not statistically significant.

Table 3.15. Relative risks for ovarian cancer for smokers compared with nonsmokers, case-control studies

Study	Number of cases	Number of controls	Source of controls	Relative risk (95% confidence interval)		
				Ever smoked	Current smokers	Former smokers
Byers et al. 1983	274	1,034	Hospital	0.9*		
Smith et al. 1984	58	612	Population		0.8 (0.4–1.6)[†]	
Tzonou et al. 1984	150	250	Hospital	0.8[‡]		
Franks et al. 1987b	494	4,238	Population	1.0 (0.9–1.3)	1.1 (0.9–1.4)	0.9 (0.7–1.2)
Stockwell and Lyman 1987	889	3,921	Other cancers		1.1 (0.6–1.9)[§]	0.9 (0.7–1.2)
Hartge et al. 1989	296	343	Hospital		0.8 (0.6–1.3)	1.3 (0.9–2.0)
Kato et al. 1989	417	8,920	Other cancers	0.8 (0.6–1.1)		
Shu et al. 1989	229	229	Hospital	1.8 (0.7–4.8)		
Polychronopoulou et al. 1993	189	200	Hospital visitor	1.0 (0.5–1.8)		

*Authors stated that relative risk was not statistically significant.
[†]Continuous smokers.
[‡]$p = 0.08$.
[§]Current smokers of >40 cigarettes / day.

Ovarian Cancer

Frequency of ovulation has been hypothesized in regard to risk for epithelial ovarian cancer: the greater the number of ovulatory cycles in a lifetime, the greater the risk (Whittemore et al. 1992). If smoking interrupts ovulation, as suggested by menstrual irregularity and subfecundity among smokers (see "Menstrual Function" and "Reproductive Outcomes" later in this chapter), smoking could lower the risk for ovarian cancer. On the other hand, cigarette smoke contains carcinogens, which could increase the risk for ovarian cancer. Furthermore, enzymes in the ovaries of rodents have been shown to metabolize polycyclic aromatic hydrocarbons (PAHs) to electrophilic intermediates, and exposure to these compounds through smoking may have direct toxic effects or may stimulate ovarian atresia (imperforation or closure). Thus, the risk for ovarian cancer may be increased (Mattison and Thorgeirsson 1978). A broad range of possible biological effects of smoking on ovarian tissue or on hormones exists, but studies have not examined the relationship of smoking with risk for ovarian cancer in detail. In most studies in which the effects of smoking were evaluated, only limited information on exposure was collected, and comparisons were usually dependent on hospital-based control subjects. In fact, few studies have considered the combined influence of smoking and other risk factors for ovarian cancer. Further research is also needed on the relationship of smoking with histologic subtypes of ovarian cancer.

Most investigations of the relationship between the risk for ovarian cancer and a history of ever having smoked have found no association (Byers et al. 1983; Smith et al. 1984; Baron et al. 1986b; Franks et al. 1987b; Stockwell and Lyman 1987; Hartge et al. 1989; Kato et al. 1989; Hirayama 1990; Polychronopoulou et al. 1993; Engeland et al. 1996; Mink et al. 1996). Table 3.15 shows results of case-control studies that provided estimates of RR.

Only a few studies examined the relationship of ovarian cancer with duration or intensity of smoking. Astudy in Greece found a slightly reduced risk among smokers who smoked 20 or more cigarettes per day, but the relationship was not statistically significant (Tzonou et al. 1984). The CASH study reported that

risk for ovarian cancer did not vary in relation to quantity of cigarettes smoked and duration of smoking, including the interval since smoking cessation, the number of pack-years of smoking, the interval since initiation of smoking, and age at initiation (Franks et al. 1987b). Furthermore, smoking effects did not vary by several other factors, including reproductive history, menopausal status, use of exogenous hormones, alcohol use, and family history of ovarian cancer. However, the CASH study included only women with a diagnosis of ovarian cancer before age 55 years, which limits the generalizability of the results. Studies that included a broader age range of women found no substantial relationship of ovarian cancer risk with current smoking or duration of smoking (Stockwell and Lyman 1987; Hartge et al. 1989).

Cervical Cancer

A positive correlation between the incidence of cervical cancer and other cancers known to be related to cigarette smoking across populations prompted the hypothesis that smoking may affect the risk for cervical cancer (Winkelstein 1977). Excess risk for cervical cancer among smokers was demonstrated in a number of case-control studies (Clarke et al. 1982; Marshall et al. 1983; Baron et al. 1986b; Brinton et al. 1986a; La Vecchia et al. 1986; Peters et al. 1986; Nischan et al. 1988; Licciardone et al. 1989; Bosch et al. 1992; Daling et al. 1996). (See Table 3.16 for studies that provided data on smokers and never smokers.) One cohort study also found an excess risk for cervical cancer among smokers (Greenberg et al. 1985). In these studies, the association between cervical cancer and smoking was not eliminated, even though the investigators controlled for several well-established risk factors for cervical cancer, including early age at first sexual intercourse, history of multiple sex partners, and low socioeconomic status.

Several subtypes of human papillomavirus (HPV) are recognized as the main cause of cervical cancer worldwide (Bosch et al. 1995), and the extent to which the relationship between smoking and cervical cancer reflects a causal association independent of HPV infection is not known. The association of smoking with cervical cancer may be causal, may reflect confounding or risk modification among women with HPV infection, or may even reflect an effect of smoking on risk for HPV infection. Residual confounding by sexual history may also explain observed smoking associations, and adjustment for HPV will probably address that possibility.

Most studies in which risk values were not adjusted for HPV infection reported a RR of approximately 2.0 among smokers compared with nonsmokers. Women who smoked for a long duration or at high intensity generally had the highest risk (Table 3.16). In several studies, the relationship was restricted to, or strongest among, recent or current smokers (Brinton et al. 1986a; La Vecchia et al. 1986; Licciardone et al. 1989). Two studies reported the highest risk among women who started smoking late in life (Brinton et al. 1986a; Herrero et al. 1989), but other studies reported the opposite effect, namely higher risk among women who began smoking at young ages (La Vecchia et al. 1986; Daling et al. 1996). The results from several studies showed further biological evidence to support an association between cervical cancer and smoking. The findings included an enhanced risk associated with continuous smoking (Slattery et al. 1989), use of unfiltered cigarettes (Brinton et al. 1986a), and inhaling smoke into the throat and mouth (Slattery et al. 1989). The effects of smoking appear to be restricted to squamous cell carcinoma; no relationship was observed for the rarer occurrences of adenocarcinoma or adenosquamous carcinoma (Brinton et al. 1986a).

In numerous studies, an association with smoking appears to prevail for both cervical cancer and precursor conditions, including carcinoma in situ and cervical dysplasia (also known as squamous intraepithelial neoplasia) (Harris et al. 1980; Berggren and Sjostedt 1983; Hellberg et al. 1983; Lyon et al. 1983; Trevathan et al. 1983; Clarke et al. 1985; Mayberry 1985; La Vecchia et al. 1986; Brock et al. 1989; Slattery et al. 1989; Coker et al. 1992; Gram et al. 1992; Parazzini et al. 1992a; Munoz et al. 1993; Becker et al. 1994; de Vet et al. 1994; Kjaer et al. 1996; Ylitalo et al. 1999) (Table 3.17). Most of these studies reported particularly high risk among current smokers and among those who smoked for a long time or at a high intensity, but they have been limited by the absence of information on HPV. In one study, smoking did not affect the overall risk for cervical intraepithelial neoplasia (CIN) when sexual history and HPV infection status were taken into account (Schiffman et al. 1993). However, current cigarette smoking was related to nearly a threefold increase in risk among the limited number of HPV-positive women who had a higher grade of disease (CIN II or III). Elsewhere, in a clinics-based study among HPV-infected women in which women with CIN I served as the referent group, smoking was significantly associated with CIN III (Ho et al. 1998). These findings suggested that smoking may be involved in disease progression. They were supported by results in two other studies that

Table 3.16. Relative risks for invasive cervical cancer for smokers compared with nonsmokers and for quantity or duration of smoking, case-control studies

Study	Number of cases/controls	Source of controls	Relative risk (95% confidence interval) by smoking status			Relative risk (95% confidence interval) by quantity/ duration of smoking	
			Ever smoked	Current smokers	Former smokers		
Clarke et al. 1982	178/855	Neighbor		2.3 (1.6–3.3)	1.7 (1.0–2.8)		
Marshall et al. 1983	513/490	Hospital		1.6 (1.2–2.1)	0.8 (0.5–1.4)	<½ pack/day ½–1 pack/day 1–2 packs/day >2 packs/day	1.7* 1.7* 1.0 0.4
Baron et al. 1986b	1,174/2,128	Hospital				1–14 packs/year ≥ 15 packs/year	1.4* 1.8*
Brinton et al. 1986a	480/797	Community	1.5 (1.1–1.9)	1.5 (1.2–2.0)	1.3 (0.9–1.9)	<10 years 10–19 years 20–29 years 30–39 years ≥ 40 years	1.1 1.6* 1.3 1.5* 2.2*
La Vecchia et al. 1986	230/230	Hospital		1.7 (1.1–2.3)	0.8 (0.4–1.7)	<15 cigarettes/day ≥ 15 cigarettes/day	1.7† 1.8†
Peters et al. 1986	200/200	Neighbor				2–20 years ≥ 21 years	1.5‡ 4.0*‡
Nischan et al. 1988	225/435	Hospital	1.2 (0.8–1.7)			<10 years 10–19 years 20–29 years ≥ 30 years	0.7 1.3 1.7 2.7*
Herrero et al. 1989	667/1,430	Hospital/ community		1.0 (0.7–1.2)	1.0 (0.8–1.3)	<10 years 10–19 years 20–29 years 30–39 years ≥ 40 years	1.0 1.0 1.1 0.6 1.5
Licciardone et al. 1989	331/993	Other cancers			1.7 (1.0–2.9)	<1 pack/day ≥ 1 pack/day	2.2*† 3.9*†
Bosch et al. 1992	436/387	Population	1.5 (1.0–2.2)				
Eluf-Neto et al. 1994	199/225	Hospital	1.5 (0.99–2.3)				
Daling et al. 1996	314/672	Population		2.5 (1.8–3.4)	1.5 (1.1–2.2)	<10 years 10–19 years ≥ 20 years	1.0§ 2.4* 2.8*

*Statistically significant.
†Relative risk for current smokers.
‡Relative risk for years of smoking >5 cigarettes/day. Reference group consisted of persons who smoked for ≤ 1 year.
§Referent group for the study by Daling et al. 1996.

Table 3.17. Relative risks for cervical intraepithelial neoplasia for smokers compared with nonsmokers, case-control studies

Study	Cases		Controls		Relative risk (95% confidence interval)		
	Type	Number	Source	Number	Ever smoked	Current smokers	Former smokers
Harris et al. 1980	Dysplasia / CIS‡	190	Hospital	422		2.1*†	
Lyon et al. 1983	CIS	217	Community	243		3.0 (1.9–4.8)§	
Trevathan et al. 1983	Mild, moderate dysplasia	194	Family-planning program	288	2.4 (1.6–3.7)	2.6 (1.7–4.1)	1.6 (0.8–3.6)
	Severe dysplasia	81			3.3 (1.9–5.8)	3.0 (1.6–5.6)	5.7 (2.4–13.5)
	CIS	99			3.6 (2.1–6.2)	4.2 (2.7–7.5)	2.1 (0.8–5.6)
Clarke et al. 1985	Dysplasia	250	Neighbor	500		3.1*†	1.1†
Mayberry 1985	CIN△	210¶	Clinic	317		2.0 (1.3–3.0)	1.4 (0.7–2.8)
La Vecchia et al. 1986	CIN	183	Screening program	183		2.6 (1.3–5.2)**	2.5 (0.9–6.7)
Brock et al. 1989	CIS	116	Physician	193		4.5 (2.2–9.1)	1.3 (0.6–3.0)
Slattery et al. 1989	CIS	266††	Random digit dialing	408		3.4 (2.1–5.6)	1.4 (0.8–2.5)
Coker et al. 1992	CIN II, III	103	Clinic‡‡	268	1.7 (0.9–3.3)	3.4 (1.7–7.0)	
Parazzini et al. 1992a	CIN I, II	128	Screening program	323		1.8 (1.1–2.9)	1.1 (0.4–2.9)
	CIN III	238				2.0 (1.3–3.1)	1.7 (0.8–3.5)
Munoz et al. 1993	CIN III	525	Cytology	512			
Spain						1.3 (0.7–2.3)	0.9 (0.2–3.8)
Colombia						2.0 (1.3–3.0)	1.8 (0.9–3.5)
Becker et al. 1994	CIN II, III	201	Colposcopy	337	1.4 (1.0–2.1)	1.8 (1.2–2.8)	0.9 (0.5–1.5)
de Vet et al. 1994	Dysplasia	257	Population	705		3.5 (2.1–5.9)*	2.0 (1.1–3.4)
Kjaer et al. 1996	CIS	586	Population	614	2.3 (1.6–3.2)	2.4 (1.7–3.4)	1.6 (1.0–2.7)
Ylitalo et al. 1999	CIS	422	Screening program	422		1.9 (1.3–2.8)	1.5 (0.9–2.3)

*≥ 20 cigarettes / day.
†95% confidence interval was not provided, but the results were reported as not significant.
‡CIS = Carcinoma in situ.
§90% confidence interval.
△CIN = Cervical intraepithelial neoplasia; CIN II and CIN III define disease progression.
¶Includes 35 women with severe dysplasia, 9 with CIS, and 10 with invasive carcinoma.
**≥ 15 cigarettes / day.
††Includes 36 women with invasive carcinoma.
‡‡Women with normal cervical cytologies.

were limited by the absence of data on HPV status. In those studies, smoking was a risk factor only for CIN III (Coker et al. 1992) or was a stronger risk factor for CIN III than for CIN II (Trevathan et al. 1983).

Investigators in only a few studies evaluated the interaction between smoking and other risk factors for cervical cancer. One study found no significant variation by other factors, including sexual behavior and history of sexually transmitted disease (STD) (Mayberry 1985). Two studies reported that the effects of smoking were greatest among women with a history of limited sexual activity (Nischan et al. 1988; Slattery et al. 1989). However, in another study, the effects of smoking were greatest among women who were married multiple times or who had more than one sexual partner (La Vecchia et al. 1986). Lyon and associates (1983) found the effects of smoking to be greater among Mormon women, who tend to begin to bear children at a younger age than do other women in the United States.

Because HPV infection, which is usually contracted from a sexual partner, is widely recognized as the main cause of cervical cancer, Phillips and Smith (1994) focused on ways to assess whether the association between smoking and cervical cancer is independent of HPV infection. HPV occurs frequently among women with cervical cancer but infrequently in control subjects. Thus, recent studies have examined smoking effects by status of HPV infection among subgroups of women. An early study found the effects of smoking to be most pronounced among women infected with HPV, but these results may have been limited by imprecise assays to detect HPV (Herrero et al. 1989). Several studies using reliable measures of HPV reported that smoking was not associated with risk for cervical cancer among HPV-positive women (Bosch et al. 1992; Munoz et al. 1993; Eluf-Neto et al. 1994). This finding suggested that cigarette smoking may not affect risk for cervical cancer independently of HPV infection status. However, all these studies were conducted in Latin America, where the effects of smoking on cervical cancer have been found to be weak—possibly because few women in these studies have a history of smoking for a long duration or at a high intensity (Herrero et al. 1989). Thus, it is noteworthy that two studies, one in the United States and the other in Denmark, found smoking to be a risk factor among both HPV-positive and HPV-negative women (Daling et al. 1996; Ylitalo et al. 1999).

Several research teams have attempted to define possible mechanisms by which smoking might alter the cervical epithelium. Because of the high levels of nicotine and cotinine detected in the cervical mucus of smokers, the researchers initially investigated a direct effect of smoking (Sasson et al. 1985; Schiffman et al. 1987; McCann et al. 1992). Zur Hausen (1982) also suggested that the oncogenicity of HPV may be enhanced by certain chemical compounds, including those in tobacco smoke. The results of one study supported this hypothesis (Herrero et al. 1989), but others did not find an enhanced effect of smoking among HPV-positive women (Munoz et al. 1993; Eluf-Neto et al. 1994). More recent studies reported no significant difference in smoking-related DNA damage (DNA adduct levels) in the cervical epithelium of HPV-positive and HPV-negative smokers (Simons et al. 1995). Attention also focused on whether smoking might cause local immunosuppression within the cervix as a result of a decrease in the number of Langerhans' cells (Barton et al. 1988). Some have suggested that such immunosuppression may allow the persistence of HPV. For example, one study showed that the prevalence of HPV was positively associated with the number of cigarettes smoked per day (Burger et al. 1993). Hildesheim and colleagues (1993), however, did not find smoking to be strongly associated with the risk for cervical HPV infection, when correlations with sexual behavior were taken into account. Thus, whether the relationship between smoking and cervical cancer is biological or reflects residual confounding remains unclear.

Further clues to mechanisms of the effects of smoking may be revealed by examining interaction with dietary factors. Several investigators suggested that diets low in carotenoids or vitamin C may predispose women to cervical cancer (Brock et al. 1988; La Vecchia et al. 1988; Verreault et al. 1989). The results of one study suggested that the effects of cigarette smoking were more pronounced among women with high levels of antioxidants than among those with low levels, but these findings were not statistically significant (Brock et al. 1989). Because smokers may have lower levels of plasma beta-carotene than do nonsmokers (Brock et al. 1988) and because nutrition may affect the persistence of HPV (Potischman and Brinton 1996), studies that focus on the combined effects of cigarette smoking, nutrition, and HPV persistence may prove insightful.

The effects of exposure to ETS on risk for cervical cancer began to receive attention in the 1980s. Investigators addressed these effects primarily by studying the smoking behavior of partners of women or by directly questioning women about their passive

exposure to cigarette smoke. Two studies that focused on husbands found that the prevalence of smoking was higher among husbands of women with cervical cancer than among husbands of control subjects (Buckley et al. 1981; Zunzunegui et al. 1986). However, Buckley and colleagues (1981) accounted for the number of sexual partners of the husbands and found that ETS exposure did not persist as a significant predictor of risk. In a study of intraepithelial neoplasia, Coker and colleagues (1992) found no consistent association with ETS exposure. On the other hand, Slattery and associates (1989) found that women with passive exposure to cigarette smoke for three or more hours per day had nearly a threefold increase in risk. In fact, the effect was even more enhanced for women nonsmokers. Additional studies are needed to determine whether ETS exposure actually increases risk for cervical cancer or whether it appears to do so because of confounding factors that have not been adequately controlled in some of the studies to date. McCann and associates (1992) examined nicotine and cotinine levels in cervical mucus and found no real differences between nonsmoking women who did or did not report exposure to ETS.

Vulvar Cancer

In several studies, the risk for cancer of the vulva has been higher among smokers than among nonsmokers (Newcomb et al. 1984; Mabuchi et al. 1985; Brinton et al. 1990). In one investigation, the risk was about twice as high among current smokers than among nonsmokers or former smokers and even higher among current smokers who had smoked at a high intensity (Brinton et al. 1990). The increased risk among current smokers, which was also reported for cervical cancer, is consistent with the action of cigarette smoke as a promoter in the late stages of carcinogenesis.

Results from all studies were limited by the absence of reliable information on the status of HPV infection, which is an accepted risk factor for vulvar cancer (Andersen et al. 1991). Because the risk for vulvar cancer is higher among smokers with a history of condylomata or genital warts, which are caused by HPV infection (Brinton et al. 1990), future studies should address whether data on the effects of smoking are confounded by HPV infection status and whether risk is modified by the presence of HPV. Findings from several small clinical studies (Andersen et al. 1991; Bloss et al. 1991) supported the hypothesis that smoking may predispose women to the subset of vulvar cancers most strongly linked with HPV infection—cancers with intraepithelial-like growth patterns—rather than the well-differentiated vulvar cancers more common among older women. Zur Hausen (1982) proposed that the effect of HPV infection may be enhanced by other risk factors. Immune alterations are a plausible mechanism for this synergistic relationship. Smoking has been linked with several changes in immune function (Hughes et al. 1985; Barton et al. 1988), and HPV infection occurs more commonly among persons with immunosuppression (Sillman et al. 1984).

Conclusions

1. The totality of the evidence does not support an association between smoking and risk for breast cancer.
2. Several studies suggest that exposure to environmental tobacco smoke is associated with an increased risk for breast cancer, but this association remains uncertain.
3. Current smoking is associated with a reduced risk for endometrial cancer, but the effect is probably limited to postmenopausal disease. The risk for this cancer among former smokers generally appears more similar to that of women who have never smoked.
4. Smoking does not appear to be associated with risk for ovarian cancer.
5. Smoking has been consistently associated with an increased risk for cervical cancer. The extent to which this association is independent of human papillomavirus infection is uncertain.
6. Smoking may be associated with an increased risk for vulvar cancer, but the extent to which the association is independent of human papillomavirus infection is uncertain.

Other Cancers

Smoking has been shown to increase the risk for cancer at sites outside the respiratory system, including the digestive system, the urinary tract, and the hematopoietic system. Previously, information on the effects of smoking was derived primarily from epidemiologic studies of men (USDHHS 1989b), but later data from studies of women showed generally similar patterns of risk for equivalent levels of exposure.

Oral and Pharyngeal Cancers

Numerous cohort and case-control studies have shown that the main risk factors for cancers of the mouth and pharynx are smoking and alcohol use

(Blot et al. 1996). These associations hold for cancers of the mouth, tongue, and pharynx, almost all of which are squamous cell carcinomas, but little or no association has been shown for salivary gland tumors, which are extremely rare and are generally adenocarcinomas (Preston-Martin et al. 1988; Horn-Ross et al. 1997).

In almost all populations, oral and pharyngeal cancers occur more frequently among men than among women (Parkin et al. 1992). However, smoking increases the risk for these cancers among both genders. In CPS-II, the risk for death from oral or pharyngeal cancer was five times higher among women current smokers than among women who had never smoked (Table 3.18). In a cohort study from Sweden, women who smoked also had an increased risk for oropharyngeal cancer incidence (Nordlund et al. 1997).

In a large, population-based case-control study that included more than 350 women with cancer, the risk for oral or pharyngeal cancer rose progressively with the duration of smoking and the number of cigarettes smoked. After adjustment for alcohol intake, the risk for oral and pharyngeal cancers was 10 times greater among women who were long-term (≥ 20 years), heavy (≥ 2 packs per day) smokers than among women nonsmokers. Smoking cigarettes and drinking alcohol in combination greatly increased risk. The risk for these cancers was more than 10 times greater among women who had 15 or more drinks a week and smoked 20 or more cigarettes a day for 20 or more years than among women nonsmokers and nondrinkers (Blot et al. 1988). These high RRs may exceed those among men (Blot et al. 1988; Kabat et al. 1994b; Macfarlane et al. 1995; Muscat et al. 1996; Talamini et al. 1998). Among both women and men, the risk for these cancers does not appear to be elevated among persons who had stopped smoking for 10 or more years (Blot et al. 1988; Kabat et al. 1994b; Macfarlane et al. 1995). This rapid reduction in risk suggested that smoking affects a late stage in the process of oral and pharyngeal carcinogenesis and that women can substantially decrease their risk in a fairly short time if they stop smoking. About 60 percent of oral and pharyngeal cancers among women are due to the combined effects of tobacco and alcohol (Blot et al. 1988; Negri et al. 1993), but smoking-related risk for oral and pharyngeal cancer exists even among women who do not drink alcohol (Macfarlane et al. 1995; La Vecchia et al. 1999).

Use of smokeless tobacco also increases the risk for oral cancer, particularly at sites that have direct contact with the tobacco product. This finding has been reported in India and other Asian countries, where use of smokeless tobacco is common (International Agency for Research on Cancer [IARC] 1985; USDHHS 1986a; Nandakumar et al. 1990; Sankaranarayanan 1989a,b, 1990), but evidence also comes from studies of women in rural areas of the southern United States. In a study of women in North Carolina (Winn et al. 1981), the RR for cancers of the cheek and gum rose sharply with use of snuff. Among women who had used snuff for 50 or more years, the risk for oral cancer was 50 times that among women who had not used snuff. Indeed, in this population, nearly all cancers of the gum and buccal mucosa were attributable to long-term use of snuff.

Table 3.18. Relative risks for death from selected cancers among women, by smoking status, Cancer Prevention Study II, 1982–1988

Cancer type	Current smokers	Former smokers
Oral and pharyngeal cancers	5.1	2.3
Laryngeal cancer	13.0	5.2
Esophageal	7.7	2.8
Stomach cancer	1.4	1.4
Colon cancer	1.3	1.2
Rectal cancer	1.4	1.2
Liver cancer	1.6	2.1
Biliary tract cancer	0.7	0.5*
Pancreatic cancer	2.2	1.5
Bladder cancer	2.2	1.9
Kidney cancer	1.3	1.0
Myeloid leukemia	1.2	1.3
Lymphoid leukemia	1.4*	1.4
Multiple myeloma	1.2	1.1
Non-Hodgkin's lymphoma	1.3	0.8
Hodgkin's lymphoma	5.1*	2.6*

Note: Risk relative to women who never smoked.
*Based on <10 deaths.
Source: American Cancer Society, unpublished data.

Laryngeal Cancer

Laryngeal cancer is a relatively rare disease among women; the male-to-female incidence ratio is 5:1. Survival is relatively good; about 70 percent of patients live 5 or more years after diagnosis (Austin and Reynolds 1996). This cancer is caused largely by heavy smoking and heavy drinking of alcohol

(Tavani et al. 1994a; Austin and Reynolds 1996). Data are limited on the relationship between cigarette smoking and laryngeal cancer among women, but these data also showed a much higher risk among smokers than among persons who had never smoked. In CPS-II, the risk for death from laryngeal cancer among women current smokers was 13 times that among women who had never smoked (Table 3.18). Similarly, in a multisite case-control study, Williams and Horm (1977) reported a risk ratio of 17.7 for laryngeal cancer among women who had smoked more than 40 pack-years compared with women nonsmokers. In another case-control study, Wynder and Stellman (1977) found a RR of 9.0 among women who were long-term smokers (>40 years). Case-control studies from Italy and China reported even higher RRs (Zheng et al. 1992; Tavani et al. 1994a). Although the reported RR estimates were based on small numbers of subjects and consequently were not precise, they are compatible with a 10-fold higher risk among current smokers than among nonsmokers. Studies conducted largely among men indicated that smoking cessation decreases the smoking-related risks (Tuyns et al. 1988; Falk et al. 1989).

Esophageal Cancer

Esophageal cancer is also a malignant disease that occurs among men much more often than among women (Parkin et al. 1992). The high male-to-female incidence ratio applies to both squamous cell carcinoma, the most common histologic type of esophageal cancer in most populations, and adenocarcinoma, a cell type rapidly rising in incidence in the United States and parts of Europe (Blot et al. 1991). Smoking, combined with drinking alcohol, has consistently been shown to be a strong risk factor for squamous cell esophageal cancer and appears to increase the risk for adenocarcinoma (Blot 1994; Brown et al. 1994b; Vaughan et al. 1995; Gammon et al. 1997).

Only limited data are available on the effect of smoking on the risk for esophageal cancer among women, but no evidence suggests that these effects differ among women and men. In an investigation of esophageal cancer among women in northern Italy, smoking was the main risk factor and risk increased with the amount smoked; women who smoked one or more packs of cigarettes per day had five times the risk of nonsmokers (Negri et al. 1992; Tavani et al. 1993). Among women in CPS-II, the risk for death from esophageal cancer among current smokers was almost eight times higher than that among women who had never smoked (Table 3.18). Studies of smoking cessation, largely among men, have consistently found excess risk to be reduced, but not eliminated, after cessation (IARC 1986; USDHHS 1989b; Tavani et al. 1993).

Stomach Cancer

Smoking may increase the risk for stomach cancer (McLaughlin et al. 1990; Kneller et al. 1991; Hansson et al. 1994; Nomura 1996; Trédaniel et al. 1997), but some investigators have shown no association (Buiatti et al. 1989; Trédaniel et al. 1997). The excess risks reported have been smaller than those found for oral or esophageal cancer, and dose-response trends have been absent or relatively weak. Nonetheless, differences in diet between smokers and nonsmokers do not appear to totally explain the difference in risk (Hansson et al. 1994).

Among women participating in CPS-II, the risk for mortality from stomach cancer was 40 percent higher among current smokers and former smokers than among never smokers (Table 3.18). These findings are consistent with the evidence among men (McLaughlin et al. 1995a). In several case-control studies, differences by gender in smoking-related risks were small (Haenszel et al. 1972; Kono et al. 1988; Kato et al. 1990; Tominaga et al. 1991; Burns and Swanson 1995; Chow et al. 1999), but several investigators found indications of a weaker effect among women (Trédaniel et al. 1997; Inoue et al. 1999). In both cohort studies (USDHHS 1989b; McLaughlin et al. 1995b) and case-control studies (Hansson et al. 1994), risk for stomach cancer among former smokers was not significantly elevated compared with persons who had never smoked. Subjects in these studies were mostly men.

Colorectal Cancer

Smoking has been associated with a twofold to threefold excess risk for colorectal adenomas, benign precursors of most colorectal cancers (Kikendall et al. 1989; Lee et al. 1993; Neugut et al. 1993; Olsen and Kronborg 1993; Giovannucci et al. 1994a; Newcomb et al. 1995), but its association with colorectal cancer has been more controversial (Kune et al. 1992; Terry and Neugut 1998). Several cohort and case-control studies of women found no excess risk for colon or rectal cancer among smokers (Sandler et al. 1988; Akiba and Hirayama 1990; Chute et al. 1991; Kune et al. 1992; Baron et al. 1994b; Boutron et al. 1995; D'Avanzo et al. 1995a; Engeland et al. 1996; Nordlund et al. 1997; Knekt et al. 1998). However, CPS-II found small

increases in the risk for death from cancers of the colon (RR, 1.3) and rectum (RR, 1.4) among women current smokers on the basis of 6 years of follow-up (Table 3.18). A more detailed analysis after 14 years of follow-up of the CPS-II cohort found that, in general, risk for colorectal cancer death increased with the number of cigarettes smoked and with pack-years of smoking (Chao et al. 2000). Moreover, some cohort studies that had 20 years or more of follow-up showed a moderately elevated risk for colorectal cancer death among smokers, for both women (Doll et al. 1980) and men (Doll et al. 1994; Heineman et al. 1994). In a pair of related cohort studies (Giovannucci et al. 1994a,b), smoking was associated with an increased risk for developing colorectal cancer after a latent period of 35 years among both women and men. Risk for colorectal cancer also has been modestly associated with cigarette smoking in some case-control studies of women (Newcomb et al. 1995; Le Marchand et al. 1997; Slattery et al. 1997). In some analyses, excess risks for long-term smokers were not reduced substantially after smoking cessation (Chute et al. 1991; Heineman et al. 1994; Newcomb et al. 1995). Several other studies of women found smoking-related RRs to be greater for cancer of the rectum than for cancer of the colon (Doll et al. 1980; Inoue et al. 1995; Newcomb et al. 1995).

Liver and Biliary Tract Cancers

Heavy alcohol use and chronic hepatitis B infection are recognized risk factors for hepatocellular carcinoma (IARC 1988), but the role of cigarette smoking is less clear. An early study reported an increased risk for hepatocellular carcinoma, even after adjustment for alcohol intake, among women and men smokers who did not have hepatitis B infection (Trichopoulos et al. 1980). Among the women in CPS-II, the mortality rate for liver cancer was 60 percent higher among current smokers than among those who had never smoked (Table 3.18). In the studies that presented data separately for women (Table 3.19), the RR estimates for liver cancer were generally similar to those among men and ranged from no association (Stemhagen et al. 1983) to a threefold excess risk among current smokers (Tsukuma et al. 1990). Risk for liver cancer rose with increasing number of

Table 3.19. Relative risks for primary liver cancer among women for smokers compared with nonsmokers, case-control studies

Study	Number of cases/controls	Smoking status	Relative risk	95% confidence interval
Stemhagen et al. 1983	151 / 284	Ever smoked	1.0	0.6–1.7
Yu et al. 1988	73 / 202	Former smokers	1.2	NR*
		Current smokers	2.1†	NR
Tsukuma et al. 1990	34 / 73	Current smokers	2.9	1.1–7.9
Yu et al. 1991	25 / 58	Former smokers	1.4	0.3–6.5
		Current smokers	2.4	0.8–6.9
Tanaka et al. 1992	36 / 119	Former smokers	1.7	0.4–7.1
		Current smokers	1.0	0.3–3.2
Goodman et al. 1995	81 / 179,381‡	Former smokers	1.7	0.8–3.6
		Current smokers	1.6	0.9–2.9
Tanaka et al. 1995	117 / 257	Ever smoked		
		0.1–12.9 pack-years§	2.4	1.1–4.9
		≥ 13.0 pack-years	1.8	0.8–3.7

*NR = Value not specified in report of study.
†$p < 0.05$.
‡Number of cases and person-years.
§Pack-years = number of years smoking multiplied by the usual number of packs of cigarettes smoked per day.

cigarettes smoked per day in some studies (Yu et al. 1988, 1991) but not in others (Stemhagen et al. 1983; Tsukuma et al. 1990; Goodman et al. 1995; Tanaka et al. 1995). Smoking cessation has typically been associated with a modest reduction in the RR for liver cancer, particularly after sustained cessation (Yu et al. 1988, 1991; Tsukuma et al. 1990; Goodman et al. 1995), but among women in CPS-II, the RR for death from liver cancer among former smokers was not reduced (Tables 3.18 and 3.19). Thus, smoking may be a contributing factor in the development of liver cancer, but further clarification of the effect among women is needed.

Cancers of the biliary tract include malignant tumors that arise from the gallbladder, extrahepatic bile ducts, and ampulla of Vater (Fraumeni et al. 1996). Smoking-related excess risk for these tumors has been observed in a few case-control studies of women and men combined (Ghadirian et al. 1993; Chow et al. 1994; Moerman et al. 1994), but not in one other case-control study (Yen et al. 1987). Among women in CPS-II, risk for death from biliary tract cancers was lower among smokers than among women who had never smoked (Table 3.18). A nonsignificantly decreased risk for gallbladder cancer was observed in a Swedish follow-up study (Nordlund et al. 1997), but a Japanese cohort study reported a 30-percent excess mortality from this cancer among women who smoked (95 percent CI, 0 to 100 percent) (Akiba and Hirayama 1990). In a study of cancers of the extrahepatic bile duct and ampulla of Vater, the risk was three times higher among women who had smoked more than 50 pack-years than among women who had never smoked, but women who smoked less than 50 pack-years had no excess risk (Chow et al. 1994). Estimates from both the Swedish and Japanese studies were based on a few cases and were imprecise.

Pancreatic Cancer

Studies have consistently demonstrated that smoking increases the risk for pancreatic cancer. Among women in CPS-II, the risk for death from pancreatic cancer was about twice as high among current smokers as among women who had never smoked (Table 3.18). A doubling of risk among women who smoked was also reported in the U.S. Nurses' Health Study (Fuchs et al. 1996) and the Iowa Women's Health Study (Harnack et al. 1997). Cohort studies from Ireland (Tulinius et al. 1997), Japan (Akiba and Hirayama 1990), Norway (Engeland et al. 1996), and Sweden (Nordlund et al. 1997) also indicated elevated risks for pancreatic cancer incidence or mortality among women who smoked. In a large case-control study of pancreatic cancer in the United States, risk was twice as high among current smokers as among women and men who had never smoked. The RRs were similar among women and men and increased with both the number of cigarettes smoked and the duration of smoking (Silverman et al. 1994). The risk was elevated more than threefold among smokers who smoked 40 or more cigarettes per day for at least 40 years. Other investigators found similar elevations in RRs among women and men (MacMahon et al. 1981; Kinlen and McPherson 1984; Wynder et al. 1986; Cuzick and Babiker 1989; Muscat et al. 1997).

Studies that have included both women and men make clear that the excess risk for pancreatic cancer associated with smoking declines after smoking cessation, regardless of the number of cigarettes smoked or the duration of smoking (Mack et al. 1986; Howe et al. 1991; Silverman et al. 1994; Ji et al. 1995; Fuchs et al. 1996). Nonetheless, former smokers who stop smoking for more than 10 years may retain a 20- to 30-percent excess risk (Howe et al. 1991; Silverman et al. 1994). The risk associated with smoking is not explained by the confounding effects of alcohol consumption—another suspected risk factor (Velema et al. 1986). Up to one-third of pancreatic cancers among women may be attributable to smoking (USDHHS 1989b; Silverman et al. 1994).

Urinary Tract Cancers

Cancers of the urinary tract comprise only about 7 percent of all cancers, but their incidence is rising (Devesa et al. 1990, 1995). Bladder cancer accounts for about 67 percent of all urinary tract cancers, cancer of the renal parenchyma (renal cell cancer) 23 percent, cancer of the renal pelvis 5 percent, and ureteral and miscellaneous tumors 5 percent. For these cancers, male-to-female incidence ratios are 3.9 for bladder cancer, 2.3 for renal cell cancer, 2.3 for cancer of the renal pelvis, and 2.9 for cancer of the ureter.

Smoking is a significant risk factor for cancer of each part of the urinary tract (McLaughlin et al. 1996; Silverman et al. 1996). The transitional cell cancers of the lower urinary tract (renal pelvis, ureter, and bladder) are more strongly related to smoking than are the adenocarcinomas of the renal parenchyma (renal cell cancers). For cancers of the renal pelvis and ureter, risk increases markedly with the number of cigarettes smoked and the duration of smoking. Long-term smokers (>45 years) have up to a sevenfold excess risk (Ross et al. 1989; McLaughlin et al. 1992).

In CPS-II, mortality from bladder cancer among women was more than 100 percent higher among current smokers than among those who had never smoked (Table 3.18); mortality from kidney cancer was 30 percent higher. Similar excess risks from smoking were found for bladder cancer mortality or incidence among women in cohort studies from Japan (Akiba and Hirayama 1990), Norway (Engeland et al. 1996), and Sweden (Nordlund et al. 1997). In the largest studies of specific urinary tract cancers and smoking, the lowest RR among women was found for renal cell cancer (adenocarcinoma of the renal parenchyma) and the highest for cancer of the renal pelvis and ureter; the risk for bladder cancer was intermediate (McLaughlin et al. 1992, 1995b; Hartge et al. 1993) (Table 3.20). Dose-response patterns were found for each cancer site. For each of these cancers, the risk among former smokers was less than that among current smokers (Hartge et al. 1987, 1993; Ross et al. 1989; McLaughlin et al. 1992,

Table 3.20. Relative risks for urinary tract cancer among women for smokers compared with nonsmokers, case-control studies

Study	Number of cases/controls	Exposure	Relative risk	95% confidence interval
		Renal pelvis		
McLaughlin et al. 1992	115 / 181	Never smoked	1.0	
		Ever smoked	2.0	1.2–3.5
		<20 cigarettes / day	1.4	0.7–3.0
		20–39 cigarettes / day	2.7	1.4–5.2
		≥ 40 cigarettes / day	3.4	0.9–13.4
		Ureter		
McLaughlin et al. 1992	56 / 181	Never smoked	1.0	
		Ever smoked	3.1	1.4–7.0
		<20 cigarettes / day	2.4	0.9–6.4
		20–39 cigarettes / day	4.2	1.6–11.3
		≥ 40 cigarettes / day	3.7	0.4–38.9
		Bladder		
Hartge et al. 1993	666 / 1,401	White women	1.0	
		Never smoked		
		Former smokers		
		<20 cigarettes / day	2.0	1.4–2.7
		≥ 20 cigarettes / day	1.3	0.9–2.0
		Current smokers		
		<20 cigarettes / day	2.0	1.5–2.7
		≥ 20 cigarettes / day	3.1	2.4–4.2
		Black women		
		Never smoked	1.0	
		Former smokers		
		<20 cigarettes / day	3.6	1.0–13.0
		≥ 20 cigarettes / day	5.0	0.9–28.0
		Current smokers		
		<20 cigarettes / day	1.7	0.6–4.7
		≥ 20 cigarettes / day	2.1	0.4–10.0
		Renal parenchyma		
McLaughlin et al. 1995b	682 / 880	Never smoked	1.0	
		Ever smoked	1.2	0.9–1.5
		1–20 cigarettes / day	1.1	0.9–1.4
		>20 cigarettes / day	2.2	1.1–3.2

1995b; Silverman et al. 1996). Other studies confirmed these findings (McCredie et al. 1982; Morrison et al. 1984; Piper et al. 1986; Jensen et al. 1988; Wynder et al. 1988; Burch et al. 1989; La Vecchia et al. 1990; Burns and Swanson 1991; McCredie and Stewart 1992; Nordlund et al. 1997; Yuan et al. 1998).

The large-scale studies described in Table 3.20 reported that, among women, the proportion of cancers due to smoking was 9 percent for renal cell cancer (McLaughlin et al. 1995b), 31 percent for cancer of the renal pelvis and 46 percent for cancer of the ureter (McLaughlin et al. 1992), and 32 percent for bladder cancer (Hartge et al. 1987, 1993). Other studies of renal cell cancer reported population attributable risks ranging from 14 to 24 percent among women (McLaughlin et al. 1984; McCredie and Stewart 1992).

Thyroid Cancer

Although thyroid cancer is often studied as a single entity, four principal histologic types are recognized: papillary, follicular (well differentiated), medullary, and anaplastic (poorly differentiated). Papillary thyroid cancer is the most common type (50 to 80 percent of thyroid cancers in a given series), and follicular thyroid cancer is the next most common type (10 to 40 percent). Mortality from anaplastic thyroid cancer is high, but the five-year survival rates among patients with the other histologic types approach 95 percent (Ron 1996). Because papillary and follicular thyroid carcinomas occur more frequently among women than among men, women have a higher overall risk for thyroid cancer than do men.

Exposure to ionizing radiation is a well-established risk factor for thyroid cancer. Thyroid diseases such as goiter, thyrotoxicosis, and benign nodules have also been associated with an increased risk (McTiernan et al. 1984b; Preston-Martin et al. 1987; Ron et al. 1987; D'Avanzo et al. 1995b; Galanti et al. 1995b). A high body mass index (BMI) may also be a risk factor (Ron et al. 1987; Goodman et al. 1992; Preston-Martin et al. 1993).

The higher incidence of thyroid cancer among women than among men suggests a causative role for female sex hormones. In fact, evidence indicated that estrogens probably act as late promoters of thyroid tumor growth in rodents (Mori et al. 1990). In epidemiologic studies of women, use of exogenous steroid hormones (OCs and hormone replacement therapy [HRT]) has inconsistently been associated with an increased risk for thyroid cancer (Franceschi et al. 1993), and reproductive history may be associated with risk (Preston-Martin et al. 1987, 1993; Ron et al. 1987; Franceschi et al. 1990; Kolonel et al. 1990; La Vecchia et al. 1993b; Levi et al. 1993; Galanti et al. 1995a; Paoff et al. 1995).

Investigations of smoking and risk for thyroid cancer have reported conflicting results. Studies that did not separate findings among women and men have not presented a consistent pattern (Ron et al. 1987; Sokic et al. 1994). Apparently no association exists specifically among men, but the data are scanty (Williams and Horm 1977; Kolonel et al. 1990; Hallquist et al. 1994). Among women, however, the majority of studies have found an inverse association between smoking and risk for thyroid cancer (McTiernan et al. 1984a; Kolonel et al. 1990; Hallquist et al. 1994; Galanti et al. 1996).

A Scandinavian case-control study has presented the most detailed data on smoking and thyroid cancer among women (Galanti et al. 1996). Risk was lower among premenopausal women who had ever smoked than among those who had never smoked (RR, 0.6; 95 percent CI, 0.4 to 0.96), particularly among those who started smoking before the age of 15 years (RR, 0.4; 95 percent CI, 0.3 to 0.8). Findings in this study also suggested a dose-response effect related to the number of cigarettes smoked per day and the duration of smoking. The results persisted after careful control of covariates such as reproductive history, use of exogenous hormones, and socioeconomic indicators.

One case-control study explored the association between maternal cigarette smoking during pregnancy and risk for thyroid cancer among their offspring (Paoff et al. 1995). More control mothers than case mothers smoked during pregnancy, but the investigators found no evidence of a dose-response relationship.

It is not clear why cigarette smoking would be associated with a reduced risk for thyroid cancer. Smokers have lower levels of thyroid-stimulating hormone than do nonsmokers (Bertelsen and Hegedüs 1994), and they could have a lower thyroid cancer risk because of reduced thyroid stimulation. However, this mechanism should lead to a reduced risk among both women and men. Another possible explanation for a reduced risk among women is the antiestrogenic effect of smoking (Baron et al. 1990), which could counteract the excess risk due to estrogen-related stimuli among women. Identification of thyroid cancer and particularly of papillary

cancers among young women is, however, largely influenced by the intensity of medical surveillance (Ron 1996). Because nonsmoking women are more health conscious than are smokers, their excess risk for thyroid cancer may be partially explained by enhanced diagnosis of the disease. This possibility may also explain the inconsistent results among former smokers.

Lymphoproliferative and Hematologic Cancers

Of the various hematopoietic malignant diseases, only acute myeloid leukemia has been consistently associated with smoking. RRs among smokers have ranged from 1.3 to nearly 3.0, but typically have been about 1.5 (Siegel 1983; Brownson et al. 1993; Kabat et al. 1994a). In CPS-II, women current smokers had an increased risk for mortality from myeloid and lymphoid leukemias (Table 3.18). A limited number of other studies presented gender-specific results. The excess risk for leukemia associated with smoking was similar among women and men in some of these studies (Williams and Horm 1977; Brownson et al. 1991), but in other investigations, the association was stronger among men (Garfinkel and Boffetta 1990; Friedman 1993). An upward trend in the risk for leukemia with increasing cigarette consumption was suggested in several studies (Kabat et al. 1994a), including one that reported separate data for women (Williams and Horm 1977). Limited evidence suggests that RRs may be reduced with increasing years of smoking cessation (Severson et al. 1990).

In general, multiple myeloma has not been associated with tobacco use (Garfinkel 1980; Boffetta et al. 1989; Brownson 1991; Heineman et al. 1992; Linet et al. 1992; Friedman 1993; Adami et al. 1998), although a few studies—generally those based on few participants—reported an increase in risk (Williams and Horm 1977; Mills et al. 1990). Findings specific among women are scant, but in both CPS-I and CPS-II, mortality from multiple myeloma was similar among women who smoked and among those who had never smoked (Garfinkel 1980) (Table 3.18). Two other cohort studies also found no association between multiple myeloma and cigarette smoking among women (Friedman 1993; Nordlund et al. 1997).

In some studies, investigators reported a modest excess risk for non-Hodgkin's lymphomas among smokers (Williams and Horm 1977; Franceschi et al. 1989; Brown et al. 1992; Linet et al. 1992; Zahm et al. 1997; De Stefani et al. 1998). In CPS-II, mortality from non-Hodgkin's lymphoma was slightly higher among women who smoked than among those who had never smoked (Table 3.18). However, other studies reported no substantial association (Hoar et al. 1986; Doll et al. 1994; Tavani et al. 1994b; McLaughlin et al. 1995a; Siemiatycki et al. 1995; Nelson et al. 1997; Herrinton and Friedman 1998). Some investigators proposed that smoking may confer higher risks among younger persons (Freedman et al. 1998) or among women (Zahm et al. 1997).

The association between Hodgkin's lymphoma and smoking has not been adequately examined. Some studies (Williams and Horm 1977; McLaughlin et al. 1995a; Siemiatycki et al. 1995; Mueller 1996; Nordlund et al. 1997; Pasqualetti et al. 1997) presented data regarding the relationship between smoking and the risk for Hodgkin's lymphoma, but the small number of cases prevents any conclusions. The risk for mortality from Hodgkin's disease was five times higher among women current smokers in CPS-II (Table 3.18) than among women who had never smoked, but this observation, based on only 10 deaths, lacks precision.

Conclusions

1. Smoking is a major cause of cancers of the oropharynx and bladder among women. Evidence is also strong that women who smoke have increased risks for cancers of the pancreas and kidney. For cancers of the larynx and esophagus, evidence among women is more limited but consistent with large increases in risk.
2. Women who smoke may have increased risks for liver cancer and colorectal cancer.
3. Data on smoking and cancer of the stomach among women are inconsistent.
4. Smoking may be associated with an increased risk for acute myeloid leukemia among women but does not appear to be associated with other lymphoproliferative or hematologic cancers.
5. Women who smoke may have a decreased risk for thyroid cancer.
6. Women who use smokeless tobacco have an increased risk for oral cancer.

Cardiovascular Disease

Cardiovascular diseases (CVDs) are disorders of the circulatory system, including diseases of the heart, cerebrovascular diseases, atherosclerosis, and other diseases of blood vessels. This group of diseases accounts for a greater proportion of deaths among women (42.3 percent) than among men (38.1 percent) (Murphy 2000). These disease processes interfere with the blood supply to important organs and can lead to serious clinical events such as myocardial infarction (MI; heart attack) and stroke. Impairment of the blood supply to the limbs can lead to pain and even a need for amputation. In this section, evidence on the relationship between smoking and the following cardiovascular conditions among women is reviewed: coronary heart disease (CHD), cerebrovascular disease, carotid atherosclerosis, peripheral vascular disease, abdominal aortic aneurysm, and hypertension.

Coronary Heart Disease

Smoking-Associated Risks

Each year, more than 500,000 women in the United States have an MI, and about one-half of them die from the event (Rich-Edwards et al. 1995). Despite a continuing decline since the 1960s in mortality from CHD, this condition still ranks first among the causes of death for middle-aged and older women (Eaker et al. 1993).

Epidemiologic data gathered during the past 40 years clearly point to the causative role of smoking in CHD: more than a dozen prospective studies indicated that women who smoke are at increased risk (Table 3.21). Studies in addition to those listed in Table 3.21 include the Tecumseh (Michigan) Community Health Study (Higgins et al. 1987), the Walnut Creek (California) Study (Perlman et al. 1988), and the Lipid Research Clinics Follow-up Study (Bush et al. 1987).

More than 20 years ago, smoking was recognized as a major independent cause of CHD among women—increasing their risk for CHD by a factor of about 2 (USDHHS 1980, 1983). The risk for CHD rises with the number of cigarettes smoked daily, the total number of years of smoking, the degree of inhalation, and early age at initiation of smoking. In the U.S. Nurses' Health Study, even women who smoked as few as one to four cigarettes per day had twice the risk for CHD as women who had never smoked (Willett et al. 1987; Kawachi et al. 1994); an analysis of data from that large cohort study after 14 years of follow-up found that 41 percent of coronary events in the study population were attributable to current smoking (Stampfer et al. 2000). Cigarette smoking acts together with other risk factors, particularly elevated serum cholesterol and hypertension, to greatly increase the risk for CHD. When the amount smoked and the duration of smoking are taken into account, the relative increase in death rates from CHD among smokers is similar for women and men, but the absolute increase in risk is higher among men (USDHHS 1983).

The effect of smoking on CHD risk among women seems to be relatively similar regardless of racial or ethnic group. In one study (Friedman et al. 1997) that included a substantial number of minority women, the age-adjusted RR for CHD mortality among current smokers compared with those who had never smoked was 2.3 ($p < 0.05$) for black women, 2.2 ($p > 0.05$) for Asian women, and 1.6 ($p < 0.05$) for white women. These RRs do not take into account the numbers of cigarettes smoked daily, so some differences in RRs may be due to differences in smoking patterns.

About 41 percent of deaths from CHD among U.S. women younger than 65 years of age and 12 percent among women older than 65 years have been attributed to cigarette smoking (USDHHS 1989b). Smoking has been associated with particularly high RRs among younger women (<50 years old) (Slone et al. 1978; Rosenberg et al. 1980a, 1985); consequently, the proportion of CHD cases attributable to cigarette smoking is high in this age group. According to one estimate in 1985, cigarette smoking may account for as much as two-thirds of the incidence of CHD among women younger than 50 years of age (Rosenberg et al. 1985).

More recent epidemiologic investigations have tended to report higher RRs for CHD among women who smoke than did earlier studies. For example, the 1989 Surgeon General's report on reducing the health consequences of smoking compared findings from the two ACS cohort studies conducted about 20 years apart (USDHHS 1989b). Both studies used identical sampling schemes. In the six-year follow-up of CPS-I in 1959–1965, the age-adjusted RRs for CHD among current smokers compared with those who had never

smoked were 1.8 (95 percent CI, 1.7 to 2.0) among women aged 35 through 64 years and 1.2 (95 percent CI, 1.1 to 1.4) among women aged 65 years or older. In CPS-II, with follow-up during 1982–1986, the age-adjusted RRs for CHD were 3.0 (95 percent CI, 2.5 to 3.6) among women aged 35 through 64 years and 1.6 (95 percent CI, 1.4 to 1.8) among women aged 65 years or older. The latter findings were replicated in a six-year follow-up of CPS-II (Thun et al. 1997a).

Several factors could explain the higher RRs found in more recent studies of the association between smoking and CHD among women. These factors include the declines in overall cardiovascular mortality, as well as the higher number of cigarettes smoked daily and the longer duration of smoking among women in more recent years (Thun et al. 1997a). Early age at initiation of smoking is also associated with a markedly elevated risk for CHD, presumably because it is related to longer duration of smoking. In the U.S. Nurses' Health Study, early age at initiation was one of the strongest risk factors for CHD (Kawachi et al. 1994). Compared with women who had never smoked, women current smokers who started smoking before age 15 years had a RR of 9.3 (95 percent CI, 5.3 to 16.2). Even among women former smokers, the RR was 7.6 (95 percent CI, 2.5 to 22.5) for those who started smoking before age 15 years compared with those who had never smoked. The age at smoking initiation steadily declined for successive birth cohorts of U.S. women up to the 1960 birth cohort (see "Smoking Initiation" in Chapter 2). Data from the National Health Interview Survey (NHIS) indicated that the proportion of women who started to smoke before age 16 years increased from 7.2 percent among those born in 1910–1914 to 20.2 percent among those born in 1950–1954 (USDHHS 1989b). Thus, in more recent birth cohorts, duration of exposure to smoking has been longer because of early age at initiation.

The data on smoking cessation and CHD risk indicated a rapid, partial decline in risk followed by a gradual decline that eventually reaches the level of risk among persons who had never smoked (USDHHS 1990). The excess risk for CHD associated with smoking is reduced by 25 to 50 percent after 1 year of smoking abstinence; after 10 to 15 years of abstinence, the risk for CHD is similar to that of persons who had never smoked. Although most of the data were derived from white men, sufficient information is available about women to indicate that similar conclusions can be drawn for both genders (USDHHS 1990).

Studies of the effects of smoking cessation on the risk for CHD among women are summarized in Tables 3.22 and 3.23. The findings indicated a rapid decline in risk for CHD soon after smoking cessation. The case-control studies indicated a reduction of 30 to 45 percent in excess CHD risk among former smokers within one year of smoking cessation (Table 3.22). This reduction represents 35 to 70 percent of the eventual benefit (reduction in CHD risk) from permanent cessation. Similarly, two cohort studies (Omenn et al. 1990; Kawachi et al. 1994) found a 25-percent reduction in risk for CHD among former smokers within two years of cessation. This reduction represents one-third to one-half of the full potential benefit of cessation (Table 3.23).

These studies (Tables 3.22 and 3.23) also suggested that 10 years or more of smoking cessation must elapse before the risk for CHD among former smokers approaches that among persons who had never smoked. The case-control study by Dobson and colleagues (1991a) showed almost a complete reversal in risk after 3 years of cessation (RR, 1.3) among former smokers, but the other data summarized in Tables 3.22 and 3.23 indicated that virtually complete reversal of risk is achieved only after more prolonged cessation.

Data from two studies (LaCroix et al. 1991; Paganini-Hill and Hsu 1994) that included women older than 65 years of age demonstrated that the benefits of smoking cessation also apply to older women. Indeed, the Established Populations for Epidemiologic Studies of the Elderly found a complete reversal in risk for CHD within five years of cessation (RR, 1.0; 95 percent CI, 0.5 to 2.1) (LaCroix et al. 1991). Risk declined among women who had stopped smoking either before or after 65 years of age. In contrast, the Leisure World Cohort Study found a significant difference in RR by age at cessation (Paganini-Hill and Hsu 1994). The study indicated that women who had stopped smoking at ages younger than 65 years had a RR for CHD mortality of 1.2 (95 percent CI, 0.9 to 1.5) and that women who had stopped at age 65 years or older had a RR of 1.6 (95 percent CI, 1.2 to 2.0).

Although the RR for CHD among current smokers tends to be lower for older persons than for younger persons, smoking cessation among older persons has a greater absolute effect because the rate of CHD is much higher in this group (USDHHS 1990). For example, in CPS-II, the RR for CHD mortality was 7.2 among women current smokers aged 45 through 49 years compared with women in the same age group who had never smoked; the corresponding RR among women aged 75 through 79 years was 1.6 (Thun et al. 1997c). However, the absolute difference in CHD mortality among smokers and nonsmokers aged 45

Table 3.21. Relative risks for coronary heart disease (CHD) among women for current smokers compared with nonsmokers, cohort studies

Study	Population	Number of years of follow-up	Outcome	Number of cases	Smoking status	Relative risk (95% confidence interval)
Cederlöf et al. 1975	28,000 women Aged 18–69 years Sweden	10	Death from CHD	457	Never smoked Current smokers Aged 50–59 years Aged 60–69 years	1.0 2.6* 1.1*
Doll et al. 1980	6,194 women physicians Aged ≥ 20 years United Kingdom	22	Death from CHD	179	Never smoked Current smokers 1–14 cigarettes / day 15–24 cigarettes / day ≥ 25 cigarettes / day	1.0 1.0* 2.2* 2.1*
Barrett-Connor et al. 1987	2,048 women Aged 50–79 years United States	10	Death from CHD	59	Aged 50–64 years Never smoked Current smokers Aged 65–79 years Never smoked Current smokers	 1.0 2.7* 1.0 1.0*
Hirayama 1990	142,857 women Aged ≥ 40 years Sampled from Japanese census	17	Death from ischemic heart disease	1,378	Nonsmokers[†] Current smokers 1–9 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.7 (1.4–2.5) 2.3 (1.9–2.7) 3.8 (2.9–4.9)
LaCroix et al. 1991	4,469 women Aged ≥ 65 years United States	10	Death from CHD	NR[‡]	Never smoked Current smokers	1.0 1.7 (1.3–2.3)
Freund et al. 1993	2,587 women Aged 45–84 years United States	34	Angina Coronary insufficiency Myocardial infarction Death from CHD	303	Aged 45–64 years Nonsmokers[†] Current smokers Aged 65–84 years Nonsmokers Current smokers	 1.0 1.2 (1.0–1.6) 1.0 1.2 (0.9–1.6)

*95% confidence interval was not reported.
[†]Women who were never smokers and women who were former smokers combined.
[‡]NR = Value not specified in report of study.

through 49 years was 23.8 deaths per 100,000 woman-years; among women aged 70 through 79 years, the difference was 316.6 deaths per 100,000 woman-years.

Some investigations have reported that persons who stop smoking tend to have smoked fewer cigarettes per day and to have started at an older age than those who continue to smoke (USDHHS 1990). In most of the studies discussed in this chapter, risk estimates were not adjusted for the number of cigarettes smoked per day before cessation or for age at smoking initiation—omissions that could lead to overestimation of the benefits of cessation (Kawachi et al. 1993a). In practice, however, such a bias does not seem to occur. In the U.S. Nurses' Health Study, the temporal pattern in reduction of CHD risk after smoking cessation was similar among women regardless of the number of cigarettes smoked per day before cessation, the age at smoking initiation, and

Table 3.21. Continued

Study	Population	Number of years of follow-up	Outcome	Number of cases	Smoking status	Relative risk (95% confidence interval)
Kawachi et al. 1994	117,006 women nurses	12	CHD incidence	215	Never smoked	1.0
	Aged 30–55 years				Current smokers	
	United States			93	1–14 cigarettes / day	2.5 (1.8–3.5)
				242	15–24 cigarettes / day	4.8 (3.8–6.1)
				123	25–34 cigarettes / day	5.5 (4.1–7.4)
				79	≥ 35 cigarettes / day	5.5 (3.9–7.8)
Paganini-Hill and Hsu 1994	8,869 women	10	Death from CHD	NR	Never smoked	1.0
	Median age, 73 years				Current smokers	1.5 (1.1–1.9)
	United States					
Njølstad et al. 1996	5,701 women	12	CHD incidence	20	Never smoked	1.0
	Aged 35–52 years			73	Current smokers	3.6 (2.2–6.0)
	Norway			19	1–9 cigarettes / day	2.3 (1.2–4.2)
				40	10–19 cigarettes / day	4.1 (2.4–7.1)
				13	≥ 20 cigarettes / day	5.9 (2.9–11.8)
Burns et al. 1997b	594,551 women	12	Death from CHD	7,065	Never smoked	1.0
	Aged >30 years			1,248	Current smokers	1.4 (1.3–1.5)
	United States					
Freidman et al. 1997	36,035 women	6	Death from CHD	134	Never smoked	1.0
	Aged ≥ 35 years				Current smokers	
	Enrolled in health maintenance organization			20	≤ 19 cigarettes / day	1.4*
				30	≥ 20 cigarettes / day	2.2*
Thun et al. 1997c	676,527 women	6	Death from CHD	3,717	Never smoked	1.0
	Aged >30 years			1,161	Current smokers	1.6 (1.4–1.7)
	United States					

*95% confidence interval was not reported.

other risk factors for CVD (Kawachi et al. 1994) (Table 3.23). Similarly, in a case-control study from Italy, Negri and colleagues (1994) reported that the time course of reduction in risk for acute MI after smoking cessation was similar among women and men who had smoked less than 30 years and among those who had smoked longer.

The benefits of smoking cessation seem to apply even among women with established coronary atherosclerosis. The Coronary Artery Surgery Study, which included 5,386 women evaluated by angiography (Omenn et al. 1990), showed that the time course of reduction in risk for CHD mortality after smoking cessation was similar among women with or without coronary atherosclerosis.

In summary, studies of smoking cessation among women indicated a substantial (25- to 45-percent) reduction in excess risk for CHD within 1 to 2 years of cessation. This immediate benefit is followed by an additional gradual benefit: at least 5 years and perhaps 10 to 15 years of cessation or more may be needed for the risk among former women smokers to be reduced to the risk among women who had never smoked. These benefits are, however, available to women regardless of current age, age at smoking initiation, age at cessation, number of cigarettes smoked daily before cessation, duration of smoking, and presence of established CHD.

Smoking and Use of Oral Contraceptives

Epidemiologic investigation of the effects of oral contraceptives (OC) use on health is complicated because of changes in prescribing practices that resulted from early studies suggesting an association between OC use and CHD. Physicians may avoid prescribing OCs for women considered at increased risk for CHD, and heightened suspicion of disease in those who use OCs may have led to intensive investigation of symptoms (Stolley et al. 1989). Moreover, the composition of OC pills has changed over time. When OCs were introduced 30 years ago, they contained 150 µg of ethinyl estradiol and 10 mg of progestin, 5 and 10 times the current doses, respectively. As early as 1974, the estrogen component was as low as 20 µg in some preparations, but even in 1983 about one-half of OC prescriptions were still for formulations containing 50 µg or more of ethinyl estradiol (Mishell 1991). OCs now in widespread use in the United States contain 30 or 35 µg of estrogen (Petitti et al. 1996).

Studies conducted before the 1983 Surgeon General's report on smoking and CVD (USDHHS 1983) indicated that OC users had an increased risk for CHD (Stadel 1981; Sartwell and Stolley 1982). Overall, women who used OCs were reported to

Table 3.22. Relative risks for coronary heart disease (CHD) among women, by time since smoking cessation, case-control studies

Study	Population	Type of CHD	Number of controls	Source of controls	Number of cases	Smoking status	Relative risk (95% confidence interval)
Thompson et al. 1989	Women physicians Aged 45–69 years United Kingdom	275 definite, 84 possible myocardial infarctions	718	British women physicians	NR* NR NR NR NR NR NR NR	Never smoked Current smokers Former smokers Cessation for: 1–2 years 3–5 years 6–10 years 11–15 years >15 years	1.0 2.6† 1.1† 1.9† 1.6† 1.2† 0.95† 0.7†
Dobson et al. 1991a	Women Aged 35–69 years Australia	Nonfatal myocardial infarction and fatal CHD	1,031	Participants in community survey of risk factor prevalence	174 127 86 15 7 19 9 9 7 19	Never smoked Current smokers Former smokers Cessation for: <6 months 6–<12 months 1–3 years 4–6 years 7–9 years 10–12 years >12 years	1.0 4.7 (3.4–6.6) 1.5 (1.1–2.2) 3.2 (1.2–9.2) 10.0 (2.1–47.1) 2.9 (1.2–6.7) 1.3 (0.5–3.4) 1.3 (0.5–3.2) 1.7 (0.6–4.9) 0.7 (0.4–1.4)
Negri et al. 1994	Women Aged 24–74 years Italy	Acute myocardial infarction	130	Hospital patients	115‡	Never smoked Current smokers Former smokers Cessation for: 1–5 years >5 years	1.0 5.8† 2.5† 0.7†

*NR = Value not specified in report of study.
†95% confidence interval was not reported.
‡There were 115 cases altogether; number was not split by type of smoker or by years of smoking cessation.

have about 4 times the MI risk of nonusers, but smokers who used OCs had a risk for MI about 10 times that of women who neither used OCs nor smoked (USDHHS 1983). In some studies, women who used OCs and smoked heavily (≥ 25 cigarettes per day) had up to a 40-fold increase in risk than did those who did not smoke or use OCs (Shapiro et al. 1979). Thus the risk from combined tobacco and OC exposure was greater than expected from the magnitude of the risk from OCs or smoking alone (Croft and Hannaford 1989).

The more recently available lower dose OC pills may be associated with a lower risk for CHD than are the higher dose preparations (Mant et al. 1987; Porter et al. 1987; Thorogood et al. 1991; Palmer et al. 1992; Sidney et al. 1998; Dunn et al. 1999). Nevertheless, studies continued to report a substantial excess risk for CHD among heavy smokers who currently use OCs (Rosenberg et al. 1985; Stampfer et al. 1988b; D'Avanzo et al. 1994; WHO Collaborative Study 1997) and indicated that the risk for MI associated with OCs may be concentrated among women who smoke (Stampfer et al. 1988b). In a case-control study of acute MI among women (Rosenberg et al. 1985), the RR was 3.1 (95 percent CI, 0.4 to 22.0) for current OC users who smoked 1 to 24 cigarettes per day compared with nonsmokers who used OCs. Among OC users who smoked 25 or more cigarettes per day, the RR was 23.0 (95 percent CI, 6.6 to 82.0). In the WHO Collaborative Study (1997), women who smoked 10 or more cigarettes per day and used OCs had a multivariate RR of 87.0 (95 percent CI, 29.8 to 254.0) compared with nonsmokers who did not use OCs. This elevation in risk is considerably greater than that which would be expected from the individual effects of smoking and OCs. The RR for MI associated with OC use among nonsmokers was 4.0 (95 percent CI, 1.5 to 10.4), and the RR for smoking 10 or more cigarettes per day among women who did not use OCs was 11.1 (95 percent CI, 5.7 to 21.8). Only exceedingly sparse data are currently available on the risk for CHD among smokers who use "third-generation" OCs—preparations containing 30 µg or less of ethinyl estradiol and either gestodene or desogestrel (Lewis et al. 1996).

The clinical recommendation has been that women who smoke, especially older women (e.g., >40 years), should be counseled against using OCs. A consensus panel reviewed the evidence on the health effects of OC use and smoking and recommended that women older than 35 years of age who smoke more than 15 cigarettes per day should not take OCs (Schiff et al. 1999). However, because cigarette smoking confers a higher risk for MI than does OC use, it may be more appropriate to advise women who use OCs to stop smoking (Hennekens and Buring 1985).

Smoking and Hormone Replacement Therapy

A meta-analysis of 31 case-control and cohort studies published before 1991 found a highly significant reduction in CHD risk (RR, 0.6; 95 percent CI, 0.5 to 0.6) for women who were taking HRT (Stampfer and Colditz 1991). Because smoking accelerates catabolism of oral estrogens, serum estrogen levels are lower among postmenopausal smokers who receive oral HRT than among nonsmokers who receive HRT (Jensen et al. 1985; Cassidenti et al. 1990). Consequently, the potential beneficial effects of HRT on CHD risk may be attenuated among smokers. This was indeed the case in one prospective study (Henderson et al. 1988), although the statistical significance of the finding was not addressed. In a case-control study, the protective effect of estrogen replacement therapy on fatal ischemic heart disease was similarly more marked among nonsmokers (Ross et al. 1981). In a case-control study of women aged 45 through 64 years, the protective effect of HRT on MI risk was also confined to nonsmokers (Mann et al. 1994). The RR among HRT users was 0.7 (95 percent CI, 0.5 to 1.0) for nonsmokers and 1.1 (95 percent CI, 0.7 to 1.5) for current smokers. However, smoking status was unknown for about one-half of the participants, and the data were more complete among case subjects than among control subjects.

A different interaction between HRT use and smoking status was reported from a 12-year follow-up study of 1,868 women aged 50 through 79 years who resided in a planned community (Criqui et al. 1988). Among HRT users, current smokers had a RR for CHD mortality of 0.4 (95 percent CI, 0.1 to 1.3), but former smokers had a RR of 2.3 (95 percent CI, 0.8 to 6.6); for women who had never smoked, the RR was 0.95 (95 percent CI, 0.5 to 2.0). In other studies, no substantial difference was observed in the effect of HRT between women who smoked and those who did not (Rosenberg et al. 1980b, 1993; Grodstein and Stampfer 1998; Hulley et al. 1998).

Thinking about the role of estrogens in heart disease is now tempered by the results of a randomized clinical trial of estrogen plus progestin for the secondary prevention of heart disease (Hulley et al. 1998) and by very preliminary results from the Women's Health Initiative, a large trial that is investigating whether HRT affects risk for CVD and other outcomes (Kolata 2000). Contrary to expectation, both studies

Table 3.23. Relative risks for coronary heart disease (CHD) among women, by time since smoking cessation, cohort studies

Study	Population	Number of years of follow-up	Outcome	Number of cases	Smoking status	Relative risk (95% confidence interval)
Omenn et al. 1990	5,386 U.S. women Aged >35 years‡	10	Death from CHD	NR*†	Never smoked	1.0
					Current smokers	1.7 (1.3–2.3)
					Former smokers	
					Cessation for:	
					≤ 1 year	1.3 (0.96–1.9)
					2–9 years	1.3 (0.9–1.8)
					10–19 years	1.1 (0.7–1.9)
					≥ 20 years	0.9 (0.4–1.8)
LaCroix et al. 1991	4,469 women Aged ≥ 65 years 3 U.S. communities	5	Death from cardiovascular disease	NR§	Never smoked	1.0
					Current smokers	1.7 (1.3–2.4)
					Former smokers	
					Cessation for:	
					≤ 5 years	1.0 (0.5–2.1)
					6–10 years	1.0 (0.5–2.0)
					11–20 years	0.5 (0.2–1.1)
					>20 years	0.8 (0.4–1.4)
Kawachi et al. 1994	117,006 U.S. women nurses Aged 30–55 years	12	Nonfatal myocardial infarction	418	Current smokers	1.0
				166	Never smoked	0.2 (0.2–0.3)
				138	Former smokers	
					Cessation for:	
				36	< 2 years	0.8 (0.5–1.3)
				22	2–4 years	0.4 (0.3–0.7)
				26	5–9 years	0.4 (0.2–0.6)
				13	10–14 year	0.3 (0.1–0.5)
				41	≥ 15 years	0.3 (0.2–0.4)
			Death from CHD	123	Current smokers	1.0
				49	Never smoked	0.2 (0.2–0.4)
				47	Former smokers	
					Cessation for:	
				7	< 2 years	1.5 (0.4–5.2)
				9	2–4 years	0.6 (0.2–1.4)
				14	5–9 years	0.7 (0.4–1.4)
				4	10–14 years	0.3 (0.1–0.9)
				13	≥ 15 years	0.3 (0.2–0.7)

*NR = Value not specified in report of study.
†392 deaths from CHD among all women (never smokers, current smokers, and former smokers).
‡75% had coronary artery disease.
§729 deaths from cardiovascular disease among men and women.

suggested the possibility of adverse cardiovascular effects. Thus, more evidence, including effects by smoking status, is clearly warranted. Regardless of any interaction between HRT and smoking, every woman who receives HRT should be counseled to stop smoking because HRT cannot negate the excess risk for CHD associated with cigarette smoking.

Cerebrovascular Disease

Smoking-Associated Risks

Stroke, the major form of cerebrovascular disease, is the third-leading cause of death among middle-aged and older U.S. women; it accounts for 87,000 deaths each year. Stroke is also the leading cause of

Table 3.23. Continued

Study	Population	Number of years of follow-up	Outcome	Number of cases	Smoking status	Relative risk (95% confidence interval)
Kawachi et al. 1994 (continued)			CHD	541	Current smokers	1.0
				215	Never smoked	0.2 (0.2–0.3)
				185	Former smokers	
					Cessation for:	
				43	<2 years	0.8 (0.5–1.2)
				31	2–4 years	0.5 (0.3–0.7)
				40	5–9 years	0.4 (0.3–0.7)
				17	10–14 years	0.3 (0.1–0.5)
				54	≥ 15 years	0.3 (0.2–0.4)
Paganini-Hill and Hsu 1994	8,869 women Median age, 73 years U.S. retirement community	10	Death from CHD	NR	Never smoked	1.0
					Current smokers	1.5 (1.1–2.0)
					Former smokers	
					Cessation for:	
					≤ 5 years	1.3 (0.8–2.0)
					6–10 years	1.4 (0.9–2.2)
					11–20 years	1.5 (1.1–2.0)
					≥ 21 years	1.1 (0.8–1.4)
Burns et al. 1997b	594,551 women Aged >30 years 25 U.S. states	12	Death from CHD	NR	Never smoked	1.0
					Current smokers	1.4 (1.3–1.5)
					Former smokers	
					Cessation for[Δ]:	
					2–4 years	2.2[¶]
					5–9 years	1.5[¶]
					10–14 years	1.0[¶]
					15–19 years	0.8[¶]
					20–24 years	0.9[¶]
					25–29 years	1.0[¶]
					30–34 years	0.6[¶]
					35–39 years	0.6[¶]
Friedman et al. 1997	36,035 U.S. women Aged ≥ 35 years Enrolled in health maintenance organization	6	Death from CHD	134	Never smoked	1.0
					Current smokers	
				7	≤ 19 cigarettes/day	1.4[¶]
				13	≥ 20 cigarettes/day	2.2[¶]
					Former smokers	
					Cessation for:	
				9	2–10 years	1.4[¶]
				14	11–20 years	1.4[¶]
				12	>20 years	1.1[¶]

[Δ]Data are for white women only; number of black former smokers was insufficient for separate analyses.
[¶]95% confidence interval was not reported.

severe disability and costs about $15.3 billion annually in medical care, including rehabilitation (Eaker et al. 1993). Smoking has long been recognized as a major cause of stroke (USDHHS 1989b). In CPS-II, 55 percent (95 percent CI, 45 to 65 percent) of deaths from cerebrovascular disease among women younger than 65 years and 6 percent of deaths from cerebrovascular disease among women aged 65 years or older were attributable to smoking (USDHHS 1989b).

In a meta-analysis of 32 studies of smoking and stroke that were published before May 1988, the overall RR for stroke among women and men current smokers was 1.5 (95 percent CI, 1.5 to 1.6) (Shinton and Beevers 1989). A strong dose-response relationship was found between the risk for stroke and the number of cigarettes smoked per day. Increased risks were found for subarachnoid hemorrhage (RR, 2.9; 95 percent CI, 2.5 to 3.5) and cerebral infarction (RR, 1.9; 95 percent CI, 1.7 to 2.2), but no increase in risk was found for hemorrhagic stroke (mainly intracerebral hemorrhage) (RR, 1.01; 95 percent CI, 0.8 to 1.3) or for intracerebral hemorrhage alone (RR, 0.7; 95 percent CI, 0.6 to 0.98). The estimate for hemorrhagic stroke was based on pooled data from only four studies and was strongly influenced by a single study that showed a marked inverse association with smoking (RR, 0.2 among men) (Bell and Ambrose 1982). In 26 studies, the number of women was sufficient to allow stratification by gender. In these data, the pooled risk for any stroke was slightly higher among women smokers (RR, 1.7; 95 percent CI, 1.6 to 1.9) than among men smokers (RR, 1.4; 95 percent CI, 1.4 to 1.5) (Shinton and Beevers 1989).

Subsequent studies generally have found a twofold to threefold excess risk for ischemic stroke and subarachnoid hemorrhage among women who smoked compared with women who had never smoked; the risk has been generally higher among heavy smokers (Tables 3.24 and 3.25). A possible explanation for the increase in RR over time is that control of hypertension has improved in the United States during the past two decades. Thus, smoking is a more prominent risk factor for stroke than it was in the past (USDHHS 1990). An alternative explanation is that women who have recently reached the peak ages of stroke incidence tend to be heavier smokers than smokers in previous decades.

Although smoking is a clearly established risk factor for ischemic stroke and subarachnoid hemorrhage among both women and men, the relationship with primary intracerebral hemorrhage is less certain (Tables 3.24 and 3.25). One small population-based study found smoking to be a significant risk factor (Jamrozik et al. 1994). In contrast, a hospital-based, case-control study from Finland found that smoking was not an independent risk factor for intracerebral hemorrhage among either women or men (Juvela et al. 1995). In the U.S. Nurses' Health Study (Kawachi et al. 1993b), current smoking was associated with a multivariate-adjusted RR for cerebral hemorrhage of 1.4 (95 percent CI, 0.8 to 2.8) (Table 3.25). In the case-control study by Gill and colleagues (1989), current smoking was associated with an adjusted RR for cerebral hemorrhage of 1.3 (95 percent CI, 0.5 to 3.4) among women (Table 3.24) and 1.8 (95 percent CI, 0.9 to 3.7) among men. These data were based on few cases, however, because primary intracerebral hemorrhage tends to be the least common subtype of stroke among white women.

Smoking cessation has been reported to reduce the risk for both ischemic stroke and subarachnoid hemorrhage. After smoking cessation, the risk for stroke seems to return to the level of risk among those who had never smoked (USDHHS 1990). In some studies, the risk for stroke among women former smokers approached that of nonsmokers within 5 years of cessation (Wolf et al. 1988; USDHHS 1990 [CPS-II data for women in 50 states]). In other studies, 10 to 15 years of abstinence from smoking have been required (Rogot and Murray 1980; Donnan et al. 1989; USDHHS 1990 [CPS-II data for men in 50 states]).

Additional investigations since the late 1980s (Table 3.26) considered the relationship between duration of abstinence from smoking and the risk for stroke among women (Thompson et al. 1989; Kawachi et al. 1993b; Burns et al. 1997b; Friedman et al. 1997). In the U.S. Nurses' Health Study (Kawachi et al. 1993b), the risk for stroke among women former smokers approached the level of risk among women who had never smoked after 2 to 4 years of abstinence. The reduction of risk persisted after control for the number of cigarettes previously smoked daily, age at smoking initiation, and other known risk factors for stroke (data not shown). However, in a case-control study in the United Kingdom, only after 11 to 15 years of smoking cessation did stroke risk among female former smokers approximate that among women who had never smoked (Thompson et al. 1989).

In CPS-I, the risk for death from stroke among women former smokers approached that among women who had never smoked, at 15 to 19 years after smoking cessation (Burns et al. 1997b) (Table 3.26). The time it took for risk to decline differed by the number of cigarettes smoked daily before cessation (data not shown). For example, among women former smokers who had smoked fewer than 20 cigarettes per day, the risk approached that among women who had never smoked 5 to 9 years after cessation. Among former smokers who had smoked 20 or more cigarettes per day, an excess risk for stroke mortality persisted even after 20 to 24 years of cessation. A similar pattern was reported from a small study of men in the United Kingdom (Wannamethee et al. 1995).

In summary, the findings in most studies with data on women indicated that the increased stroke risk associated with smoking is reversible after smoking cessation. However, the duration of abstinence required for the excess risk to dissipate varied from 5 to 15 years.

Smoking and Use of Oral Contraceptives

Smokers who use OCs are at a significantly increased risk for stroke, especially subarachnoid hemorrhage, and part of this risk may result from the combined effects of smoking and OC use (USDHHS 1983). Studies published in the 1970s (Collaborative Group for the Study of Stroke in Young Women 1975; Petitti and Wingerd 1978) reported a particularly high risk for stroke among women who were heavy smokers and who used OCs; RRs ranged from more than 4.0 to 22.0. The dose of estrogen in OC preparations has been substantially reduced since then, and the risk for CVD associated with OC use and smoking may have changed from that observed for the early higher dose preparations (USDHHS 1990).

Most studies published since 1990 found that currently prescribed lower dose OC preparations are not associated with a substantially increased risk for stroke (Hirvonen and Idänpään-Heikkilä 1990; Thorogood et al. 1992; Lidegaard 1993; Lindenstrøm et al. 1993; WHO Collaborative Study 1996a,b; Schwartz et al. 1998). However, some studies reported that smoking increases the risk for stroke associated with OCs (Hannaford et al. 1994; Petitti et al. 1996; WHO Collaborative Study 1996a,b). For example, a multicenter, hospital-based, case-control study reported an adjusted RR for ischemic stroke of 7.2 (95 percent CI, 3.2 to 16.1) among current smokers who used OCs compared with nonsmokers who did not use OCs (WHO Collaborative Study 1996a). On the other hand, some data suggested no such interaction (Lidegaard 1993; Schwartz et al. 1998).

Smoking and Hormone Replacement Therapy

The data on the effects of HRT on the risk for stroke are sparse and inconsistent. Some investigators have observed a protective effect of HRT (Paganini-Hill et al. 1988; Finucane et al. 1993), others an increased risk (Wilson et al. 1985), and several no effect (Stampfer et al. 1991; Pedersen et al. 1997; Petitti et al. 1998).

A 12-year follow-up study of 7,060 women in the Copenhagen City Heart Study showed a statistically significant ($p < 0.04$) interaction between smoking status and HRT use (Lindenstrøm et al. 1993). HRT use appeared to be protective for stroke and transient ischemic attack (TIA) among current smokers but not among nonsmokers (both former smokers and women who had never smoked). Among current smokers who used HRT, the risk for stroke or TIA was about one-third the risk among women current smokers who did not use HRT. Among nonsmokers, however, HRT use was not associated with cerebrovascular events (RR, 1.0; 95 percent CI, 0.6 to 1.8). A similar pattern was observed in a population-based, case-control study of subarachnoid hemorrhage (Longstreth et al. 1994). In contrast, a more recent study found no interaction between HRT use and smoking in relation to stroke risk (Pedersen et al. 1997).

Carotid Atherosclerosis

Smoking is a major cause of carotid atherosclerosis, a marker of risk for TIA and stroke (USDHHS 1983). In several cross-sectional studies that included women, atherosclerotic lesions were more severe and diffuse among current smokers than among nonsmokers (Tell et al. 1989, 1994; Ingall et al. 1991). Ingall and colleagues (1991) reported results from a cross-sectional study of 1,004 patients (404 women) aged 40 through 69 years who had intracranial carotid artery arteriography. After adjustment for other cerebrovascular risk factors, duration of smoking was a strong predictor of the severity of atherosclerosis among both women and men. A similar finding was reported for severe atherosclerosis of the extracranial carotid arteries (Whisnant et al. 1990). In a study of 49 male and female pairs of identical twins discordant for smoking status, the total area of atherosclerotic carotid plaques was 3.2 times larger among smokers than among nonsmokers (Haapanen et al. 1989).

The association of smoking with carotid atherosclerosis persists with age. In a cross-sectional study of 5,116 participants (2,837 women) older than 64 years of age who were evaluated by ultrasonography, the prevalence of clinically significant (≥ 50 percent) stenosis of the internal carotid artery was 4.4 percent among persons who had never smoked, 7.3 percent among former smokers, and 9.5 percent among current smokers ($p < 0.0001$) (Tell et al. 1994). This study also showed a dose-response relationship between pack-years of smoking and mean thickness of the carotid artery wall ($p < 0.0001$). The difference in wall thickening among current smokers and persons who had never smoked was greater than the difference associated with 10 years of aging. In the Framingham study, an association was observed between time-integrated measures of smoking and carotid artery stenosis

Table 3.24. Relative risks for stroke among women for current smokers compared with nonsmokers, case-control studies

Study	Population	Number of cases	Number of controls	Source of controls	Type of stroke	Smoking status	Relative risk (95% confidence interval)
Donnan et al. 1989	Women Aged 25–85 years Australia	166 hospitalized for stroke	166	General population	Cerebral ischemia	Never smoked Current smokers	1.0 3.0 (1.3–7.1)
Gill et al. 1989	Women Mean age, 53.4 years United Kingdom	281 hospitalized for stroke	303	Participants in factory screening survey	Total	Never smoked Current smokers 1–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 1.8 (0.7–4.7) 1.6 (0.8–3.0) 2.8 (1.7–4.7)
					Cerebral infarction	Never smoked Current smokers	1.0 2.3 (1.2–4.2)
					Cerebral hemorrhage	Never smoked Current smokers	1.0 1.3 (0.5–3.4)
					Subarachnoid hemorrhage	Never smoked Current smokers	1.0 2.5 (1.4–4.5)
Thompson et al. 1989	Women physicians Aged 45–69 years United Kingdom	37 fatal stroke 207 nonfatal stroke	488	Women physicians	Total	Never smoked Current smokers	1.0 2.3*
Longstreth et al. 1992	Women ≥ 18 years United States	103 subarachnoid hemorrhage	206	General population	Subarachnoid hemorrhage	Never smoked Current smokers	1.0 4.6 (2.6–8.1)
Morris et al. 1992	Women admitted to Department of Neurosurgery United Kingdom	131 subarachnoid hemorrhage	131	Women admitted with nonvascular or spinal pathologic condition	Subarachnoid hemorrhage	Never smoked Current smokers	1.0 1.9 (1.4–2.6)

*95% confidence interval was not reported.

greater than 25 percent on ultrasound among both women and men. Smoking at the time of the examination was associated with stenosis only among women (RR, 2.6; 95 percent CI, 1.6 to 4.3) (Wilson et al. 1997).

A few prospective studies have evaluated the relationship between smoking and progression of carotid atherosclerosis. In a two-year follow-up of 308 apparently healthy women in France aged 45 through 55 years (Bonithon-Kopp et al. 1993), current smoking was a strong predictor of the development of new carotid atheromatous plaques, as assessed by B-mode ultrasound (multivariate-adjusted RR, 3.6; 95 percent CI, 1.5 to 8.7). A two-year follow-up of Finnish men similarly showed that pack-years of smoking was one of the strongest predictors of progression of carotid atherosclerosis (Salonen and Salonen 1990). More than

Table 3.24. Continued

Study	Population	Number of cases	Number of controls	Source of controls	Type of stroke	Smoking status	Relative risk (95% confidence interval)
Juvela et al. 1993	Women Aged 15–60 years Finland	133 hospitalized with subarachnoid hemorrhage	150	Hospitalized women	Subarachnoid hemorrhage	Never smoked Current smokers ≤ 10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 2.4 (1.5–3.9) 1.2 (0.5–2.7) 3.6 (1.3–9.6) 2.0 (0.95–4.1)
Lidegaard 1993	Women Aged 15–44 years	321 hospitalized for stroke	1,198	General population	Ischemic stroke or transient ischemic attack	Never smoked Current smokers <10 cigarettes / day ≥ 10 cigarettes / day	1.0 1.6 (1.1–2.6) 1.5 (1.1–2.0)
Hannaford et al. 1994	Denmark Women physicians Aged 21–70 years United Kingdom	253 incident stroke or amaurosis fugax	759	Nested in cohort	Incident stroke or amaurosis fugax	Never smoked Current smokers 1–14 cigarettes / day ≥ 15 cigarettes / day	1.0 2.1 (1.5–2.9) 2.5 (1.7–3.7)
Pedersen et al. 1997	Women Aged 45–64 years Denmark	Hospitalized for cerebrovascular attack and surviving 160 subarachnoid hemorrhage 835 thrombo-embolic infarction 321 transient ischemic attack	3,171	General population	Subarachnoid hemorrhage	Never smoked Current smokers 1–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 3.7 (2.2–6.1) 4.4 (2.7–7.1) 3.7 (1.1–12.0)
					Thrombo-embolic infarction	Never smoked Current smokers 1–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 2.4 (1.8–3.2) 3.4 (2.6–4.5) 6.4 (3.7–11.0)
					Transient ischemic attack	Never smoked Current smokers 1–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 2.5 (1.7–3.7) 2.8 (1.9–4.1) 3.9 (1.7–9.0)

10,000 women and men were followed for three years in the Atherosclerosis Risk in Communities Study (Howard et al. 1998). Current smoking was associated with a 50-percent increase in the progression of carotid atherosclerosis.

Cessation of smoking appears to slow the progression of carotid atherosclerosis. In a cross-sectional study of 1,692 patients (829 women) admitted for diagnostic evaluation of the carotid arteries, the plaque measured by B-mode ultrasonography was 0.35 mm thicker among former smokers than among persons who had never smoked (95 percent CI, 0.17 to 0.54 mm). The plaque thickness of current smokers was 0.63 mm greater than that of persons who had never smoked (95 percent CI, 0.45 to 0.81 mm; $p < 0.001$ by multivariate analysis of variance). This finding suggested that the rate of progression of carotid atherosclerosis may be slower among persons who stop smoking than among continuing smokers (Tell et al. 1989).

Table 3.25. Relative risks for stroke among women for current smokers compared with nonsmokers, cohort studies

Study	Population	Number of years of follow-up	Outcome	Smoking status	Relative risk (95% confidence interval)
Hirayama 1990	142,857 women Aged ≥ 40 years Sampled from census Japan	17	Death from cerebrovascular disease	Nonsmokers Current smokers 1–9 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.2 (1.1–1.3)* 1.1 (0.99–1.2)* 1.3 (1.1–1.6)*
			Death from subarachnoid hemorrhage	Nonsmokers Current smokers 1–9 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.5 (1.2–2.5) 1.4 (0.9–2.2) 2.1 (0.9–4.6)
Kiyohara et al. 1990	904 women Aged >40 years Japan	23	Nonembolic cerebral infarction	Never smoked Current smokers	1.0 0.8 (0.4–1.4)
Knekt et al. 1991	Population samples Aged 20–69 years Finland	12	Subarachnoid hemorrhage	Nonsmokers Current smokers	1.0 2.4 (1.4–4.0)
Kawachi et al. 1993b	117,006 women nurses Aged 30–55 years United States	12	Total stroke	Never smoked Current smokers 1–14 cigarettes / day 15–24 cigarettes / day 25–34 cigarettes / day ≥ 35 cigarettes / day	1.0 2.0 (1.3–3.1) 3.3 (2.4–4.7) 3.1 (1.9–4.9) 4.5 (2.8–7.2)
			Subarachnoid hemorrhage	Never smoked Current smokers	1.0 4.9 (2.9–8.1)

*90% confidence interval.

Rogers and colleagues (1983) found significantly lower cerebral perfusion among long-term smokers than among nonsmokers; the reduction in cerebral blood flow was directly related to the number of cigarettes smoked daily. In a cross-sectional study, these investigators showed that smoking cessation was associated with a substantial improvement in cerebral perfusion within one year of cessation (Rogers et al. 1985).

Peripheral Vascular Disease

Peripheral vascular disease is associated with both functional limitations and increased risk for mortality. For example, in a 10-year follow-up study of 309 women and 256 men (average age, 66 years) with large-vessel peripheral arterial disease, the total mortality rate was 2.7 times higher (95 percent CI, 1.2 to 6.0) among women with large-vessel disease than among women free of disease. The corresponding RR for death from CVD was 5.7 (95 percent CI, 1.4 to 23.2) (Criqui et al. 1992).

Smoking is a strong, independent risk factor for arteriosclerotic peripheral vascular disease among women, and smoking cessation improves the prognosis of the disorder and has a favorable effect on vascular potency after reconstructive surgery (USDHHS 1980; Fowkes 1989). In general, the risk for intermittent claudication, a major clinical manifestation of peripheral vascular disease, has been reported to be lower among former smokers than among current smokers (USDHHS 1990). Among patients with established peripheral artery disease,

Table 3.25. Continued

Study	Population	Number of years of follow-up	Outcome	Smoking status	Relative risk (95% confidence interval)
Kawachi et al. 1993b (continued)			Ischemic stroke	Never smoked	1.0
				Current smokers	2.5 (1.9–3.4)
			Cerebral hemorrhage	Never smoked	1.0
				Current smokers	1.4 (0.8–2.8)
Lindenstrøm et al. 1993	7,060 women Aged >35 years Denmark	12	Total stroke or transient ischemic attack	Never smoked	1.0
				Current smokers	1.4 (1.02–1.9)
Burns et al. 1997b	594,551 women Aged >30 years 25 U.S. states	12	Death from stroke	Never smoked	1.0
				Current smokers	
				Aged 35–49 years	2.5[†]
				Aged 50–64 years	2.2[†]
				Aged 65–79 years	1.3[†]
				Aged ≥ 80 years	0.8[†]
Friedman et al. 1997 (see Table 3.23)	36,035 women Aged ≥ 35 years United States	6	Death from stroke	Never smoked	1.0
				Current smokers	
				1–19 cigarettes / day	0.9[†]
				≥ 20 cigarettes / day	1.9[†]
Thun et al. 1997c	676,527 women Aged >30 years 50 U.S. states	6	Death from stroke	Never smoked	1.0
				Current smokers	1.5 (1.2–1.7)

[†]95% confidence interval was not reported.

smoking cessation has also been associated with improved performance (greater maximum treadmill walking distance and reduction of pain at rest), better prognosis (longer duration between initial and subsequent operations, lower amputation rate, and greater potency of vascular grafts), and longer overall survival (USDHHS 1990).

Studies published since 1990 continued to confirm a higher risk for peripheral vascular disease among smokers than among nonsmokers. Most studies were cross-sectional rather than prospective. However, in the 34-year follow-up of participants in the Framingham study (Freund et al. 1993), current smoking was a powerful predictor of intermittent claudication; RR was 2.3 (95 percent CI, 1.4 to 3.5) for current smokers compared with nonsmokers among women 45 through 64 years old. Among women aged 65 through 84 years, the RR was 2.2 (95 percent CI, 1.3 to 3.7).

The Edinburgh Artery Study (Fowkes et al. 1994) examined the ankle brachial pressure index (ABPI) in a random population sample of 783 women and 809 men aged 55 through 74 years. (The ABPI is a validated index inversely related to the degree of peripheral atherosclerosis.) In that study, lifetime history of cigarette smoking was correlated with lower ABPI among both women and men ($r = -0.27$; $p < 0.001$). Smoking was a stronger predictor of the prevalence of peripheral vascular disease than of CHD (Fowkes et al. 1992).

Epidemiologic studies are generally concerned with establishing the association of risk factors with clinical events, such as MI, stroke, or symptomatic peripheral vascular disease. The development of clinical disease is, however, the end point of a progression of pathophysiologic changes (Kuller et al. 1994). In the past, evaluation of the extent of atherosclerosis

Table 3.26. Relative risks of stroke for women former smokers versus women who never smoked, by time since smoking cessation, case-control and cohort studies

Study	Type of study	Outcome	Smoking status	Relative risk (95% confidence interval)
Thompson et al. 1989 (see Table 3.24)	Case-control	Total stroke	Never smoked	1.0
			Former smokers	
			Cessation for:	
			1–2 years	1.9*
			3–5 years	1.6*
			6–10 years	1.7*
			11–15 years	1.0*
			≥ 15 years	0.8*
Kawachi et al. 1993b (see Table 3.25)	Cohort	Total stroke	Current smokers	1.0
			Never smoked	0.4 (0.3–0.5)
			Former smokers	
			Cessation for:	
			<2 years	0.8 (0.5–1.5)
			2–4 years	0.4 (0.2–0.9)
			5–9 years	0.4 (0.2–0.8)
			10–14 years	0.8 (0.4–1.5)
			≥ 15 years	0.4 (0.2–0.7)
		Ischemic stroke	Current smokers	1.0
			Never smoked	0.4 (0.3–0.5)
			Former smokers	
			Cessation for:	
			<2 years	0.6 (0.3–1.5)
			2–4 years	0.2 (0.04–0.96)
			5–9 years	0.5 (0.2–1.2)
			10–14 years	0.9 (0.5–1.9)
			≥ 15 years	0.4 (0.2–0.8)
		Subarachnoid hemorrhage	Current smokers	1.0
			Never smoked	0.2 (0.1–0.3)
			Former smokers	
			Cessation for:	
			<2 years	1.3 (0.5–3.6)
			2–4 years	0.7 (0.2–2.8)
			5–14 years	0.5 (0.1–1.5)
			≥ 15 years	0.4 (0.1–0.97)
Burns et al. 1997b (see Table 3.23)	Cohort	Death from stroke	Never smoked	1.0
			Former smokers	
			Cessation for:	
			2–4 years	2.3*
			5–9 years	1.2*
			10–14 years	1.3*
			15–19 years	1.01*
			20–24 years	1.1*
			25–29 years	0.8*
			30–34 years	0.6*
			35–39 years	0.9*
Friedman et al. 1997 (see Table 3.23)	Cohort	Death from stroke	Never smoked	1.0
			Former smokers	
			Cessation for:	
			1–10 years	0.3*
			11–20 years	1.2*
			≥ 21 years	0.9*

*95% confidence interval was not reported.

was limited to postmortem studies or to studies that used invasive techniques such as angiography. The advent of noninvasive diagnostic methods has made it feasible to study the extent of subclinical atherosclerosis in asymptomatic persons. Kuller and colleagues (1994) examined the relationship of smoking with subclinical atherosclerosis among 5,201 Medicare enrollees (2,955 women and 2,246 men) aged 65 years or older. Subclinical disease was defined as major electrocardiographic abnormalities, low ejection fraction or ventricular wall motion abnormality on echocardiogram, more than 25 percent stenosis or more than a 25-percent increase in wall thickness of the carotid artery or the internal carotid artery, decreased ABPI (≤ 0.9 mm Hg), and angina or intermittent claudication, as determined by a research questionnaire. In this cross-sectional study, current smoking was associated with increased risk for subclinical disease among women (RR for current smokers compared with nonsmokers, 2.0; 95 percent CI, 1.5 to 2.7) and among men (RR, 2.4; 95 percent CI, 1.6 to 3.6). In summary, current smoking among women is associated with increased risk for both clinical and subclinical peripheral vascular atherosclerosis. Smoking cessation is associated with improvement in symptoms, prognosis, and survival.

Abdominal Aortic Aneurysm

Smoking aggravates or accelerates aortic atherosclerosis, and the death rate for ruptured aortic aneurysm is higher among smokers than among nonsmokers (USDHHS 1983; Blanchard 1999). Excess risk for aortic aneurysm remains substantial even after 20 years' cessation of cigarette smoking (USDHHS 1983). Data for women are sparse; a previous Surgeon General's report summarized data from five prospective studies that examined the risk for death from aortic aneurysm; only two of these studies included data for women (Doll et al. 1980; USDHHS 1990, p. 242 [CPS-I tabulations]). Both studies found a higher risk for mortality from aortic aneurysm among women who smoked than among women who did not smoke.

In CPS-I (Burns et al. 1997b), the RR for death from abdominal aortic aneurysm was 3.9 among women current smokers compared with women who had never smoked. Risk increased with the number of cigarettes smoked; RRs were 3.5, 4.6, or 4.8 among women who smoked 1 to 19, 20, or 21 or more cigarettes per day, respectively. In a census-based cohort study in Japan that included 142,857 women aged 40 years or older, the RR for death from aortic aneurysm was 4.4 (90 percent CI, 2.7 to 7.3) among women current smokers compared with women who had never smoked (Hirayama 1990).

In a prospective study of 43 patients (10 women) who had small abdominal aortic aneurysms (diameter <5 cm), a median growth rate of 0.13 cm/year was recorded by serial ultrasound during follow-up (mean, three years) (MacSweeney et al. 1994). The growth rate was not associated with the initial diameter of the aneurysm, systolic or diastolic blood pressure, or serum cholesterol level. However, 30 of the 43 patients were current smokers, and smoking was associated with growth of the aneurysm. The median annual growth rate of aneurysms was 0.16 cm among smokers and 0.09 cm among nonsmokers ($p = 0.03$).

In a population-based cohort study, 758 women aged 45 through 64 years were examined by radiography for the development or progression of atherosclerotic plaques in the abdominal aorta, as indicated by calcified deposits (Witteman et al. 1993). After 9 years of follow-up, the investigators reported a dose-response association between atherosclerotic change and the number of cigarettes smoked per day. In a comparison with women who had never smoked, the multivariate-adjusted RR for development or progression of aortic atherosclerosis was 1.4 (95 percent CI, 1.0 to 2.0) among women who smoked 1 to 9 cigarettes per day, 2.0 (95 percent CI, 1.6 to 2.5) among women who smoked 10 to 19 cigarettes per day, and 2.3 (95 percent CI, 1.8 to 3.0) among women who smoked 20 or more cigarettes per day. Inhaling (compared with not inhaling) and duration of smoking were also statistically significant predictors of risk, after adjustment for intensity of smoking. The RR for aortic atherosclerosis declined after smoking cessation, but a residual excess risk among women former smokers compared with women who had never smoked was still apparent 5 to 10 years after smoking cessation (RR, 1.6; 95 percent CI, 1.1 to 2.2). These data are compatible with the reported slow reversibility of smoking-induced atherosclerotic damage in the abdominal aorta (USDHHS 1983).

Hypertension

Severe or malignant hypertension has been reported to be more common among women who smoke than among those who do not smoke (USDHHS 1980), yet epidemiologic and laboratory studies have produced conflicting results on the association between smoking and blood pressure. Several epidemiologic studies have shown that when blood pressure

is measured in a physician's office, the readings among smokers are similar to or lower than those among nonsmokers, even after the lower BMI of smokers is taken into account (Greene et al. 1977; Gofin et al. 1982; Green et al. 1986). In contrast, laboratory studies have shown that cigarette smoking acutely raises blood pressure even among long-term smokers; the peak rise in blood pressure ranges from 3 to 12 mm Hg systolic pressure and 5 to 10 mm Hg diastolic pressure for a 20- to 30-minute duration of effect (Freestone and Ramsay 1982; Mann et al. 1989; Berlin et al. 1990; Groppelli et al. 1992).

Ambulatory measurement of blood pressure may clarify these results. Mann and colleagues (1991) compared blood pressure measurements taken in a physician's office with the 24-hour ambulatory blood pressure measurements for 77 women and 100 men with hypertension (diastolic blood pressure ≥ 90 mm Hg) who were not receiving medication. Participants in this study were 26 women and 33 men who currently smoked at least one pack of cigarettes per day and 51 women and 67 men nonsmokers. Blood pressure readings taken in a physician's office were similar among smokers and nonsmokers (means, 141/93 vs. 142/93 mm Hg). However, the mean ambulatory systolic blood pressure was much higher among smokers than among nonsmokers (145 vs. 140 mm Hg; $p < 0.05$). Findings were similar among women and men. The lack of difference in physician's office readings for smokers and nonsmokers was attributed to abstinence from smoking during the minutes or hours preceding the blood pressure measurement. This explanation may also account for the lack of association between smoking and blood pressure measurements in epidemiologic studies, in which blood pressure is often assessed without consideration of time since the last cigarette. Similar findings on ambulatory blood pressure emerged from later studies of women and men (De Cesaris et al. 1992; Narkiewicz et al. 1995; Poulsen et al. 1998), but contrary data have also been reported (Mikkelsen et al. 1997). A study of salivary cotinine levels reported data consistent with higher blood pressure among smokers: higher pressures among women and men with higher salivary cotinine levels (Istvan et al. 1999). These findings also suggested that the effects of smoking on blood pressure are transient.

Conclusions

1. Smoking is a major cause of coronary heart disease among women. For women younger than 50 years, the majority of coronary heart disease is attributable to smoking. Risk increases with the number of cigarettes smoked and the duration of smoking.
2. The risk for coronary heart disease among women is substantially reduced within 1 or 2 years of smoking cessation. This immediate benefit is followed by a continuing but more gradual reduction in risk to that among nonsmokers by 10 to 15 or more years after cessation.
3. Women who use oral contraceptives have a particularly elevated risk of coronary heart disease if they smoke. Currently evidence is conflicting as to whether the effect of hormone replacement therapy on coronary heart disease risk differs between smokers and nonsmokers.
4. Women who smoke have an increased risk for ischemic stroke and subarachnoid hemorrhage. Evidence is inconsistent concerning the association between smoking and primary intracerebral hemorrhage.
5. In most studies that include women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5 to 15 years of abstinence, the risk approaches that of women who have never smoked.
6. Conflicting evidence exists regarding the level of the risk for stroke among women who both smoke and use either the oral contraceptives commonly prescribed in the United States today or hormone replacement therapy.
7. Smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women. Smoking cessation appears to slow the rate of progression of carotid atherosclerosis.
8. Women who are current smokers have an increased risk for peripheral vascular atherosclerosis. Smoking cessation is associated with improvements in symptoms, prognosis, and survival.
9. Women who smoke have an increased risk for death from ruptured abdominal aortic aneurysm.

Chronic Obstructive Pulmonary Disease and Lung Function

Chronic obstructive pulmonary disease (COPD) is a term defined differently by clinicians, pathologists, and epidemiologists, and each discipline uses different criteria based on physiologic impairment, pathologic abnormalities, and symptoms (Samet 1989a). The hallmark of COPD is airflow obstruction, as measured by spirometric testing, with persistently low forced expiratory volume in one second (FEV_1) and low ratio of FEV_1 to forced vital capacity (FVC) (FEV_1/FVC), despite treatment.

COPD may include chronic bronchitis characterized by a chronic cough productive of sputum with airflow obstruction, and emphysema accompanied by airflow obstruction. Emphysema is defined as "a condition of the lung characterized by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis" (American Thoracic Society 1987, p. 225). However, like bronchitis, emphysema is not consistently associated with airflow obstruction. Chronic bronchitis and emphysema with airflow obstruction are both included in the clinical diagnosis of COPD, but other lung diseases associated with airflow obstruction are specifically excluded from the clinical definition of COPD; these include asthma, bronchiectasis, and cystic fibrosis.

In epidemiologic studies, the diagnosis of COPD may be derived from surveys or databases. Questionnaire responses that may be used to diagnose COPD include reports of symptoms (e.g., dyspnea, cough, and phlegm), reports of physician diagnoses (e.g., emphysema, chronic bronchitis, or COPD), or both. Spirometry is often performed in epidemiologic studies to provide objective evidence of airflow obstruction among subjects with or without symptoms. Sources of data for descriptive or analytic studies of COPD include databases containing hospital discharge information or vital statistics (e.g., from death certificates). The standard terms used for COPD in these databases include terms from the *International Classification of Diseases,* ninth revision (*ICD-9*) (USDHHS 1989a)—"chronic bronchitis" (*ICD-9*, item 491); "emphysema" (*ICD-9*, item 492); and "chronic airways disease not otherwise classified" (*ICD-9*, item 496). The quality of these data sources may vary greatly.

Gender-specific differences have been observed in the likelihood of having a diagnosis of COPD, and it is unclear whether these differences result from diagnostic bias or reflect true gender-related differences in susceptibility. For example, in the Tucson (Arizona) Epidemiologic Study of Obstructive Lung Diseases, Dodge and colleagues (1986) found that, among subjects aged 40 years or older with a new diagnosis of asthma, emphysema, or chronic bronchitis based on self-report, women were more likely than men to receive a physician diagnosis of asthma or chronic bronchitis, and men were more likely to receive a diagnosis of emphysema. In the same population, Camilli and colleagues (1991) reported that a diagnosis of obstructive airways disease was stated on the death certificates of only 37 percent of 157 patients who had this diagnosis before death and that the proportion was lower among women (28 percent) than among men (42 percent).

Spirometric testing provides the most objective basis for diagnosing COPD. Among persons with a diagnosis of mild disease based on spirometric testing, reporting of obstructive airways disease on the death certificates was slightly higher among women (45 percent) than among men (34 percent), whereas for those with moderate-to-severe disease, reporting was higher among men (81 percent) than among women (57 percent). (For mild disease, the criteria were $FEV_1/FVC < 65$ percent and predicted FEV_1 50 to 70 percent of that in the normal reference population. For moderate-to-severe disease, the criteria were $FEV_1/FVC < 65$ percent and predicted $FEV_1 < 50$ percent of that in the normal reference population.)

Evidence suggested that changes in the structure and function of small airways (bronchioles) are fundamental for the development of smoking-induced COPD (Wright 1992; Thurlbeck 1994). An inflammatory process of the small airways (respiratory bronchiolitis) develops in all cigarette smokers; but in susceptible smokers, this process progresses and causes narrowing of these airways (Bosken et al. 1990; USDHHS 1990; Aguayo 1994). The inflammatory process may extend into the peribronchiolar alveoli and destroy the alveolar walls, which is the hallmark of emphysema. The rate of expiratory airflow depends on elastic recoil forces from the alveoli and on the diameter of the small airways. Complex interactions between changes in the structure and function of small airways and lung parenchyma result in the physiologic finding of chronic airflow limitation.

Cigarette smoking as a cause of COPD was extensively reviewed in earlier reports of the Surgeon General (USDHHS 1980, 1984, 1989b, 1990). (In the 1980 and 1984 Surgeon General's reports, COPD was referred to as chronic obstructive lung disease [COLD].) In the 1980 Surgeon General's report on the health consequences of smoking for women (USDHHS 1980), the major conclusions relevant to COPD were as follows: (1) The death rate for COPD among women was rising, and the data available demonstrated an excess risk for death among women who smoked compared with nonsmokers, with a much greater risk for heavy smokers than for light smokers. (2) Women's overall risk for COPD appeared to be somewhat lower than men's, a difference possibly due to differences in previous smoking habits. (3) The prevalence of chronic bronchitis increased with the number of cigarettes smoked per day. (4) Evidence on differences in the prevalence of chronic bronchitis among women and men who smoked was inconsistent. (5) The presence of emphysema at autopsy exhibited a dose-response relationship with cigarette smoking during life. (6) A close relationship existed between cigarette smoking and chronic cough or chronic sputum production among women, which increased with total pack-years of smoking. (7) Women current smokers had poorer pulmonary function, by spirometric testing, than did women former smokers or nonsmokers, and the relationship was related to the number of cigarettes smoked.

In the 1984 Surgeon General's report on smoking and COPD (USDHHS 1984), the major additional conclusions relevant to morbidity and mortality from COPD among women were as follows: (1) Cigarette smoking was the major cause of COPD mortality among both women and men in the United States. (2) Both male and female smokers were found to develop abnormalities in the small airways, but the data were not sufficient to define possible gender-related differences in this response. (3) The risk for COPD mortality among former smokers did not decline to that among persons who had never smoked, even 20 years after smoking cessation.

In the 1990 Surgeon General's report on the health benefits of smoking cessation (USDHHS 1990), the major conclusions relevant to COPD were as follows: (1) Compared with continued smoking, cessation reduces rates of respiratory symptoms (e.g., cough, sputum production, and wheezing) and of respiratory infections (e.g., bronchitis and pneumonia). (2) Among persons with overt COPD, smoking cessation improves pulmonary function about 5 percent within a few months after cessation. (3) Cigarette smoking accelerates the age-related decline in lung function that occurs among persons who have never smoked, but with sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that among persons who have never smoked. (4) With sustained abstinence, the COPD mortality rates among former smokers decline compared with those among continuing smokers.

Much of the more recent research on the relationship between COPD and cigarette smoking has focused on determining predictors of susceptibility (e.g., childhood respiratory illness and degree of airway hyperactivity) and on early detection (Samet 1989a; USDHHS 1994). The following discussion summarizes the research that has developed since previous Surgeon General's reports on smoking and provides more recent information on the epidemiology of COPD among women.

Smoking and Natural History of Development, Growth, and Decline of Lung Function

Although longitudinal data on the effects of cigarette smoking and development of COPD are not available for childhood through adulthood, study findings suggested that the development of COPD among adults may result from impaired lung development and growth, premature onset of decline of lung function, accelerated decline of lung function, or any combination of these conditions (USDHHS 1990). Airway development in utero and alveolar proliferation through age 12 years are critical to the mechanical functioning of the lungs, and impaired lung growth in utero from exposure to maternal smoking may enhance susceptibility to later development of COPD. Exposure to ETS in infancy and childhood and active smoking during childhood and adolescence may further contribute to impairment of lung growth and the risk for developing COPD (Fletcher et al. 1976; Samet et al. 1983; USDHHS 1984; Tager et al. 1988; Sherrill et al. 1991; Helms 1994; Samet and Lange 1996).

Lung Development in Utero

In utero exposure to maternal smoking is associated with wheezing and affects lung function during infancy (U.S. Environmental Protection Agency [EPA] 1992), but only limited information exists on gender-specific effects. Young and colleagues (1991) measured pulmonary function and airway hyperresponsiveness

to histamine among 63 healthy infants from a prenatal clinic in Perth, Australia. The infants were categorized into four groups on the basis of family history of asthma and parental cigarette smoking during pregnancy, but prenatal and postnatal exposures to cigarette smoke could not be separated. At a mean age of 4.5 weeks, rates of forced expiratory flow did not differ among the four groups. However, airway responsiveness was greater among infants whose parents smoked during pregnancy.

Hanrahan and colleagues (1992) measured forced expiratory flow rates among 80 healthy infants (average age, four weeks) from the East Boston Neighborhood Health Center, Massachusetts. These infants included 47 born to mothers who did not smoke during pregnancy, 21 to mothers who smoked throughout pregnancy, and 12 to mothers who reported varying smoking status or who had urine cotinine levels that were inconsistent with not smoking. After adjustment for infant size, age, gender, and ETS exposure after birth, expiratory flow rates were shown to be lower among infants whose mothers smoked during pregnancy than among infants whose mothers did not smoke. To determine the longitudinal effects of maternal smoking during pregnancy, Tager and colleagues (1995) studied 159 infants from the East Boston Neighborhood Health Center and obtained follow-up pulmonary function tests at 4 through 6, 9 through 12, and 15 through 18 months of age. On average, maternal smoking during pregnancy was associated with a 16-percent reduction in the expiratory flow rate at functional residual capacity among infant girls and a 5-percent reduction among infant boys. In contrast, exposure to ETS after birth was not associated with a significant decrement in longitudinal change in pulmonary function during infancy. A consequence of reduction in expiratory airflow and airway hyperresponsiveness may be an increased risk for lower respiratory tract illnesses, including wheezing. In a sample of 97 infants from the East Boston Neighborhood Health Center, Tager and colleagues (1993) found maternal smoking during pregnancy to be associated with an elevated risk for lower respiratory tract illnesses (RR, 1.5; 95 percent CI, 1.1 to 2.0). The finding was identical among infant girls and infant boys.

The decrement in pulmonary function associated with in utero exposure to smoke that is evident at birth and throughout infancy may persist into childhood and into adulthood. In a cross-sectional survey, Cunningham and colleagues (1994) measured pulmonary function among 8,863 children, aged 8 through 12 years, from 22 North American communities. In multivariate analyses, the children whose mothers reported smoking during pregnancy had significantly lower forced expiratory flows and reduction in forced expiratory volume in three-fourths of a second ($FEV_{0.75}$) and FEV_1/FVC than did the children of mothers who did not smoke during pregnancy, but absolute differences tended to be greater among boys than among girls. After adjustment for maternal smoking during pregnancy, current maternal smoking was not associated with significant decrement of lung function. Cunningham and colleagues (1995) also examined the relationship between maternal smoking during pregnancy and level of lung function among 876 Philadelphia schoolchildren aged 9 through 11 years. Overall, maternal smoking during pregnancy was associated with significant deficits in forced expiratory flow between 25 and 75 percent of FVC ($FEF_{25–75}$) (-8.1 percent; 95 percent CI, -12.9 to -3.1 percent) and FEV_1/FVC (-2.0 percent; 95 percent CI, -3.0 to -0.9 percent) among the children. This association remained after adjustment for the children's height, weight, age, gender, area of residence, race, socioeconomic status, and current exposure to ETS at home. The largest effects of maternal smoking on lung function were observed among boys and among black children; the deficit among girls was not significant: $FEF_{25–75}$ was -3.1 percent (95 percent CI, -9.9 to 4.2 percent), and FEV_1/FVC was -1.1 percent (95 percent CI, -2.5 to 0.4 percent).

Sherrill and colleagues (1992) in New Zealand examined the effects of maternal smoking during pregnancy among 634 children who were enrolled at age 3 years in a longitudinal study and had spirometric tests at ages 9, 11, 13, and 15 years. Gender-specific findings were not discussed, but compared with children of mothers who did not smoke, no significant changes in pulmonary function were found among children whose mothers smoked during pregnancy, within three months after childbirth, or at both times. However, details of the analysis were not presented, and power to detect differences may have been limited because most mothers who smoked during pregnancy also smoked during the three months after pregnancy (n = 219); few mothers smoked only during pregnancy (n = 10) or only after pregnancy (n = 18).

Growth of Lung Function in Infancy and Childhood

Beside the effects of in utero exposure to maternal smoking on lung function during infancy and childhood, substantial evidence suggested that ETS is an

important determinant of impaired lung function during childhood (National Research Council [NRC] 1986; USDHHS 1986b; EPA 1992). The 1992 EPA report concluded "that there is a causal relationship between ETS exposure and reductions in airflow parameters of lung function… in children" (EPA 1992, p. 7-63). However, few studies gave separate consideration to prenatal, infant, and childhood exposures to tobacco smoke, which may all be highly correlated, and few longitudinal studies on the effects of such exposure were performed. Wang and colleagues (1994b) analyzed longitudinal data on pulmonary function among 8,706 white children (4,290 girls and 4,416 boys) who did not smoke. The children entered the study at about 6 years of age and were followed up through 18 years of age to determine the association between parental cigarette smoking and growth of lung function among the children. Maternal smoking during the first five years of life and at the time of pulmonary testing was a significant predictor of lung function level among both girls and boys. In multiple regression models, current maternal smoking was the only significant predictor of growth of pulmonary function. Among children aged 6 through 10 years, rates for growth of lung function per each pack of cigarettes smoked daily by the mother were significantly lower for FVC (-2.8 mL/year), FEV_1 (-3.8 mL/year), and $FEF_{25–75}$ (-14.3 mL/second per year). Among children aged 11 through 18 years, current maternal smoking was significantly associated with slower growth rates only for $FEF_{25–75}$ (-7.9 mL/second per year).

In a longitudinal study in New Zealand, Sherrill and colleagues (1992) analyzed spirometric data collected bienially from 634 children ages 9 through 15 years. The FEV_1/FVC ratio was significantly lower among boys (-1.57 percent) but not among girls whose parents both smoked when the children were ages 7, 9, and 11, compared with those whose parents did not smoke. Among children who had wheezing or asthma by age 15 years, those whose parents smoked had lower mean FEV_1/FVC ratios than those whose parents did not smoke (a reduction of 2.3 percent for girls and 3.9 percent for boys). The effect of ETS on pulmonary function may have been underestimated because of misclassification of ETS exposure. A child was categorized as exposed only if parental smoking was reported consecutively during three surveys when the child was 7, 9, and 11 years old. Children were considered to be unexposed if their parents reported smoking at two or fewer of these surveys.

The association between ETS exposure in childhood and pneumonia (USDHHS 1986b; EPA 1992) provides additional evidence that may indirectly link ETS exposure and COPD in adulthood. Study findings indicated that ETS exposure increases the occurrence of lower respiratory tract illnesses, which are associated with small airway and alveolar inflammation, and that the inflammation provides a pathogenic basis for linking ETS exposure, lower respiratory tract illnesses, and development of COPD.

Beside the adverse effects on pulmonary function of in utero exposure to maternal smoking and postnatal exposure to parental smoking, active cigarette smoking in childhood and adolescence impairs growth of lung function, thus increasing the risk for COPD in adulthood (USDHHS 1994).

Decline of Lung Function

The effects of cigarette smoking on growth and decline of lung function were examined in longitudinal studies in East Boston, Massachusetts (Tager et al. 1988), and Tucson, Arizona (Sherrill et al. 1991). In the East Boston study, estimates of the age range when lung function begins to decline were wide but tended to be at earlier ages among current smokers (19 through 29 years) than among asymptomatic nonsmokers (18 through 42 years) or symptomatic nonsmokers (21 through 35 years). On average, the decline of lung function was more rapid among current smokers (-20 mL/year) than among asymptomatic nonsmokers (-10 mL/year) and symptomatic nonsmokers (-5 mL/year). Results were not presented separately by gender, but overall, the results from this study suggested that cigarette smokers experience premature onset of the decline of lung function and a more rapid decline than do nonsmokers. These findings were consistent with those of a longitudinal analysis of lung function from the Tucson Epidemiologic Study of Obstructive Lung Diseases (Sherrill et al. 1991).

Cross-sectional and longitudinal studies of ventilatory function showed, on average, higher rates of decline of FEV_1 among current smokers than among former smokers and nonsmokers (Table 3.27). As the amount of cigarette smoking increased, the rate of decline of FEV_1 also increased (Xu et al. 1992, 1994; Vestbo et al. 1996).

Identification of the minority of smokers who will have an accelerated decline of FEV_1 has been the focus of an increasing number of investigations, but generally data have not been presented for women and men separately. Predictors of a rapid decline of FEV_1 among smokers include respiratory symptoms (Jedrychowski et al. 1988; Sherman et al. 1992; Vestbo et al. 1996), level of lung function (Burrows et al.

1987), and bronchial hyperresponsiveness (Kanner et al. 1994; Paoletti et al. 1995; Rijcken et al. 1995; Villar et al. 1995). Among cigarette smokers, bronchial hyperresponsiveness to a variety of stimuli (e.g., histamine and methacholine) was associated with an accelerated rate of decline in FEV_1. Rijcken and colleagues (1995) analyzed the results of histamine challenge tests and longitudinal spirometric data obtained between 1965 and 1990 from 698 women and 921 men in two communities in the Netherlands. The average annual rate of FEV_1 decline was -33.1 mL/year among women who smoked during the entire study period and who had bronchial hyperresponsiveness; the rate among consistent smokers who did not have bronchial hyperresponsiveness was -27.3 mL/year. A similar pattern was observed among men. Tashkin and colleagues (1996) examined the relationship between bronchial hyperreactivity to methacholine and FEV_1 decline among 5,733 smokers, 35 through 60 years of age, with mild COPD (mean FEV_1/FVC, 65 percent; predicted FEV_1, 78 percent). After adjustment for age, gender, baseline smoking history, changes in smoking status, and baseline level of lung function, the investigators found that airway hyperreactivity during the five-year follow-up was a strong predictor of change in FEV_1 percent predicted. The greatest average decline of 2.2 percent predicted was among women who had the highest degree of hyperreactivity and who continued to smoke; the corresponding value among men was 1.7 percent predicted. In two cross-sectional analyses (Kanner et al. 1994; Paoletti et al. 1995), prevalence of bronchial hyperresponsiveness was higher among women smokers than among men smokers.

Cross-sectional and longitudinal investigations of decline in lung function among cigarette smokers provided conflicting results about the relative rate of decline among women compared with men (Xu et al. 1994). Xu and colleagues (1994) suggested that women may have a higher rate of FEV_1 decline. They hypothesized that gender differences in the distribution of unhealthy subjects in nonsmoking reference groups may explain conflicting results in studies that compared rates of FEV_1 decline among women and men.

Other study factors that may modify the effects of smoking and contribute to differences in study findings by gender include the year of birth of study participants (birth cohort) and the time period of a study (Samet and Lange 1996). In the Vlagtwedde-Vlaardingen study, Xu and colleagues (1995) reported a significant interaction between age and birth cohort in relation to decline in FEV_1 among women but not among men. The modifying effects of birth cohort may partly reflect changes in smoking behaviors.

Some studies have reported that sustained abstinence from smoking among former smokers slowed the decline in pulmonary function to that of women and men who had never smoked (USDHHS 1990) (Table 3.27). As suggested by the conceptual model for the development of COPD, age at the start of smoking cessation may substantially influence the level of lung function associated with aging, and recent evidence suggested that the benefits of smoking cessation are greatest for persons who stop smoking at younger ages (Camilli et al. 1987; Sherrill et al. 1994; Xu et al. 1994; Frette et al. 1996).

Among 147 women aged 18 years or older at entry in the prospective Tucson Epidemiological Study of Airways Obstructive Disease, Sherrill and colleagues (1994) found that, on average, smoking cessation was associated with a 4.3-percent improvement in FEV_1 at age 20 years and a 2.5-percent improvement at age 80 years. During 24 years of follow-up in the Dutch Vlagtwedde-Vlaardingen study that included 3,092 women aged 15 through 54 years at entry, Xu and associates (1994) found that mean FEV_1 loss was 20 mL/year less among women who had stopped smoking before age 45 years but only 5.4 mL/year less among women who had stopped smoking at age 45 years or older than among women who continued to smoke. As part of the Rancho Bernardo (California) Heart and Chronic Disease Study, 826 women and 571 men aged 51 through 95 years had spirometry testing in 1988–1991 (Frette et al. 1996). Among women former smokers who had stopped smoking before 40 years of age, FEV_1 was similar to that among women who had never smoked (2.09 and 2.13 L, respectively). Average FEV_1 among women who had stopped smoking at 40 through 60 years of age was 2.02 L, which was intermediate between that among women nonsmokers (2.13 L) and that among women current smokers (1.71 L). Women who had stopped smoking after 60 years of age had FEV_1 similar to that among current smokers (1.72 and 1.71 L, respectively). The same pattern of FEV_1 level in relation to age at smoking cessation was found among men.

Within the first year of smoking cessation, a small improvement in FEV_1 and a slowing in the rate of decline in FEV_1 are seen among former smokers compared with continuing smokers. In the Lung Health Study, Anthonisen and colleagues (1994) enrolled 5,887 women (37 percent) and men (63 percent) aged 35 through 60 years who were current smokers with mild COPD. During the first five years of follow-up,

Table 3.27. Rate of decline in forced expiratory volume in 1 second (FEV_1) among women and men, by smoking status, population-based studies, 1984–1996

Study	Population	Period of study/follow-up	FEV_1 change	Type of study or comments
Tashkin et al. 1984	1,309 women, 1,092 men Aged 25–64 years Southern California	Baseline 1973–1975 Follow-up 1978–1980	Women Continuing smokers: -54 mL / year Former smokers: -38 mL / year Never smoked: -41 mL / year Men Continuing smokers: -70 mL / year Former smokers: -52 mL / year Never smoked: -56 mL / year	Longitudinal study
Krzyzanowski et al. 1986	1,065 women, 759 men Aged 19–70 years Kraków, Poland	Baseline 1968 Follow-up 1981	Women Continuing smokers: -42 mL / year Former smokers: -38 mL / year Never smoked: -38 mL / year Men Continuing smokers: -59 mL / year Former smokers: -63 mL / year Never smoked: -47 mL / year	Longitudinal study
Camilli et al. 1987	970 women, 735 men Aged 20–90 years Tucson, Arizona	Baseline 1972–1973 Mean follow-up 9.4 years	Women* Current smokers: -7.38 mL / year† Former smokers: -0.73 mL / year Never smoked: -0.42 mL / year Men‡ Current smokers: -19.03 mL / year† Former smokers: -4.06 mL / year Never smoked: -6.13 mL / year	Longitudinal study Smoking cessation at age <35 years resulted in greatest improvement in FEV_1
Dockery et al. 1988	4,477 women, 3,714 men Aged 25–27 years 6 U.S. cities	1974–1977	Women Lifetime smoking: -4.4 mL / pack-year§ Additional affect of current smoking: -107.1 mL / pack / day (current) Men Lifetime smoking: -7.4 mL / pack-year§ Additional affect of current smoking: -123.3 mL / pack / day (current)	Cross-sectional study
Tager et al. 1988	1,814 females, 1,767 males Aged ≥ 5 years East Boston, Massachusetts	Baseline 1975 Follow-up 10 years	Women Current smokers: -20 to -30 mL / year Nonsmokers: -10 to -35 mL / year Men Current smokers: -25 to -40 mL / year Nonsmokers: -20 to -35 mL / year	Longitudinal study

*FEV_1 decline >100 mL / year, 0.6%.
†Observed / expected ≥ FEV_1 for subjects aged <70 years, adjusted for age and height.
‡FEV_1 decline >100 mL / year, 4.2%.
§FEV_1 adjusted for height.

Table 3.27. Continued

Study	Population	Period of study/follow-up	FEV_1 change	Type of study or comments
Lange et al. 1990a	4,986 women, 3,139 men Aged ≥ 20 years Copenhagen, Denmark	Baseline 1976–1978 Follow-up 1981–1983	Women Plain cigarettes: -34 mL / year Filter-tipped cigarettes: -28 mL / year Nonsmokers: -25 mL / year Men Plain cigarettes: -40 mL / year Filter-tipped cigarettes: -42 mL / year Nonsmokers: -30 mL / year	Longitudinal study No significant difference in rate of decline for smokers of plain or filter-tipped cigarettes Inconsistent association of inhalation with rate of decline
Peat et al. 1990	634 women, 350 men Population-based sample Brusselton, Australia	Baseline 1966 Follow-up every 3 years through 1984		Longitudinal study Slope of FEV_1 decline greater for smokers than for nonsmokers; slope increased with age No significant difference in slope for women and men Rate of decline associated with current number of cigarettes smoked
Chen et al. 1991	605 women, 544 men Aged 25–59 years Rural Saskatchewan, Alberta, Canada	1977	Women: -6.2 mL / pack-year[Δ¶] Men: -2.0 mL / pack-year[Δ]	Cross-sectional study
Xu et al. 1992	6,643 women, 5,437 men Aged 25–78 years 6 U.S. cities	Follow-up 6 years 3 examinations	Women Continuing smokers: -38.0 mL / year** <15 cigarettes / day: -31.2 mL / year** 15–24 cigarettes / day: -42.0 mL / year ≥ 25 cigarettes / day: -38.9 mL / year Former smokers: -29.6 mL / year Never smoked: -29.0 mL / year Men Continuing smokers: -52.9 mL / year** <15 cigarettes / day: -37.4 mL / year 15–24 cigarettes / day: -47.2 mL / year ≥ 25 cigarettes / day: -59.9 mL / year Former smokers: -34.3 mL / year Never smoked: -37.8 mL / year	Longitudinal study

[Δ]FEV_1 adjusted for age, height, and weight.
[¶]Pack-years = Average number of packs smoked / day x number of years of smoking.
**Age-adjusted average rate.

Table 3.27. Continued

Study	Population	Period of study/follow-up	FEV_1 change	Type of study or comments
Xu et al. 1994	3,092 women, 3,294 men Aged 15–75 years Vlaardingen, The Netherlands	Baseline 1965–1969 Follow-up every 3 years through 1990	Women Continuing smokers <15 cigarettes / day: -15.0 mL / year 15–24 cigarettes / day: -20.4 mL / year ≥ 25 cigarettes / day: -30.1 mL / year Former smokers: -19.2 mL / year Never smoked: -14.8 mL / year Men Continuing smokers <15 cigarettes / day: -18.8 mL / year 15–24 cigarettes / day: -26.3 mL / year ≥ 25 cigarettes / day: -33.2 mL / year Former smokers: -20.0 mL / year Never smoked: -5.8 mL / year	Longitudinal study
Frette et al. 1996	826 women, 571 men Aged 51–95 years Rancho Bernardo, California	1988–1991	Women Current smokers Aged <70 years: -49 mL / year Aged 70–79 years: -74 mL / year Aged ≥ 80 years: -112 mL / year Former smokers Aged <70 years: -44 mL / year Aged 70–79 years: -28 mL / year Aged ≥ 80 years: -20 mL / year Never smoked Aged <70 years: -37 mL / year Aged 70–79: -23 mL / year Aged ≥ 80 years: -35 mL / year Men Current smokers Aged <70 years: -70 mL / year Aged 70–79 years: -91 mL / year Aged ≥ 80 years: 367 mL / year Former smokers Aged <70 years: -53 mL / year Aged 70–79 years: -27 mL / year Aged ≥ 80 years: -14 mL / year Never smoked Aged <70 years: -10 mL / year Aged 70–79 years: -28 mL / year Aged ≥ 80 years: -37 mL / year	Cross-sectional study

Table 3.27. Continued

Study	Population	Period of study/follow-up	FEV_1 change	Type of study or comments
Vestbo et al. 1996	5,354 women, 4,081 men Aged 30–79 years Copenhagen, Denmark	Baseline 1976–1978 Follow-up 1981–1983	Women 1–14 g tobacco / day: -7.2 mL / year[††] 15–24 g tobacco / day: -7.8 mL / year[††] ≥ 25 g tobacco / day: -24.8 mL / year[††] Chronic hypersecretion of mucus: -11.3 mL / year[‡‡] Men 1–14 g / day: -3.3 mL / year[††] 15–24 g / day: -12.4 mL / year[††] ≥ 25 g / day: -14.1 mL / year[††] Chronic hypersecretion of mucus: -23.0 mL / year[‡‡]	Longitudinal study
Prescott et al. 1997	5,020 women, 4,063 men Aged ≥ 20 years Copenhagen, Denmark	Baseline 1976–1978	Women Smoke inhalers: -7.4 mL / pack-year Noninhalers: -2.6 mL / pack-year Men Smoke inhalers: -6.3 mL / pack-year Noninhalers: -1.0 mL / pack-year	Longitudinal studies
	2,383 women, 2,431 men Glostrup, Denmark	Baseline 1964 Follow-up 7–16 years	Women Smoke inhalers: -10.5 mL / pack-year Noninhalers: -12.4 mL / pack-year Men Smoke inhalers: -8.1 mL / pack-year Noninhalers: -4.7 mL / pack-year	

[††]In excess of nonsmokers at baseline survey.
[‡‡]In excess of subjects without chronic hypersecretion of mucus at any survey.

persons who sustained abstinence from smoking experienced an increase in postbronchodilator FEV_1 for the first two years of follow-up and then a decline, whereas continuing smokers had a persistent decline in FEV_1. Among persons who had stopped smoking by the one-year follow-up, FEV_1 had increased an average of 57 mL. In contrast, among those who continued to smoke, FEV_1 declined an average of 38 mL in the first year of follow-up. During the entire five-year follow-up, the average rate of decline in FEV_1 was 34 mL / year among those with sustained abstinence and 63 mL / year among continuing smokers. Results for women and men were combined in this analysis. Tashkin and colleagues (1996) found that the greatest improvements of FEV_1 occurred during the first year of cessation among women and men with the highest levels of airway reactivity.

Prevalence of Chronic Obstructive Pulmonary Disease

In the United States, the major national databases on prevalence of COPD include NHIS, the National Hospital Discharge Survey, and the National Hospital Ambulatory Medical Care Survey. Mortality data are derived from the National Vital Statistics System.

Overall, nationwide data suggested that the prevalence of COPD increased among women aged 55 through 84 years over the period 1979–1985 (Feinleib et al. 1989). In NHIS, the age-adjusted prevalence of self-reported COPD among women increased from 8.8 percent in 1979 to 11.9 percent in 1985. The prevalence of COPD increased with age and peaked at ages 65 through 74 years. Data from the National Hospital Ambulatory Medical Care Survey showed that 11.4

Table 3.28. Prevalence of airflow limitation as measured by forced expiratory volume in 1 second (FEV_1) among women and men, population-based, cross-sectional studies, 1989–1994

Study	Population	Measure
Lange et al. 1989	4,905 women, 4,001 men Random, age-stratified sample Aged 20–90 years Denmark	FEV_1 <60% FEV_1/FVC* <0.7
Peat et al. 1990	634 women, 350 men Population-based sample Australia	FEV_1 <65% predicted on ≥ 2 occasions FEV_1/FVC <0.65
Bang 1993	328 black women, 243 black men Aged 25–75 years Spirometry testing in first National Health and Nutrition Examination Survey United States	FEV_1 <65%
Higgins et al. 1993	2,869 women, 2,198 men Population-based sample Aged ≥ 65 years United States	FEV_1 <5th percentile for healthy women and men
Isoaho et al. 1994	708 women, 488 men Population sample Aged ≥ 64 years Finland	FEV_1/FVC ≥ 0.65
Sherrill et al. 1994	891 women,[§] 633 men[§] Population sample Aged ≥ 55 years at 1st survey United States	FEV_1 <75%

*FVC = Forced vital capacity.
[†]Never smoked.
[‡]Current and former smokers.
[§]Survivors at 9th or 10th survey, spanning a period of ≤ 14 years.

percent of office visits by women in 1979 and 12.2 percent in 1985 were for COPD. In the National Hospital Discharge Survey, 0.8 percent of hospitalizations among women in 1979 and 0.9 percent in 1985 were for COPD.

Reported prevalence of COPD among women in Manitoba, Canada, also increased (Manfreda et al. 1993) between 1983–1984 and 1987–1988. The investigators used data from the Manitoba Health Services Commission, a registry of the entire Manitoba population and their use of inpatient and outpatient physician services. Prevalences of physician-diagnosed COPD and asthma were estimated for these two periods. Among women aged 55 years or older, COPD increased 23.3 percent—from 163.8 cases per 10,000 in 1983–1984 to 202 cases per 10,000 in 1987–1988. Larger increases were reported for combinations of diagnoses, including COPD and asthma (28.8 percent), COPD and bronchitis (29.5 percent), and COPD and asthmatic bronchitis (45.5 percent).

In population-based, cross-sectional studies conducted worldwide (Table 3.28), prevalence estimates for COPD among women, based on spirometric data, varied widely. The estimates ranged from

Prevalence (%)				
			Smokers	
Nonsmokers	**Former smokers**	**Current smokers**	**<15 (g/day)**	**≥ 15 (g/day)**
Women: 1.6 Men: 2.6	Women: 3.1 Men: 4.4		Women: 6.2 Men: 6.4	Women: 37.1 Men: 7.7
Women: 7.6 Men: 5.2		Women: 17.8 Men: 23.6		
Women: 8.4[†] Men: 0.0[†]		Women: 5.0[‡] Men: 5.4[‡]		
Women: 13.6[†] Men: 7.3[†]	Women: 28.2 Men: 18.5	Women: 47.4 Men: 45.1		
Women: 1.9[†] Men: 2.0[†]	Women: 14.3 Men: 12.3	Women: 12.5 Men: 34.7		
Women: 5.9 Men: 8.0	Women: 17.9 Men: 13.8	Women: 29.6 Men: 36.4		

approximately 2 percent among nonsmokers aged 40 years or older (Lange et al. 1989) to 47 percent among current smokers aged 65 years or older (Higgins et al. 1993). The wide variation in the prevalence of COPD may be the result of many factors, including differences in spirometric criteria for the diagnosis and differences in age distribution and exposure among populations. Regardless of the criteria for diagnosing COPD, prevalence was lowest among nonsmokers (Table 3.28). One exception to this pattern was reported by Bang (1993): black women who had never smoked (8.4 percent) had a higher prevalence of FEV_1 impairment than did current smokers and former smokers combined (5.0 percent). Although few recent analyses examined the relationship between dose or duration of smoking and the prevalence of COPD (Table 3.28), an inverse dose-response relationship between cigarette smoking and level of lung function is firmly established (USDHHS 1984).

Mortality from Chronic Obstructive Pulmonary Disease

Since the late 1970s, COPD has been the fifth-leading cause of death in the United States. In 1992, 85,415 deaths were attributed to COPD (*ICD-9* items 491, 492, and 496), and 44 percent of these deaths occurred among women (NCHS 1996). Cigarette smoking is the most important cause of COPD among both women and men (USDHHS 1984).

Mortality from COPD has steadily increased in the United States during the twentieth century as the

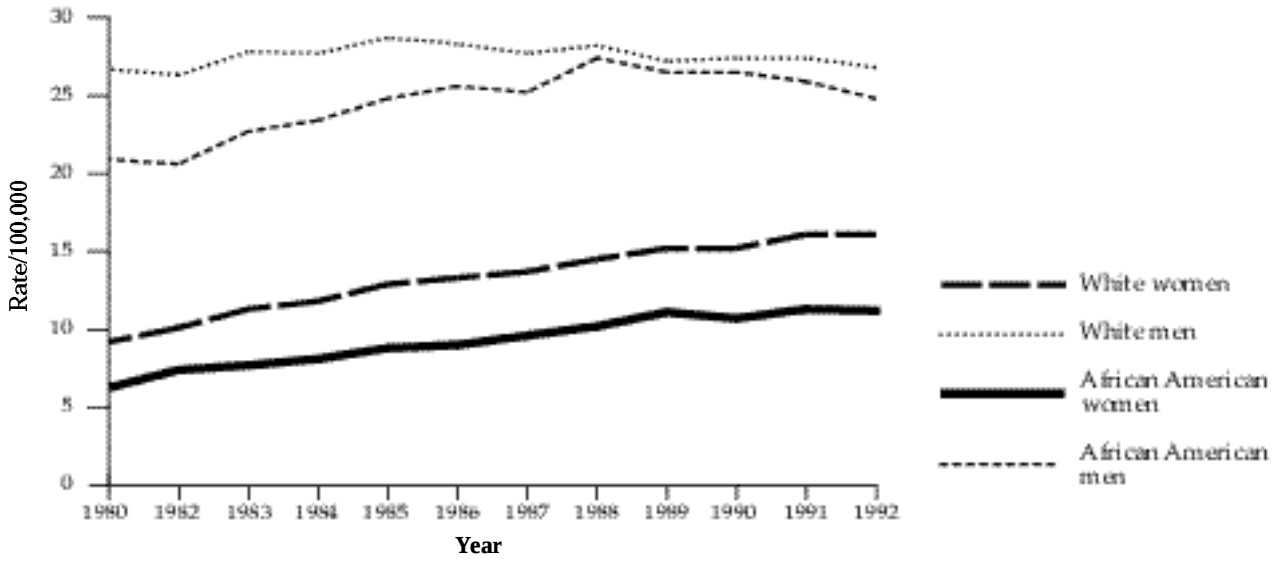
full impact of widespread cigarette smoking that began early in the century has taken effect (Speizer 1989). During 1979–1985, the annual age-adjusted death rates for COPD among women 55 years or older increased by 73 percent, from 46.6 per 100,000 to 80.7 per 100,000. Although the death rates for COPD among men were higher, the percent increase during 1979–1985 among men was only 16 percent, from 169.2 per 100,000 to 196.4 per 100,000.

According to NCHS (1995), the steep rise in mortality from COPD among women in the United States continued during 1980–1992 and was similar among white women and African American women (Figure 3.9). The age-adjusted death rates increased 75 percent among white women and 78 percent among African American women. In 1992, COPD mortality was 44 percent higher among white women than among African American women. During the same period, the age-adjusted death rate for men increased only 0.4 percent among whites and 19 percent among African Americans. In 1992, the overall age-adjusted death rates were 1.67 times higher among white men than among white women and 2.21 times higher among African American men than among African American women.

The prospective studies of ACS (CPS-I and CPS-II) provided further evidence for a marked increase in mortality from COPD among women (Thun et al. 1995, 1997a). Using CPS-I data, Thun and colleagues (1995) examined death rates during the period 1959–1965 among 298,687 current smokers and 487,700 nonsmokers. Age-adjusted death rates among women were 17.6 per 100,000 person-years for current smokers and 2.6 per 100,000 person-years for nonsmokers (RR, 6.7). The corresponding figures among men were 73.6 per 100,000 person-years and 8.0 per 100,000 person-years (RR, 9.3). In CPS-II, 228,682 current smokers and 482,681 nonsmokers were followed up in 1982–1988. In CPS-II, the death rate among women current smokers (61.6 per 100,000 person-years) was three times higher than that among women current smokers in CPS-I. The RR for mortality was 12.8 among women current smokers compared with women who had never smoked. Among men current smokers in CPS-II, the death rate (103.9 per 100,000 person-years) was 41 percent higher than that among men current smokers in CPS-I. The RR for mortality was 11.7 among men current smokers compared with men who had never smoked.

Using CPS-I and CPS-II data on RR for COPD mortality, Thun and colleagues (1997a,c) calculated the percentage of COPD deaths attributable to cigarette smoking. Among women in CPS-I, 85.0 percent of COPD deaths were attributable to smoking; this proportion increased to 92.2 percent in CPS-II. The corresponding values among men were 89.2 and 91.4 percent.

Figure 3.9. Age-adjusted death rates for chronic obstructive pulmonary disease, by gender and race, United States, 1980–1992



Source: National Center for Health Statistics 1995.

As in the United States, COPD mortality has increased among women worldwide (Brown et al. 1994a; Crockett et al. 1994; Guidotti and Jhangri 1994). For the period 1979–1988, Brown and colleagues (1994a) reported that COPD death rates among women increased in 16 of 31 countries they studied, remained constant in 9, and declined in 6. Increasing mortality from COPD among women was also reported from Alberta, Canada (Guidotti and Jhangri 1994), and from Australia (Crockett et al. 1994). During 1964–1990, age-standardized COPD mortality rates increased 2.6-fold among women in Australia (Crockett et al. 1994). It is difficult to correlate data on COPD trends with smoking patterns because of differences over time in the diagnostic coding of COPD from death certificates and because of scant longitudinal data on the prevalence of current smoking for many of the countries studied.

Several longitudinal studies specifically examined risk factors for mortality from COPD among women (Doll et al. 1980; USDHHS 1984, 1990; Speizer et al. 1989; Tockman and Comstock 1989; Lange et al. 1990b; Thun et al. 1995, 1997c; Friedman et al. 1997). Speizer and colleagues (1989) studied predictors of COPD mortality among 4,617 women and 3,806 men who were followed up for 9 through 12 years in the Harvard Six Cities Study of the effects of ambient air pollution on health. During the follow-up period, only 19 women and 26 men had died, but the ratio of observed-to-expected deaths from COPD generally appeared to increase with lifetime pack-years of smoking among both women and men. In the Copenhagen City Heart Study, Lange and colleagues (1990b) enrolled 7,420 women and 6,336 men from 1976 through 1978 and performed follow-ups through 1987. During this period, 47 women and 117 men died with obstructive lung disease as the underlying or contributory cause of death. Among women, with nonsmokers as the reference group, the RR for COPD-related death increased with lifetime pack-years of smoking: a RR of 6.7 (95 percent CI, 1.5 to 31) among smokers who inhaled and had less than 35 pack-years of smoking and a RR of 18.0 (95 percent CI, 1.3 to 94) among smokers who inhaled and had 35 or more pack-years of smoking. Self-report of inhalation of cigarette smoke was associated with a higher risk for COPD-related mortality among both women and men. Overall, the proportion of COPD-related mortality attributable to tobacco smoking was 90 percent among women and 78 percent among men.

Thun and colleagues (1997c) presented mortality rates for COPD in CPS-II in relation to the number of cigarettes currently smoked at baseline. The RR for death increased with the number of cigarettes smoked per day: 5.6 for 1 to 9 cigarettes per day, 7.9 for 10 to 19 cigarettes per day, 23.3 for 20 cigarettes per day, 22.9 for 21 to 39 cigarettes per day, and 25.2 for 40 cigarettes per day, all among women current smokers compared with women who had never smoked. The corresponding RRs among men current smokers compared with men who had never smoked were 8.8, 8.9, 10.4, 16.5, and 9.3.

Investigators determined mortality through 1987 in a cohort of 60,838 members of the Kaiser Permanente Medical Care Program aged 35 years or older between 1979 and 1986 (Friedman et al. 1997). The RRs for COPD mortality among women current smokers compared with women who had never smoked increased with the amount smoked, from 5.4 for 19 or fewer cigarettes per day to 13.9 for 20 or more cigarettes per day. The RRs among men were 9.2 and 10.9, respectively.

Limited data are available on the effects of smoking cessation on COPD mortality among women (USDHHS 1990). In the 22-year follow-up of 6,194 women in the British doctors' study, Doll and colleagues (1980) reported a standardized mortality ratio of 5 for chronic bronchitis and emphysema among women former smokers and a ratio of more than 10 among women current smokers. Similar overall results were found in CPS-II (USDHHS 1990). Even after 16 or more years of smoking cessation, mortality rates for COPD were higher among women who had stopped smoking than among women who had never smoked.

Conclusions

1. Cigarette smoking is a primary cause of COPD among women, and the risk increases with the amount and duration of smoking. Approximately 90 percent of mortality from COPD among women in the United States can be attributed to cigarette smoking.
2. In utero exposure to maternal smoking is associated with reduced lung function among infants, and exposure to environmental tobacco smoke during childhood and adolescence may be associated with impaired lung function among girls.
3. Adolescent girls who smoke have reduced rates of lung growth, and adult women who smoke experience a premature decline of lung function.

4. The rate of decline in lung function is slower among women who stop smoking than among women who continue to smoke.
5. Mortality rates for COPD have increased among women over the past 20 to 30 years.
6. Although data for women are limited, former smokers appear to have a lower risk for dying from COPD than do current smokers.

Sex Hormones, Thyroid Disorders, and Diabetes Mellitus

Sex Hormones

Many studies have reported findings that indicate an effect of smoking on estrogen-related disorders among women (Baron et al. 1990). Women who smoke have an increased risk for disorders associated with estrogen deficiency and a decreased risk for some diseases associated with estrogen excess. Together, these patterns suggested that smoking has an "antiestrogenic" effect (Baron et al. 1990). The effects of smoking on hormone-related events (e.g., endometrial cancer) seem to be more common among postmenopausal women than among premenopausal women (Baron et al. 1990). The mechanisms underlying this effect are not clear. As discussed later in this section, it is unlikely that smoking-related changes in estrogen levels can explain this effect.

Changes in plasma levels of endogenous estradiol and estrone have not been associated with smoking among either premenopausal or postmenopausal women (Jensen et al. 1985; Friedman et al. 1987; Khaw et al. 1988; Longcope and Johnston 1988; Baron et al. 1990; Barrett-Connor 1990; Key et al. 1991; Berta et al. 1992; Cassidenti et al. 1992; Austin et al. 1993; Law et al. 1997a). In general, adjustment for weight has not altered the relationship between smoking and estrogen levels (Khaw et al. 1988; Baron et al. 1990).

Comparisons of urinary estrogen excretion among smokers and nonsmokers have not been entirely consistent. Among premenopausal women, excretion of some estrogens may be lower for smokers (MacMahon et al. 1982; Michnovicz et al. 1988; Berta et al. 1992; Westhoff et al. 1996), but details of the excretion patterns have varied among studies, and one investigation found no differences (Berta et al. 1992). One study of postmenopausal women found no association between smoking and urinary estrogen excretion (Trichopoulous et al. 1987).

Smoking clearly has effects on estrogen levels during pregnancy. Smokers have lower circulating levels of estriol (Targett et al. 1973; Mochizuki et al. 1984) and estradiol than do nonsmokers (Bernstein et al. 1989; Cuckle et al. 1990b; Petridou et al. 1990). Moreover, the conversion of dehydroepiandrosterone sulfate (DHEAS) to estradiol among pregnant smokers may be impaired (Mochizuki et al. 1984).

Jensen and colleagues (1985) showed that, among postmenopausal women taking oral estrogens and progestins for at least one year, levels of serum estrone and estradiol were lower for smokers than for nonsmokers. The results of this study, confirmed by Cassidenti and colleagues (1990), provided evidence that postmenopausal smokers who receive oral HRT have lower estradiol and estrone levels than do comparable nonsmokers. These results suggested that smoking affects the gastrointestinal absorption, distribution, or metabolism of these hormones.

Michnovicz and colleagues (1986) reported that smokers and nonsmokers metabolize estrogens differently. They found that, compared with female nonsmokers, women who smoked had a higher rate of formation of 2-hydroxyestradiol, which has virtually no estrogenic activity. In contrast, nonsmokers formed relatively more estriol, which has weak agonist properties. These findings could indicate that nonsmokers had more circulating active estrogens than did smokers. They are consistent with the increased activity of 2-hydroxylation and 4-hydroxylation in placental tissues of smokers (Chao et al. 1981; Juchau et al. 1982) and with reduced urinary excretion of estriol (Michnovicz et al. 1986, 1988; Key et al. 1996; Westhoff et al. 1996).

Data on plasma levels of testosterone among women have been inconclusive. Friedman and colleagues (1987) reported that serum testosterone

concentrations were significantly higher among postmenopausal smokers than among postmenopausal nonsmokers. However, other investigators reported no association of smoking with serum levels of testosterone among postmenopausal women (Khaw et al. 1988; Cauley et al. 1989).

Thyroid Disorders

For unknown reasons, most thyroid disorders are more common among women than among men (Larsen and Ingbar 1992). Enlargement of the thyroid gland (goiter) can occur because of inflammation, the metabolic stress of maintaining adequate thyroid hormone levels, or masses such as cysts or neoplasms. A relatively common cause of hyperthyroidism is Graves' disease, a systemic condition that typically includes hyperthyroidism with a diffuse goiter.

Several studies investigated the relationship between cigarette smoking and clinically apparent goiter, but findings have varied. Two population-based surveys of patients with a clinical diagnosis of goiter reported that the prevalence of goiter was 50 to 100 percent higher among women smokers than among women nonsmokers (Christensen et al. 1984; Ericsson and Lindgärde 1991). A study of hospital employees found that the prevalence of goiter among cigarette smokers was 10 times that among nonsmokers (30 vs. 3 percent; $p < 0.001$ for analysis of combined data for women and men) (Hegedüs et al. 1985). Other studies of women (Petersen et al. 1991) and studies in which data for women and men were combined (Bartalena et al. 1989; Prummel and Wiersinga 1993) did not find an association between smoking and goiter.

One investigation that used ultrasonography to measure thyroid volume among female smokers and nonsmokers reported that thyroid glands among smokers were 75 percent larger than those among nonsmokers (25 vs. 14 mL; $p < 0.001$) (Hegedüs et al. 1985). A small study of women and men confirmed these findings (Hegedüs et al. 1992). Another small study with a combined analysis of women and men did not find a difference between smokers and nonsmokers, but there was no adjustment for age or gender (Berghout et al. 1987).

A series of studies, mostly clinic based, have reported that cigarette smokers have a higher risk for Graves' disease with ophthalmopathy (eye involvement) than do nonsmokers (Hägg and Asplund 1987; Bartalena et al. 1989; Shine et al. 1990; Tellez et al. 1992; Prummel and Wiersinga 1993; Winsa et al. 1993). Various analyses were presented in these studies, and some made no adjustment for age and gender. Nonetheless, these findings consistently suggest that smoking modestly increases the risk for Graves' hyperthyroidism and greatly increases the risk for Graves' disease with ophthalmopathy. Only one of the studies reported results for women alone (Bartalena et al. 1989), but in most of the other investigations, at least three-fourths of the study participants were women. The data reported by Prummel and Wiersinga (1993) were analyzed in the most detail. Patients with Graves' disease who were attending an endocrinology clinic were compared with a control group selected from patients attending an ophthalmology clinic and persons accompanying patients to the endocrinology clinic. Cigarette smoking conferred a RR of 1.9 (95 percent CI, 1.1 to 3.2) for Graves' disease without ophthalmopathy and a RR of 7.7 (95 percent CI, 4.3 to 13.7) for Graves' disease with ophthalmopathy.

Data on the association of smoking with other thyroid disorders are limited. Available data have suggested, however, that smoking is not strongly associated with hypothyroidism, autoimmune thyroiditis, or autoimmune hypothyroidism (Bartalena et al. 1989; Ericsson and Lindgärde 1991; Petersen et al. 1991; Nyström et al. 1993; Prummel and Wiersinga 1993).

Comparison of the levels of the major thyroid hormones (triiodothyronine [T_3] and thyroxine [T_4]) among smokers and nonsmokers has not revealed a consistent pattern. Different investigations reported higher, lower, or equivalent hormone levels among smokers and nonsmokers (Bertelsen and Hegedüs 1994). However, in most studies, levels of thyroid-stimulating hormone (TSH) have been lower among smokers than among nonsmokers (Bertelsen and Hegedüs 1994).

These diverse effects of smoking on the thyroid gland are difficult to explain with a single mechanism. A higher prevalence of goiter among smokers than among nonsmokers would suggest that cigarette smoking impairs the synthesis or secretion of thyroid hormones. Indeed, cigarette smoke contains several substances, in particular thiocyanate, that may have such an effect (Sepkovic et al. 1984; Karakaya et al. 1987). However, evidence that TSH levels may be lower among smokers than among nonsmokers does not support such an interference with thyroid function, since TSH levels rise when patients become hypothryoid through effects on the thyroid gland. It is possible that goitrogenic effects of smoking are

combined with thyroid-stimulating effects, for example, through the catecholamine release associated with smoking. The manner in which smoking increases the risk for Graves' ophthalmopathy is also not clear. Study findings suggested that thyroid-stimulating antibodies, the hallmark of this disease, are not increased among smokers (Hegedüs et al. 1992; Winsa et al. 1993).

Diabetes Mellitus

Diabetes mellitus is a heterogeneous group of disorders, all characterized by high levels of blood glucose. The main types of diabetes have been defined as follows: type 1 (previously known as insulin-dependent diabetes mellitus), type 2 (previously known as non-insulin-dependent diabetes mellitus), gestational diabetes, and other specific types of diabetes (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). Type 2 diabetes accounted for 90 to 95 percent of the estimated 5.6 million cases of diabetes diagnosed among U.S. women older than 20 years of age in 1997, and the number of undiagnosed cases of diabetes among women was estimated at 2.5 million (Harris et al. 1998). The total prevalence of diabetes (diagnosed and undiagnosed combined) is similar among women and men, and little evidence exists that suggests the risk for type 2 diabetes differs by gender (Rewers and Hamman 1995; Harris et al. 1998). The detrimental effects of smoking on diabetic complications, particularly nephropathy and macrovascular morbidity and mortality, are well established (Moy et al. 1990; Muhlhauser 1994), but only a few studies have investigated cigarette smoking as a cause of diabetes.

Type 1 diabetes often occurs among children and young adolescents, for whom smoking is uncommon. Although no studies have investigated the relationship between smoking and type 1 diabetes, three have investigated the effect of parental smoking on the risk for type 1 diabetes among children. None of them showed an association (Siemiatycki et al. 1989; Virtanen et al. 1994; Wadsworth et al. 1997). However, maternal smoking during pregnancy has been associated with the development of microalbuminuria and macroalbuminuria among term offspring who later develop type 1 diabetes (Rudberg et al. 1998).

Data on the effect of active smoking on the risk for type 2 diabetes have been conflicting. A positive association was reported among women in the U.S. Nurses' Health Study (Rimm et al. 1993) but not among women in the Tecumseh (Butler et al. 1982), Nauru (Balkau et al. 1985), or Framingham (Wilson et al. 1986) studies or among Pima Indian women (Hanson et al. 1995).

The U.S. Nurses' Health Study (Rimm et al. 1993) was the largest and most rigorous of these studies. Self-reported information on cigarette smoking, other behavioral risk factors, and diagnosis of diabetes was updated every 2 years during 12 years of follow-up. Supplementary questionnaires elicited information on diabetes symptoms, blood glucose levels, and the use of hypoglycemic medications. The data were used to apply established criteria to confirm reported diabetes. The investigators reviewed medical records for a random sample of women who reported a diagnosis of diabetes and judged the validity of the confirmation of diabetes to be high. After adjustment for age, BMI, family history of diabetes, menopausal status, hormone use, alcohol intake, and physical activity, the RR for diabetes among smokers compared with nonsmokers was 1.0 (95 percent CI, 0.8 to 1.2) for women who smoked 1 to 14 cigarettes per day, 1.2 (95 percent CI, 0.99 to 1.4) for women who smoked 15 to 24 cigarettes per day, and 1.4 (95 percent CI, 1.2 to 1.7) for women who smoked more than 25 cigarettes per day. Tests for trends across the three levels of current cigarette consumption were statistically significant ($p < 0.01$) in all analyses. The RR for diabetes among women former smokers compared with women who had never smoked was 1.1 (95 percent CI, 1.0 to 1.2). Further adjustment for hypertension; total caloric intake; and intakes of vegetable fat, potassium, calcium, and magnesium did not alter the estimates. Moreover, heightened detection of diabetes among smokers did not explain the relationship observed: the number of physician visits did not differ between women current smokers and women who had never smoked, and restriction of the model to women with symptoms of diabetes did not alter the results.

In contrast, none of the other follow-up studies of women (Butler et al. 1982; Balkau et al. 1985; Wilson et al. 1986; McPhillips et al. 1990; Hanson et al. 1995) found a significant association between cigarette smoking and the risk for type 2 diabetes. Not all studies, however, adequately controlled for diabetes risk factors. For example, the lack of adjustment for alcohol intake in the Framingham study (Wilson et al. 1986) may have masked the relationship between smoking and type 2 diabetes, because alcohol intake is correlated with smoking and may be negatively associated with type 2 diabetes (Stampfer et al. 1988a; Rimm et al. 1995). Nonetheless, smoking did not predict progression to diabetes, even after multiple covariates were controlled for, in two studies of women

and men with impaired glucose tolerance (Keen et al. 1982; King et al. 1984). In one of these studies, smoking status was also not related to reversion to normoglycemia (Keen et al. 1982). Findings from studies examining the relationship between smoking and diabetes among men are similarly conflicting (Medalie et al. 1975; Butler et al. 1982; Balkau et al. 1985; Wilson et al. 1986; Ohlson et al. 1988; Feskens and Kromhout 1989; Shaten et al. 1993; Hanson et al. 1995; Perry et al. 1995; Rimm et al. 1995; Kawakami et al. 1997).

Data on the relationship between gestational diabetes and cigarette smoking have also not been consistent. In one study, more than 10,000 pregnant women in New York City underwent screening for glucose intolerance. They were given 50 g of glucose, and blood glucose was measured one hour later. Those with a blood glucose level higher than 135 mg / dL were further evaluated with a three-hour glucose tolerance test. Cigarette smoking during pregnancy was determined from a computer database drawn from medical records. Smoking was unrelated to gestational diabetes (RR, 0.8; 95 percent CI, 0.5 to 1.2) (Berkowitz et al. 1992). In a population-based study using birth certificate data abstracted from medical records, no association was found between smoking and a clinical diagnosis of gestational diabetes (Heckbert et al. 1988). Finally, in a cohort study of 116,000 female nurses aged 25 through 42 years, the multivariate RR for diagnosis of gestational diabetes during follow-up was 1.4 (95 percent CI, 1.1 to 1.8) among current smokers and 0.9 (95 percent CI, 0.8 to 1.1) among former smokers (Solomon et al. 1997).

Smoking appears to be associated with metabolic processes related to diabetes, including glucose homeostasis, hyperinsulinemia, and insulin resistance. Among both women and men with normal glucose tolerance, levels of hemoglobin A_{1c}, which reflect glucose levels in the previous few months, have been reported to be higher among smokers than among nonsmokers (Modan et al. 1988). In one study of 40 persons without diabetes (28 women and 12 men), a higher proportion of smokers than nonsmokers had hyperinsulinemia in response to a glucose tolerance test challenge (75 g of glucose given orally) (Facchini et al. 1992). Also, smokers have been found to be more insulin resistant than nonsmokers in response to a continuous infusion of glucose, insulin, and somatostatin (Modan et al. 1988). Other studies reported similar findings (Boyle et al. 1989; Eliasson et al. 1994; Zavaroni et al. 1994; Frati et al. 1996), although contradictory results have also been published (Nilsson et al. 1995; Mooy et al. 1998). The degree of insulin resistance may be related to the number of cigarettes smoked. In a study of 57 middle-aged male smokers, insulin resistance increased with increasing daily cigarette consumption (Eliasson et al. 1994).

The mechanisms that underlie these findings are not clear. Smoking may directly affect pancreatic insulin secretion, or the association of smoking with increased circulating levels of counterregulatory hormones, such as cortisol and catecholamines, may play a role. Moreover, higher levels of androstenedione and DHEAS have been observed among women who smoke. Hyperandrogenicity has been associated with a higher risk for type 2 diabetes (Lindstedt et al. 1991; Haffner et al. 1993; Andersson et al. 1994; Goodman-Gruen and Barrett-Connor 1997), but it is not known whether insulin resistance precedes or follows androgen excess. Smoking has been associated with upper-body fat distribution (see "Body Weight and Fat Distribution" later in this chapter), which is related to increased basal levels of insulin (Wing et al. 1991), two-hour postload plasma glucose (Wing et al. 1991; Mooy et al. 1995), two-hour postload insulin (Wing et al. 1991), and increased risk for type 2 diabetes (Björntorp 1988; Kaye et al. 1990; Carey et al. 1997).

Conclusions

1. Women who smoke have an increased risk for estrogen-deficiency disorders and a decreased risk for estrogen-dependent disorders, but circulating levels of the major endogenous estrogens are not altered among women smokers.
2. Although consistent effects of smoking on thyroid hormone levels have not been noted, cigarette smokers may have an increased risk for Graves' ophthalmopathy, a thyroid-related disease.
3. Smoking appears to affect glucose regulation and related metabolic processes, but conflicting data exist on the relationship of smoking and the development of type 2 diabetes mellitus and gestational diabetes among women.

Menstrual Function, Menopause, and Benign Gynecologic Conditions

Menstruation and menopause are normal aspects of female physiology, but they can affect a woman's well-being and quality of life (Daly et al. 1993; Jarrett et al. 1995). The effects of menopause on health go beyond cessation of menses. Many U.S. women now live one-half of their adult lives after menopause; the accompanying hormonal changes may result in symptoms and may also adversely affect the risk for disorders such as osteoporosis.

Menstrual disturbances and menopause are difficult to describe and study. No generally accepted definitions exist for dysmenorrhea (pain and discomfort during menstruation), menstrual irregularity (variable duration of the menstrual cycle), or amenorrhea (absence of menses). Moreover, some hormonal disturbances of menopause may precede the cessation of menstruation by several years. Menstrual symptoms and the timing of menses vary, and the point at which normal variation is exceeded and a true disorder exists may be difficult to define. Secondary amenorrhea (amenorrhea among women who have ever menstruated) also includes a continuum of menstrual irregularity, and sometimes the distinction between secondary amenorrhea and early menopause is difficult. The duration of amenorrhea required for menopause has varied in the literature. Currently, 12 months of amenorrhea is generally accepted as the definition of menopause (McKinlay 1996).

This presentation summarizes research on the relationship between cigarette smoking and several aspects of menstrual function, including dysmenorrhea, menstrual irregularity, secondary amenorrhea, and natural menopause.

Menstrual Function and Menstrual Symptoms

Studies have investigated the relationship between smoking and dysmenorrhea (Table 3.29) or amenorrhea (Table 3.30). Some of these were cross-sectional investigations that could not directly address whether smoking led to the menstrual symptoms or whether the menstrual symptoms led to smoking. The proportion of women who reported dysmenorrhea varied widely across studies; these differences may be due to several other factors, including variation in the age of the participants and in the definitions of dysmenorrhea or amenorrhea. Except for a survey of 19-year-old women (Andersch and Milsom 1982), most studies found the prevalence of dysmenorrhea to be higher among current smokers than among former smokers or women who had never smoked (Kauraniemi 1969; Wood 1978; Wood et al. 1979; Sloss and Frerichs 1983; Brown et al. 1988; Pullon et al. 1988; Teperi and Rimpelä 1989; Sundell et al. 1990; Parazzini et al. 1994) (Table 3.29). The majority of studies did not report RRs, but the findings suggested that the prevalence of self-reported amenorrhea tends to be about 50 percent higher among smokers than among nonsmokers.

One survey found a weak trend of increasing prevalence of dysmenorrhea with increasing amount smoked (Wood et al. 1979) (Table 3.29). In a case-control study of women seeking care for pelvic symptoms at a clinic in Italy, smokers of 1 to 9 cigarettes daily were no more likely than nonsmokers to have dysmenorrhea, but the adjusted RR was 1.9 (95 percent CI, 0.8 to 5.0) among women who smoked 10 or more cigarettes daily (Parazzini et al. 1994). The adjusted RR was particularly high (3.4; 95 percent CI, 1.3 to 8.9) among long-term smokers (9 to 20 years). A follow-up study found that the mean duration of menstrual pain was 0.4 days longer among smokers than among nonsmokers (Hornsby et al. 1998). Other surveys also reported increasing risk for dysmenorrhea with increasing numbers of cigarettes smoked but did not present details (Pullon et al. 1988; Sundell et al. 1990).

Four studies of smoking and dysmenorrhea took into account the possible effects of multiple covariates, such as age, alcohol intake, and use of OCs (Table 3.29). A study from New Zealand found an independent effect of smoking on dysmenorrhea, but no estimate of RR was given (Pullon et al. 1988). In the study of clinic patients in Italy, the effect of smoking persisted after adjustment for multiple factors (Parazzini et al. 1994), but a Finnish investigation reported that the statistical significance of the effect of smoking was lost after adjustment for alcohol use, physical activity, gynecologic history, and health practices (Teperi and Rimpelä 1989). In a U.S. study, women who smoked reported about a half-day more pain with menses than did nonsmokers (Hornsby et al. 1998) (Table 3.29).

Data on menstrual irregularity and secondary amenorrhea are less extensive (Table 3.30). In a few surveys, the proportion of current smokers who reported menstrual irregularity and intermenstrual

Table 3.29. Findings regarding smoking and dysmenorrhea

Study	Study type/ population	Findings	Comment
Kauraniemi 1969	Population survey Aged 25–60 years Finland	Prevalence of dysmenorrhea 2,446 never smoked: 7.2% 258 former smokers: 9.7% 786 current smokers: 13.4%	
Wood et al. 1979	Clinic survey Aged 15–59 years Australia	Prevalence of dysmenorrhea 227 never smoked: 37% 72 former smokers: 43% 227 current smokers: 60%	Weak trend of increasing prevalence of dysmenorrhea with increasing amount smoked
Andersch and Milsom 1982	Population survey Aged 19 years Sweden	573 participants Statistically significant inverse association between dysmenorrhea score and smoking	
Brown et al. 1988	Medical practice-based survey Aged 18–49 years England	Prevalence of dysmenorrhea 1,006 never smoked: 30.5% 458 former smokers: 32.1% 628 current smokers: 36.0%	
Pullon et al. 1988	Medical practice-based survey Aged 16–54 years New Zealand	1,826 participants Higher prevalence of dysmenorrhea among smokers than among nonsmokers Apparent dose-response pattern	
Teperi and Rimpelä 1989	Population sample Aged 12–18 years Finland	Prevalence of dysmenorrhea 546 nonsmokers: 19% 221 occasional smokers: 25% 253 daily smokers: 31%	Association with smoking not statistically significant after adjustment for alcohol use, physical activity, gynecologic history, health practices
Sundell et al. 1990	Population survey Aged 19 years at start of 5-year follow-up Sweden	Prevalence of dysmenorrhea 269 nonsmokers: 25.7% 198 current smokers: 40.4%	Dose-response pattern found
Parazzini et al. 1994	Case-control study Clinic patients Aged 15–44 years Italy	Relative risk for dysmenorrhea for current smokers of 10–30 cigarettes / day: 1.9 (95% confidence interval, 0.9–4.2)	Findings similar after adjustment for education, alcohol use, menstrual flow
Hornsby et al. 1998	Follow-up study Aged 37–39 years United States	Mean duration of pain with menses 275 nonsmokers: 2 days 83 smokers: 2.5 days	

Table 3.30. Findings regarding smoking and menstrual irregularity or secondary amenorrhea

Study	Study type/ population	Findings	
		Menstrual irregularity	Secondary amenorrhea
Hammond 1961	Cohort study Aged 30–39 years United States	Prevalence 1,050 never smoked: 16.3%* 842 current smokers: 18.2%*	
Pettersson et al. 1973	Population survey Aged 18–45 years Sweden		Prevalence 824 never smoked: 3.7% 262 former smokers: 5.9% 773 current smokers: 4.8%
Brown et al. 1988	Medical practice-based survey Aged 18–49 years England	Prevalence 1,006 never smoked: 8.9% 458 former smokers: 9.0% 628 current smokers: 14.6%	
Davies et al. 1990	Case-control study Clinic patients Aged 16–40 years England		Unadjusted relative risk for ever smoking and amenorrhea = 2.1†
Johnson and Whitaker 1992	Population survey High school students United States		Adjusted relative risk for smokers of ≥ 1 pack / day: 2.0 (95% confidence interval, 1.2–3.1)
Hornsby et al. 1998	Follow-up study Aged 37–39 years United States	Standard deviation of cycle length 275 nonsmokers: 2.1 days 83 smokers: 2.5 days	

*Amenorrhea among women who ever had menstrual periods.
†Computed from data presented in report.

bleeding was modestly higher than that of nonsmokers (Hammond 1961; Wood 1978; Sloss and Frerichs 1983; Brown et al. 1988). The menstrual cycle length of smokers seems to be more variable than that of nonsmokers (Hornsby et al. 1998; Windham et al. 1999b). Smokers also appear to have shorter cycles on average (Zumoff et al. 1990; Hornsby et al. 1998; Windham et al. 1999b). Some studies have found that smoking was associated with an increased prevalence of secondary amenorrhea (Davies et al. 1990; Johnson and Whitaker 1992). For example, 2,544 high school girls were asked about their menstrual patterns and use of cigarettes (Johnson and Whitaker 1992). The RR for having missed three or more menstrual cycles was 2.0 (95 percent CI, 1.2 to 3.1) among girls who smoked one or more packs of cigarettes per day compared with nonsmokers, after multiple covariates were controlled for. The results of other investigations, however, did not suggest such an effect. In a study from Sweden, no substantial differences were found between smokers and nonsmokers after adjustment for the effects of age, OC use, and other factors (Pettersson et al. 1973). In another study, the unadjusted RR for secondary amenorrhea among women who had ever smoked was less than 1.0 (Gold et al. 1994).

Age at Natural Menopause

The age at which menopause naturally occurs varies considerably among women. The factors that determine this variation are not well understood, and smoking is the only factor consistently associated with age at natural menopause.

Three cohort studies have reported relevant data (Table 3.31). In the Framingham study (McNamara et al. 1978), the mean age at menopause was about 0.8 years earlier among smokers than among nonsmokers.

In the U.S. Nurses' Health Study (Willett et al. 1983), the effect of smoking was greater: the median age at menopause among women who smoked 35 or more cigarettes per day was 2.0 years earlier than that among women who had never smoked. The RR for the occurrence of natural menopause was higher among smokers in all age categories, but the RRs tended to decrease with increasing age. Thus, among women aged 40 through 44 years, the RR for menopause (adjusted for weight) was 2.1 (95 percent CI, 1.7 to 2.7) for current smokers compared with women who had never smoked. Among women aged 50 through 55 years, the RR was 1.2 (95 percent CI, 1.1 to 1.3). The risk for menopause among former smokers was similar to that among women who had never smoked. In a follow-up study, the RR for menopause among current smokers compared with nonsmokers was 2.3 (McKinlay et al. 1992).

In a case-control study in Scotland, smoking strongly increased the risk for menopause among women aged 45 through 49 years, and a dose-response relationship with pack-years of smoking was demonstrated (Torgerson et al. 1994). Multivariate-adjusted RR estimates were similar with menopause defined as 6 and as 12 months of amenorrhea—2.3 and 2.7, respectively, among women with more than 20 pack-years of smoking compared with women who had never smoked. A case-control study of women hospitalized in Milan, Italy, found that smokers were less likely than nonsmokers to have menstrual periods at age 52 years (Parazzini et al. 1992b), and another case-control study found that women who had ever smoked had a higher risk for early menopause (age <47 years) than did nonsmokers (Cramer et al. 1995).

In a pooled analysis of findings from several cross-sectional surveys, the RR for being postmenopausal was 1.9 (95 percent CI, 1.7 to 2.2) among current smokers compared with women who had never smoked; risk increased with increasing amount smoked (Midgette and Baron 1990). The RR among former smokers was 1.3 (95 percent CI, 1.0 to 1.7), which suggested either that former smokers had not used tobacco as heavily as current smokers did or that the effect of smoking is largely reversible with cessation.

Numerous studies summarized the relationship between smoking and age at natural menopause by reporting the mean or median age at menopause among smokers and nonsmokers (Table 3.31). These data have been quite consistent: menopause occurs one or two years earlier among smokers than among nonsmokers. In several reports, the median or mean age at menopause was earlier among heavy smokers than among light smokers (McNamara et al. 1978; Adena and Gallagher 1982; McKinlay et al. 1985), but formal dose-response analyses were not conducted. Among former smokers, age at menopause was between that of women who had never smoked and that of current smokers (Adena and Gallagher 1982).

The mechanisms by which cigarette smoking might lead to an early menopause are not clear, but several possibilities have been advanced (Midgette and Baron 1990). Components of cigarette smoke, possibly PAHs, are toxic to ovaries in animals (Mattison 1980; Magers et al. 1995). In rodents, prolonged exposure to cigarette smoke seems to be associated with follicular atresia. Effects of nicotine on regulation of gonadotropins or sex hormone metabolism could also contribute to a detrimental effect of cigarette smoking on ovarian function (Midgette and Baron 1990).

Menopausal Symptoms

Although data on the association between smoking and symptoms of menopause are limited, at least some menopausal symptoms appear to be more common among smokers. One survey of postmenopausal women found no overall association between cigarette smoking and hot flashes during menopause, but among thin women (BMI <24.3 kg/m^2), smokers reported this symptom significantly more often than did nonsmokers (Schwingl et al. 1994). In a population sample of perimenopausal women, smoking was associated with vasomotor symptoms, largely hot flashes (Collins and Landgren 1995). Similarly, surveys from Australia and England also reported that smokers were more likely than nonsmokers to have menopausal symptoms (Greenberg et al. 1987; Dennerstein et al. 1993). Women who smoke also have been reported to have increased risk for hot flashes after hysterectomy and oophorectomy (Langenberg et al. 1997). Smokers also may tend to have a shorter perimenopausal period than do nonsmokers (McKinlay et al. 1992).

Endometriosis

Endometriosis, the presence of endometrial tissue outside the uterus, most commonly in the pelvis, is classically associated with dysmenorrhea, dyspareunia, and infertility. The prevalence of endometriosis has been difficult to assess in population-based studies because the disorder may be asymptomatic or may have nonspecific symptoms. Thus, its diagnosis may require invasive investigation (Houston et al. 1988). The best available estimate of incidence derives

Table 3.31. Smoking and age at natural menopause

Study	Population	Duration of amenorrhea before menopause	Smoking status comparison	Decrease in mean or median age at menopause (years)
Bailey et al. 1977	475 participants in health screening program United Kingdom	NR*	Current vs. former and never	1.3†
Jick et al. 1977	1,842 hospital patients 1,253 hospital patients United States	NR NR	Current vs. never Current vs. never	1.7† 1.3†
McNamara et al. 1978	926 from general population United States	12 months	Current vs. never and former	0.8‡
Lindquist and Bengtsson 1979	873 from population sample Sweden	5 months	Current vs. never and former	1.2†
Kaufman et al. 1980	656 hospital patients United States	NR	Current vs. never Former vs. never	1.7§ 0.2§
Adena and Gallagher 1982	10,995 participants in multiphasic health screening program Australia	6 months	Current vs. never Former vs. never	1.0† 0.4‡
Andersen et al. 1982b	5,645 from population sample Denmark	6 months	Current vs. never and former	1.0‡

*NR = Value not specified in report of study.
†Difference in mean ages.
‡Difference in median ages.
§Difference in ages at menopause computed by Adena and Gallagher (1982).

from a study of white women in Rochester, Minnesota (Houston et al. 1987). The findings suggested that each year approximately 0.3 percent of women aged 15 through 49 years receive a new diagnosis of endometriosis.

The association between endometriosis and smoking has been examined in numerous case-control studies (Cramer et al. 1986; FitzSimmons et al. 1987; Phipps et al. 1987; Parazzini et al. 1989; Darrow et al. 1993; Matorras et al. 1995; Sangi-Haghpeykar and Poindexter 1995; Signorello et al. 1997; Bérubé et al. 1998). Five of these studies included only cases associated with infertility (Cramer et al. 1986; FitzSimmons et al. 1987; Matorras et al. 1995; Signorello et al. 1997; Bérubé et al. 1998). All the studies except one (FitzSimmons et al. 1987) adjusted for potential confounding factors. The RRs for endometriosis associated with smoking were generally less than 1.0, typically approximately 0.7 (Cramer et al. 1986; FitzSimmons et al. 1987; Phipps et al. 1987; Darrow et al. 1993; Matorras et al. 1995; Sangi-Haghpeykar and Poindexter 1995), but in none of the studies was the inverse association statistically significant. In contrast to these findings, one study reported that women who had ever smoked had a nonsignificant increase in risk for endometriosis (Signorello et al. 1997), and two others found no association (Parazzini et al. 1989; Bérubé et al. 1998).

Endometriosis is considered an estrogen-dependent condition. Because of the antiestrogenic effect of smoking (Baron et al. 1990), it is plausible that smoking might lower the risk for this disorder. The available data are consistent with a protective effect, but no RR

Table 3.31. Continued

Study	Population	Duration of amenorrhea before menopause	Smoking status comparison	Decrease in mean or median age at menopause (years)
Willett et al. 1983	66,663 nurses United States	NR	Current (15–25 cigarettes / day) vs. never	1.4‡
McKinlay et al. 1985	5,350 from population sample United States	12 months	Current vs. never and former	1.7‡
Everson et al. 1986	261 controls United States	NR	Current vs. never	1.1‡
Hiatt and Fireman 1986	5,346 health maintenance organization members with multiphasic health examination United States	NR	Current vs. never Former vs. never	0.9† 0.5†
Stanford et al. 1987a	1,472 participants in mammography screening program United States	3 months	Ever vs. never	0.3‡
McKinlay et al. 1992	2,570 from population sample United States	12 months	Current vs. never and former	1.8‡
Luoto et al. 1994	1,505 from population sample Finland	NR	Current vs. never and former	1.6‡

†Difference in mean ages.
‡Difference in median ages.

estimate in published studies was significantly different from 1.0.

Uterine Fibroids

Uterine fibroids (leiomyomas) are benign tumors of the uterine musculature that are believed to be estrogen dependent. Leiomyomas are typically diagnosed by clinical examination and ultrasonography. Because they may be asymptomatic, the prevalence of these tumors in the population is difficult to assess. Leiomyomas may affect fecundity, possibly by inhibiting conception or affecting implantation or completion of pregnancy (Buttram and Reiter 1981; Vollenhoven et al. 1990).

Four case-control studies (Ross et al. 1986; Parazzini et al. 1988, 1997; Samadi et al. 1996) and two cohort studies (Wyshak et al. 1986; Marshall et al. 1998) investigated the epidemiology of leiomyomas in detail. These studies reported evidence of a protective effect of smoking against leiomyomas; RRs generally ranged from 0.5 among heavy smokers to 0.8 among all smokers. In three investigations, risk decreased with increasing number of cigarettes smoked per day (Ross et al. 1986; Parazzini et al. 1988, 1997). In the Walnut Creek cohort study, Ramcharan and colleagues (1981) also reported a slightly decreased risk for uterine leiomyomas among heavy smokers but did not provide RR estimates. In contrast, Matsunaga and Shiota (1980) found less smoking among Japanese women who had undergone hysterectomy for leiomyomas during pregnancy than among women who had normal pregnancies or induced abortion, but the difference was not statistically significant. In one investigation, no protective effect was found against

leiomyomas among former smokers (Parazzini et al. 1988). This finding suggested that the protective effect is reversible, but the duration of smoking cessation was not defined in the study. Another investigation of premenopausal women reported only weak evidence of an inverse association between smoking and uterine leiomyomas (Marshall et al. 1998).

Because of the antiestrogenic effect of cigarette smoking (Baron et al. 1990), a protective effect for uterine leiomyomas is biologically plausible, but this mechanism has not been examined extensively.

Ovarian Cysts

Two studies reported a higher risk for ovarian cysts among women who smoked cigarettes than among nonsmokers (Wyshak et al. 1988; Holt et al. 1994). In one of these studies, both current and former smokers had a higher risk than nonsmokers, but information on the type of cysts was not well documented (Wyshak et al. 1988). The other study showed an association between current smoking and the occurrence of functional ovarian cysts (Holt et al. 1994). An Italian study, however, did not find an association between smoking and the development of serous, mucinous, or endometrial ovarian cysts (Parazzini et al. 1989).

Conclusions

1. Some studies suggest that cigarette smoking may alter menstrual function by increasing the risks for dysmenorrhea (painful menstruation), secondary amenorrhea (lack of menses among women who ever had menstrual periods), and menstrual irregularity.
2. Women smokers have a younger age at natural menopause than do nonsmokers and may experience more menopausal symptoms.
3. Women who smoke may have decreased risk for uterine fibroids.

Reproductive Outcomes

Cigarette smoking has clinically significant effects on many aspects of reproduction. Recent research has clarified the effects of smoking on fertility, maternal conditions, pregnancy, birth outcomes, breastfeeding, and risk for sudden infant death syndrome (SIDS).

Delayed Conception and Infertility

The 1988 National Survey of Family Growth (Mosher and Pratt 1990) estimated that more than two million married couples in the United States are affected by fertility problems. Delayed conception results from a low probability of conception per menstrual cycle (Baird et al. 1986); infertility is commonly defined as the failure to conceive after unprotected sexual intercourse over a period of 12 months (Marchbanks et al. 1989). In primary infertility a woman has had no previous conception, whereas in secondary infertility at least one previous conception has occurred. Because smoking is associated with early spontaneous abortion (see "Spontaneous Abortion" later in this section), a distinction also should be made between absence of conception and very early pregnancy loss. These conditions represent two separate causes of impairment of fertility—inability to conceive and inability to carry a pregnancy to live birth.

The way in which smoking is analyzed may affect the results of studies of fertility. As noted later in this section, several investigations suggested that some effects of smoking on reproduction do not occur among former smokers. Thus, estimates for RR for infertility or conception delay among current and former smokers considered together (as ever smokers) are likely to be lower than those among current smokers. Also, several potential confounding variables need to be considered in analyses of smoking and reproductive outcomes. Maternal age is especially important because it strongly influences a woman's ability to conceive and because it is also related to the likelihood of smoking (see "Cigarette Smoking Among Pregnant Women and Girls" in Chapter 2).

Delayed Conception

Several cohort studies have evaluated the effect of smoking on pregnancy rates through follow-up among women who were attempting to become pregnant and have assessed the experiences of women who were already pregnant (Tables 3.32 and 3.33).

Almost all of these investigations found that women who smoked became pregnant less quickly than did nonsmokers. Over defined periods of time, the pregnancy rates among smokers were typically only 60 to 90 percent of those among nonsmokers (Baird and Wilcox 1985; Howe et al. 1985; de Mouzon et al. 1988; Weinberg et al. 1989; Joesoef et al. 1993; Joffe and Li 1994; Bolumar et al. 1996; Curtis et al. 1997; Spinelli et al. 1997). Several studies reported trends of increasing time to conception with increasing amount smoked (Howe et al. 1985; Bolumar et al. 1996; Curtis et al. 1997; Hull et al. 2000). Other studies examined risk factors for conception delays; most of these investigations found maternal smoking to be associated with an increased risk for delay (Olsen et al. 1983; Harlap and Baras 1984; Suonio et al. 1990; Olsen 1991; Laurent et al. 1992; Alderete et al. 1995; Bolumar et al. 1996). The effect of cigarette smoking appears to be reversible: several investigators have found similar conception rates among former smokers and those who had never smoked (Howe et al. 1985; Laurent et al. 1992; Joesoef et al. 1993; Curtis et al. 1997).

Infertility

A series of case-control studies have found current cigarette smoking to be associated with an increased risk for both primary and secondary infertility (Olsen et al. 1983; Cramer et al. 1985; Daling et al. 1987; Phipps et al. 1987; Joesoef et al. 1993; Tzonou et al. 1993) (Table 3.34). Infertility attributable to disease of the fallopian tubes in particular has repeatedly been reported among smokers (Cramer et al. 1985; Daling et al. 1987; Phipps et al. 1987). Like the cohort studies of delayed conception, no case-control study found an excess risk for infertility among former smokers (Daling et al. 1987; Phipps et al. 1987; Joesoef et al. 1993).

At least 10 investigations have compared the experience of smoking and nonsmoking women who underwent assisted reproduction such as in vitro fertilization (Trapp et al. 1986; Harrison et al. 1990; Elenbogen et al. 1991; Pattinson et al. 1991; Hughes et al. 1992; Rosevear et al. 1992; Rowlands et al. 1992; Sharara et al. 1994; Hughes and Brennan 1996; Sterzik et al. 1996; Van Voorhis et al. 1996). Some of those investigations reported findings consistent with an effect of smoking on the physiology of reproduction: lower peak serum estradiol levels during ovarian stimulation among smokers than among nonsmokers (Elenbogen et al. 1991; Gustafson et al. 1996; Sterzik et al. 1996; Van Voorhis et al. 1996) and lower concentrations of estradiol in follicular fluid among smokers (Elenbogen et al. 1991; Van Voorhis et al. 1992; Gustafson et al. 1996). Although the number of oocytes retrieved during assisted reproduction depends strongly on a woman's age, only one study adjusted for age in reporting associations with smoking (Van Voorhis et al. 1992). This study found an inverse relationship between pack-years of smoking and the number of oocytes retrieved. The largest relevant study (Harrison et al. 1990) did not adjust for age but did stratify by the number of cigarettes smoked per day. A nonsignificant trend toward fewer retrieved oocytes was noted with increasing number of cigarettes smoked. Further evidence of ovarian pathology derives from findings that smokers have a poor ovarian response to the clomiphene citrate challenge test (Navot et al. 1987).

The effect of smoking on fertilization and pregnancy rates during in vitro fertilization has varied widely in different investigations, but some studies indicated that smoking by women who were attempting to become pregnant may be detrimental (Hughes and Brennan 1996; Feichtinger et al. 1997). Only two of these analyses formally adjusted for age (Hughes et al. 1994; Van Voorhis et al. 1996), so it is possible that differences in age between smokers and nonsmokers may have affected these findings. Three studies reported that smokers had a significantly lower fertilization rate than did nonsmokers (Elenbogen et al. 1991; Rosevear et al. 1992; Rowlands et al. 1992); other investigations reported significantly fewer clinical pregnancies (Harrison et al. 1990; Gustafson et al. 1996; Van Voorhis et al. 1996; Chung et al. 1997) or nonsignificantly lower pregnancy rates (Trapp et al. 1986; Elenbogen et al. 1991) among women who smoked. In one investigation, smokers had modestly lower fertilization and implantation rates and an increased tendency for spontaneous abortion (Pattinson et al. 1991). Together, these factors resulted in a lower rate of successful delivery. However, other studies reported similar fertilization and pregnancy rates among smokers and nonsmokers (Hughes et al. 1994; Sharara et al. 1994; Sterzik et al. 1996).

Several reviews have provided useful summaries of clinical and laboratory data on the mechanisms by which smoking may affect female fertility (Stillman et al. 1986; Gindoff and Tidey 1989; Mattison et al. 1989a; Yeh and Barbieri 1989; Baron et al. 1990). Animal studies have found adverse effects of nicotine, cigarette smoke, and PAHs on the release of gonadotropins, formation of corpora lutea, gamete interaction, tubal function, and implantation of fertilized ova (Gindoff and Tidey 1989; Mattison et al. 1989b).

Table 3.32. Relative risks for conception among women smokers

Study	Study type	Population	Study period	Smoking status	Relative conception rate (95% confidence interval)
Baird and Wilcox 1985	Retrospective survey	678 pregnant women United States	1983	Nonsmokers Smokers ≤ 20 cigarettes / day >20 cigarettes / day	1.0 0.7 (0.6–0.9) 0.8 (0.6–0.9) 0.6 (0.4–0.9)
Howe et al. 1985	Cohort	6,199 episodes of attempted conception United Kingdom	1968–1983	Never smoked Former smokers Current smokers 1–5 cigarettes / day 6–10 cigarettes / day 11–15 cigarettes / day 16–20 cigarettes / day ≥ 21 cigarettes / day	1.0 1.0 (0.9–1.1) 1.0 (0.9–1.1) 1.0 (0.9–1.1) 0.9 (0.8–1.0) 0.8 (0.7–0.9) 0.8 (0.6–1.0)
de Mouzon et al. 1988	Cohort	1,887 women with planned pregnancies France	1977–1982	Nonsmokers Smokers	1.0 0.9 (0.6–1.2)
Weinberg et al. 1989	Cohort	221 women with planned pregnancies United States	1983–1985	Nonsmokers Smokers	1.0 0.6 (0.3–1.0)
Joesoef et al. 1993	Survey on deliveries	2,817 women with planned pregnancies United States	1981–1983	Never smoked Former smokers Current smokers	1.0 1.0 (0.9–1.1) 0.9 (0.8–1.0)
Florack et al. 1994	Cohort	259 women planning pregnancy The Netherlands	1987–1989	Nonsmokers Smokers 1–10 cigarettes / day >10 cigarettes / day	1.0 1.4 (0.9–2.2) 0.8 (0.5–1.3)
Joffe and Li 1994	Retrospective cohort	2,942 women enrolled at birth of infant United Kingdom	1991	Nonsmokers Smokers	1.0 0.9 (0.8–1.0)
Curtis et al. 1997	Retrospective cohort	2,607 women with planned pregnancies Canada	1986	Nonsmokers Former smokers Smokers 1–5 cigarettes / day 6–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day	1.0 1.0 (0.8–1.1) 0.9 (0.8–1.0) 1.1 (0.9–1.3) 1.0 (0.9–1.2) 0.9 (0.8–1.0) 0.7 (0.6–0.9)
Spinelli et al. 1997	Survey on deliveries	662 women with planned pregnancies Italy	1993	Nonsmokers Smokers	1.0 0.8 (0.7–1.0)

Note: Relative conception rate compares probability of conception among smokers and nonsmokers; values <1.0 indicate impairment of fecundity.

Adjustment factors
Maternal: age, body mass index, parity, previous infertility, frequency of sexual intercourse, last contraception method used, recent pregnancy, maternal alcohol consumption Paternal: smoking
Contraception (results not altered by further adjustment for social class, maternal age at marriage, parity)
Maternal: contraception use, attempt to conceive before study entry, previous delivery, social class Paternal: smoking
Education, body mass index, weight, gravidity, oral contraceptive use, induced and spontaneous abortions, previous pregnancy outcomes, termination of recent pregnancy, alcohol consumption, caffeine consumption, marijuana use, childhood exposure to cigarette smoke
Maternal: age, body mass index, education, age at menarche, gravidity, frequency of sexual intercourse, number of previous miscarriages, alcohol use, marijuana use, cocaine use
None
Maternal: age, education Paternal: smoking, education
Maternal: age, spousal smoking, recent oral contraceptive use
Maternal: working hours, shift work, use of video display terminal, industrial occupation, noisy workplace, exposure to solvents, physical stress, job decision latitude, job demands, stress from lack of support, coffee consumption, tea consumption, alcohol intake, age, parity Paternal: industrial occupation, exposure to solvents, exposure to fumes, smoking, frequency of sexual intercourse

Table 3.33. Relative risks for conception delay among women smokers

Study	Study type	Population	Study period	End point
Linn et al. 1982	Survey on deliveries	3,214 married nondiabetic women who gave birth after planned pregnancy United States	1977–1979	Relative risk for conception delay ≥ 3 months
Olsen et al. 1983	Case-control	Cases: 228 women attempting first pregnancy for ≥ 1 year Controls: 1,400 parous women who achieved first pregnancy in <1 year Denmark	1977–1980	Relative risk for conception delay ≥ 12 months (first pregnancy)
		Cases: 195 parous women attempting pregnancy for ≥ 1 year Controls: 1,800 parous women who achieved pregnancy in <1 year Denmark		Relative risk for conception delay ≥ 12 months (second or later pregnancy)
Suonio et al. 1990	Survey of pregnant women	2,198 pregnant women who conceived in ≤ 12 months Finland	1983	Relative risk for conception delay ≥ 6 months
Olsen 1991	Survey	10,886 pregnant women Denmark	1984–1987	Relative risk for conception delay ≥ 12 months

Note: Relative risk for conception delay compares risks of waiting longer than a specified time; values >1.0 indicate impairment of fecundity.

Among smokers, all these effects could lead to dysfunction of the fallopian tubes, delay of conception, infertility, spontaneous abortion, or ectopic pregnancy. Evidence has also indicated that cigarette smoking has an antiestrogenic effect among women, which could impair the fertility of female smokers (Baron et al. 1990) (see "Menstrual Function, Menopause, and Benign Gynecologic Disorders" earlier in this chapter). Women who smoke may also have an increased risk for infertility because of tubal dysfunction attributable to pelvic inflammatory disease (PID). The high rates of PID could be related to immune impairment among smokers or to sexual patterns among smokers that predispose them to STDs.

Thus, a consistent association between cigarette smoking and impairment of female fertility has been found in both case-control and cohort epidemiologic studies (Hughes and Brennan 1996; Augood et al. 1998). In addition, some investigations have reported more pronounced effects in association with higher levels of smoking. Clinical and laboratory studies have suggested plausible biological mechanisms for these associations, particularly tubal defects. Former smokers appear to have little excess risk for infertility—an observation that suggested either that the effects of smoking are reversible or that former smokers did not smoke heavily enough or long enough for adverse events to occur.

Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Nonsmokers	1.0	Maternal: contraception use, age, history of spontaneous abortion, use of diethylstilbestrol (DES) by woman's mother, body mass index, marijuana use, age at menarche, race, religion, history of pelvic inflammatory disease, history of induced abortion or ectopic pregnancy, gravidity, education, welfare status
Smokers	1.0 (0.9–1.2)	
Nonsmokers	1.0	Maternal: age, education, parity, oral contraceptive use, alcohol consumption, residence
Smokers	1.8 (1.3–2.5)	
Nonsmokers	1.0	
Smokers	1.3 (1.0–1.8)	
Nonsmokers	1.0	Maternal: age, gravidity, spontaneous abortion, induced abortion, maternal alcohol consumption, occupation, working time, strain of work Paternal: smoking, alcohol consumption
Smokers		Maternal: number of pregnancies, education, shift work, age, alcohol intake, coffee intake Paternal: age, smoking
1–4 cigarettes / day	1.0	
5–9 cigarettes / day	1.8 (1.3–2.6)	
10–14 cigarettes / day	1.8 (1.3–2.6)	
15–19 cigarettes / day	1.8 (1.2–2.5)	
≥ 20 cigarettes / day	1.7 (1.2–2.5)	

Maternal Conditions

Ectopic Pregnancy

Ectopic pregnancy results from the implantation of a fertilized ovum outside the uterus, usually in the fallopian tubes. The growth of the fetus in an abnormal location results in significant morbidity, and ectopic pregnancy has emerged as the leading cause of maternal death during the first trimester of pregnancy (Atrash et al. 1986). Between 1970 and 1989, the ectopic pregnancy rate in the United States increased almost fourfold, from 4.5 to 16.1 per 1,000 reported pregnancies (CDC 1992). An important risk factor for ectopic pregnancy is PID, which may result in anatomic abnormalities that increase the risk for ectopic pregnancy (Phipps et al. 1987; Coste et al. 1991b; Kalandidi et al. 1991). Other risk factors for ectopic pregnancy are STDs (which may lead to PID), previous ectopic pregnancy, pelvic surgery, and previous use of an intrauterine device (Coste et al. 1991b). Use of OCs or an intrauterine device at the time of conception is also a risk factor, probably because these contraceptives prevent intrauterine pregnancy but not necessarily fertilization of an ovum (Chow et al. 1987; Coste et al. 1991b).

Cigarette smoking has been associated with increased risk for ectopic pregnancy even after adjustment for factors such as previous abdominal surgery and a history of PID or STDs; adjusted RRs have typically been between 1.5 and 2.5 (Chow et al. 1988; Handler et al. 1989; Coste et al. 1991a; Tuomivaara and Ronnberg 1991; Phillips et al. 1992; Saraiya et al. 1998;

Table 3.33. Continued

Study	Study type	Population	Study period	End point
Laurent et al. 1992	Case-control	Cases: 483 women with history of conception delay ≥ 24 months Controls: 2,231 women without conception delay ≥ 24 months United States	1980–1983	Relative risk for conception delay ≥ 24 months
Bolumar et al. 1996	Population survey of pregnancy history	3,187 women with planned pregnancy Europe	1991–1993	Relative risk for conception delay >9.5 months for first pregnancy
	Prenatal survey	2,587 pregnant women with planned pregnancy Europe	1991–1993	Relative risk for conception delay >9.5 months for first pregnancy
Hull et al. 2000	Population-based survey	14,182 pregnant women who reached 24 weeks' gestation England	1991–1992	Relative risk for conception delay of >6 months*

*Conception delay of >12 months was also examined, and results were similar.

Castles et al. 1999). Some investigations have reported an increasing risk for ectopic pregnancy with an increasing number of cigarettes smoked (Handler et al. 1989; Coste et al. 1991a; Saraiya et al. 1998). However, this association was not observed in two other studies (Phillips et al. 1992; Parazzini et al. 1992c), and biases or confounding remain a concern in other investigations (Matsunaga and Shiota 1980; Levin et al. 1982; Kalandidi et al. 1991; Stergachis et al. 1991; Tuomivaara and Ronnberg 1991).

Thus, women who smoke may have an increased risk for ectopic pregnancy. The mechanisms that might explain such an association are not clear, but smoking can impair tubal transport and delay entry of the ovum into the uterus. These factors predispose a woman who smokes to ectopic pregnancy (Phipps et al. 1987; Mattison et al. 1989a; Stergachis et al. 1991; Phillips et al. 1992). As noted earlier in this section, smoking is also associated with PID, possibly through impairment of immune function (Holt 1987) or because of confounding by factors related to sexual experience.

Preterm Premature Rupture of Membranes

Premature rupture of the membranes (PROM) is generally defined as the leakage of amniotic fluid more than one hour before the onset of labor. Preterm PROM (PPROM) is premature leakage occurring before 37 weeks' gestation; it occurs in approximately 20 to 40 percent of premature deliveries (Spinillo et al. 1994d). In some instances, PPROM is associated with increased risk for transmission of human immunodeficiency virus (HIV) from the mother to the infant (Burns et al. 1994). Risk factors for PPROM include bleeding during pregnancy, previous preterm delivery, infection, cervical incompetence, and decreased maternal levels of certain nutrients such as ascorbic acid and zinc (Hadley et al. 1990; Harger et al. 1990; Ekwo et al. 1992, 1993; Williams et al. 1992; Spinillo et al. 1994d).

Early studies produced conflicting results regarding the relationship between smoking and PPROM (Underwood et al. 1965; Naeye 1982). These studies were limited, however, by small numbers of participants or by lack of control for potential

Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Nonsmokers	1.0	Maternal: age, age at first sexual intercourse, education, ethnicity, history of benign ovarian disease
Smokers		
1–4 cigarettes / day	1.0 (1.0–1.0)	
5–9 cigarettes / day	1.1 (1.0–1.1)	
10–19 cigarettes / day	1.2 (1.1–1.3)	
≥ 20 cigarettes / day	1.4 (1.1–1.6)	
Nonsmokers	1.0	Maternal: age, education, recent oral contraceptive use, frequency of sexual intercourse, paid work, alcohol consumption, coffee consumption
Smokers		
1–10 cigarettes / day	1.4 (1.1–1.7)	
≥ 11 cigarettes / day	1.7 (1.3–2.1)	
Nonsmokers	1.0	
Smokers		
1–10 cigarettes / day	1.4 (1.0–1.8)	
≥ 11 cigarettes / day	1.7 (1.3–2.3)	
Nonsmokers		Maternal: age, education, duration of oral contraceptive use, alcohol consumption, housing tenure and type, overcrowding
Smokers		Paternal: age, education, alcohol consumption
1–4 cigarettes / day	1.0	
5–9 cigarettes / day	1.2 (0.9–1.6)	
10–14 cigarettes / day	1.2 (0.9-11.6)	
15-19 cigarettes / day	1.5 (1.2-1.9)	
≥ 20 cigarettes / day	1.6 (1.3–2.0)	

confounding factors (Harger et al. 1990). In more recent studies, smoking has been consistently associated with PPROM (Castles et al. 1999) (Table 3.35). The RR estimates reported have varied from approximately 2 to 5 among smokers compared with nonsmokers, depending on the control groups under study. When women with PPROM were compared with pregnant women of the same gestational duration, the RRs among smokers were between 2.0 and 3.0 (Hadley et al. 1990; Harger et al. 1990). When the comparison included women who had term deliveries without PROM, some of the adjusted RRs were over 4.0 (Ekwo et al. 1993; Spinillo et al. 1994d). In the two studies that examined whether risk increased with the amount smoked, findings were mixed (Williams et al. 1992; Spinillo et al. 1994d) (Table 3.35). Women who had stopped smoking during pregnancy were at lower risk for PPROM than were those who continued to smoke (Harger et al. 1990; Williams et al. 1992).

Thus, women who smoke have an increased risk for PPROM. The underlying biological mechanism for the association is not known. Through its vasoconstrictive effects, smoking may disrupt the mechanical integrity of the fetal membranes, and it may affect general maternal nutritional status by impairing protein metabolism and by reducing circulating levels of amino acids, vitamin B_{12}, and ascorbic acid (Hadley et al. 1990). Smoking may also impair maternal immunity, possibly increasing susceptibility to infections that may precipitate PROM (Holt 1987). The studies cited in Table 3.35 controlled for variables such as maternal ascorbic acid level (Hadley et al. 1990), cervicovaginal infection (Spinillo et al. 1994d), and bleeding during pregnancy (Williams et al. 1992; Spinillo et al. 1994d) and observed a relationship between smoking and PPROM. Thus, those factors cannot explain the association.

Placental Complications of Pregnancy

Abruptio Placentae

Abruptio placentae is premature separation of the normally implanted placenta from the uterine wall. A leading cause of maternal and perinatal morbidity and mortality, abruptio placentae is estimated to cause 15 to 25 percent of perinatal deaths (Naeye 1980; Krohn et al. 1987; Raymond and Mills 1993;

Table 3.34. Relative risks for infertility among women smokers, case-control studies

Study	Population	Study period	End point	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Olsen et al. 1983	Cases: 213 women with primary infertility Controls: 1,296 fertile women Denmark	1977–1980	Primary infertility	Nonsmokers Smokers	1.0 1.6 (1.1–2.2)	Maternal age, parity, education, oral contraceptive use, alcohol consumption, residence
	Cases: 65 women with secondary infertility Controls: 1,651 fertile women Denmark	1977–1980	Secondary infertility	Nonsmokers Smokers	1.0 2.1 (1.3–3.6)	Maternal age, parity, education, oral contraceptive use, alcohol consumption, residence
Daling et al. 1987	Cases: 170 women with primary tubal infertility Controls: 170 fertile women never previously pregnant United States	1979–1981		Never smoked Former smokers Current smokers	1.0 1.1 (0.5–2.5) 2.7 (1.4–5.3)	Matched for race, census tract of residence, age
Phipps et al. 1987	Cases: 1,390 infertile women Controls: 1,264 women after delivery United States and Canada	1981–1983	Primary infertility	Nonsmokers Smokers, infertility thought primarily due to: Cervical factor Tubal disease Ovulatory factor Endometriosis	1.0 1.7 (1.0–2.7) 1.6 (1.1–2.2) 1.0 (0.8–1.4) 0.9 (0.6–1.3)	Maternal age, religion, contraception use, time since menarche, number of sexual partners, education
Joesoef et al. 1993	Cases: 1,815 infertile women Controls: 1,760 primiparous fertile women United States	1981–1983	Primary infertility	Never smoked Former smokers Current smokers	1.0 0.6 (0.5–0.8) 1.9 (1.5–2.3)	Maternal age, body mass index, education, age at menarche, gravidity, frequency of sexual intercourse, number of previous miscarriages, use of marijuana, use of cocaine, consumption of alcohol
Tzonou et al. 1993	Cases: 84 infertile women Controls: 168 pregnant women Greece	1987–1988	Secondary infertility	Never smoked Ever smoked	1.0 2.6 (1.2–6.0)	Maternal age, gravidity, education, residence,

Spinillo et al. 1994a). Risk factors for abruption include hypertension, abdominal trauma, intravenous drug use, previous preterm birth, stillbirth or spontaneous abortion, advanced maternal age, and residence at high altitude during pregnancy (Williams et al. 1991a,c; Raymond and Mills 1993; Spinillo 1994a).

Abruptio placentae has repeatedly been associated with maternal cigarette smoking (Karegard and Gennser 1986; Voigt et al. 1990; Saftlas et al. 1991; Williams et al. 1991a,c; Raymond and Mills 1993; Spinillo et al. 1994a; Ananth et al. 1996; Cnattingius et al. 1997; Ananth et al. 1999; Castles et al. 1999). In studies that controlled for multiple covariates, the RRs were 1.4 to 2.4 for maternal smoking (Table 3.36). The risk for abruptio placentae has been found to increase with the number of cigarettes smoked (Williams et al. 1991a; Raymond and Mills 1993; Ananth et al. 1996; Cnattingius et al. 1997). In one study, women who had stopped smoking during pregnancy had a lower risk than did women who continued to smoke throughout pregnancy (Naeye 1980).

Because of the complicated interrelationships of smoking, PPROM, preeclampsia, and abruptio placentae, the independent effects of smoking on each of these outcomes may be difficult to assess. Since prolonged PPROM may be associated with an increased risk for abruptio placentae (Nelson et al. 1986; Vintzileos et al. 1987; Gonen et al. 1989; Spinillo et al. 1994a), smoking may increase the risk for abruptio placentae in part through its association with PPROM. Other biological mechanisms could also explain the association between smoking and separation of the placenta from the uterine wall. For example, carboxyhemoglobinemia and vasoconstriction associated with smoking can lead to local hypoxia, which in turn could lead to premature placental separation (Voigt et al. 1990; Williams et al. 1991a).

Placenta Previa

Placenta previa occurs when the placenta either partially or totally obstructs the cervical os, thus increasing the risks for hemorrhage and preterm birth—outcomes with considerable morbidity and mortality for both mother and infant. Women with placenta previa also experience increased risks for cesarean section, fetal malpresentation, and postpartum hemorrhage. One study reported that placenta previa complicates nearly 5 per 1,000 deliveries annually (Iyasu et al. 1993). Risk factors for placenta previa include increasing parity, increasing maternal age, previous abortion or cesarean section, and pregnancy during residence at high altitude (Williams et al. 1991b).

Cigarette smoking has repeatedly been associated with placenta previa (Castles et al. 1999) (Table 3.36). The RR is typically between 1.5 and 3.0 among women who smoke during pregnancy compared with those who do not (Meyer et al. 1976; Meyer and Tonascia 1977; Kramer et al. 1991; Williams et al. 1991b; Zhang and Fried 1992; Handler et al. 1994; Monica and Lilja 1995; Ananth et al. 1996; Chelmow et al. 1996; McMahon et al. 1997). Adjustment for covariates such as maternal age, parity, and previous cesarean section has had little effect on the strength of the association. Significant trends of increasing risk for placenta previa with increasing number of cigarettes smoked have been found in some studies (Handler et al. 1994; Monica and Lilja 1995; McMahon et al. 1997) but not in others (Williams et al. 1991b; Ananth et al. 1996).

Smoking might lead to placenta previa through chronic hypoxia, which results in placental enlargement and extension of the placenta over the cervical os (Williams et al. 1991b). The vascular effects of smoking might also be involved (Meyer and Tonascia 1977; Zhang and Fried 1992).

Spontaneous Abortion

Spontaneous abortion (miscarriage) is usually defined as the involuntary termination of an intrauterine pregnancy before 28 weeks' (sometimes 20 weeks') gestation. The rate of spontaneous abortion usually cannot be completely ascertained, because some women may not receive medical care for a spontaneous abortion and may not even be aware of the pregnancy and its loss. Approximately 10 to 15 percent of pregnancies end in clinically recognized spontaneous abortion; measurement of human chorionic gonadotropin hormone in the urine of sexually active women has suggested that the total rate of fetal loss after implantation of a fertilized ovum may be as high as 50 percent (Wilcox et al. 1988; Eskenazi et al. 1995a). The risk for spontaneous abortion increases with maternal age and is higher among women who have had a previous miscarriage. Other purported risk factors are alcohol consumption, fever, various forms of contraception, social class, and race (Kline et al. 1989). Some spontaneous abortions involve a fetus that has chromosomal or structural abnormalities; in others, the fetus is normal. The causes of and risk factors for spontaneous abortion may differ accordingly.

An association between spontaneous abortion and maternal cigarette smoking has been suspected since the early 1960s (DiFranza and Lew 1995), but early epidemiologic studies provided inconsistent

Table 3.35. Relative risks for preterm premature rupture of membranes (PPROM) among women smokers, case-control studies

Study	Population	Study period	Smoking status	Relative risk (95% confidence interval)
Hadley et al. 1990	Black women with singleton pregnancies Cases: 133 women with PPROM Controls: 133 pregnant women (not "high risk") United States	Not reported	Nonsmokers Smokers (>10 cigarettes / day)	1.0 2.6 (1.6–4.5)
Harger et al. 1990	Cases: 341 women with singleton pregnancies and PPROM Controls: 253 pregnant women with intact membranes at 37 weeks' gestation United States	1982–1983	Nonsmokers Stopped smoking during pregnancy Continuing smokers	1.0 1.6 (0.8–3.3) 2.1 (1.4–3.1)
Williams et al. 1992	Cases: 307 women with singleton pregnancies and PPROM Controls: 2,252 women with term deliveries and no PROM United States	1977–1980	Never smoked Stopped smoking before conception Stopped smoking during first trimester Nonsmokers during pregnancy Smokers throughout pregnancy Smokers at some time during pregnancy 1–9 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.4 (0.9–2.0) 1.6 (0.8–2.9) 1.0 2.2 (1.4–3.5) 1.6 (1.1–2.4) 1.8 (1.1–2.8) 1.5 (0.9–2.4) 1.7 (1.0–2.6)
Ekwo et al. 1993	Cases: 184 women with PPROM Controls: 184 pregnant women United States	1985–1990	No smoke exposure Passive smokers only Active smokers only Active and passive smokers	1.0 1.0 (0.6–1.8) 4.2 (1.8–10.0) 2.1 (1.2–3.5)
Spinillo et al. 1994d	Cases: 138 women with PPROM (24–35 weeks' gestation) Controls: 267 women with term pregnancies Italy	1988–1992	Nonsmokers Smokers ≤ 10 cigarettes / day >10 cigarettes / day	1.0 1.9 (1.1–3.2) 1.1 (0.5–2.2) 4.0 (1.9–8.8)

findings (USDHHS 1980). These inconsistencies may have been due to the limitations of small sample size, inadequate control for covariates, and differences in ascertainment of smoking among case subjects and control subjects (Stillman et al. 1986).

Major studies published since 1975 that reported RRs for the association between smoking and spontaneous abortion are summarized in Table 3.37. Some studies found an increase in risk among smokers (Kline et al. 1977; Himmelberger et al. 1978; Armstrong et al. 1992; Dominguez-Rojas et al. 1994), whereas others reported no association or only a weak relationship (Hemminki et al. 1983; Sandahl 1989; Windham et al. 1992). Although the few studies that included both clinically recognized and unrecognized fetal losses were small, they provided some evidence that the risk for spontaneous abortion is higher among current smokers than among nonsmokers (Wilcox et al. 1990; Eskenazi et al. 1995a). Another study found that the risk among former smokers was similar to that among nonsmokers (Stein et al. 1981).

Two studies showed a clear dose-response relationship between smoking and spontaneous abortion; noticeable effects were seen among women who

Adjustment factors
Matched for maternal age, parity, gestational age
Adjustment for previous PPROM, fundal placental location
None
Race, education, age, welfare status, martial status, marijuana and alcohol use, parity, previous spontaneous or therapeutic abortion, cervical incompetence, bleeding during pregnancy, body mass index, coffee consumption
Matched for maternal age, parity, race
Previous term and preterm deliveries, social class, prepregnancy body mass index, bleeding during pregnancy, incompetent cervix, preeclampsia, low hematocrit on hospital admission for delivery, documented cervicovaginal infection during pregnancy

smoked more than 10 cigarettes per day (Armstrong et al. 1992; Dominguez-Rojas et al. 1994). In their study population, Armstrong and colleagues (1992) estimated that cigarette smoking accounted for 11 percent of all spontaneous abortions and could have explained 40 percent of spontaneous abortions among women smoking 20 or more cigarettes per day. In a small case-control study of habitual abortion (two or more spontaneous abortions), current smokers had a RR of 1.4 compared with women who had never smoked (95 percent CI, 0.8 to 2.9); risk increased with the number of cigarettes smoked per day (Parazzini et al. 1991a).

Only a few studies separately investigated spontaneous abortions of chromosomally normal and abnormal fetuses. Kline and colleagues (1989) reported an association between cigarette smoking during pregnancy and spontaneous abortion of a chromosomally normal fetus or abortion of a fetus with nontrisomic chromosomal aberration. A French study found that among women younger than 30 years old, the proportion of spontaneous abortions that were chromosomally normal was higher in smokers who inhaled than in noninhalers or nonsmokers (Boué et al. 1975). No such association was found among women aged 30 years or older. Yet another study reported that the proportion of losses of a chromosomally normal fetus increased with the number of cigarettes smoked during pregnancy (Alberman et al. 1976). Kline and colleagues (1995) later reported the findings on all 2,305 karyotyped cases of spontaneous abortion and 4,076 control pregnancies studied over a decade in public and private facilities of three New York City hospitals. Compared with nonsmokers, women who smoked 14 or more cigarettes per day at the time of conception had a significantly higher risk for spontaneous abortion of a chromosomally normal fetus (adjusted RR, 1.3; 95 percent CI, 1.1 to 1.7) and a nonsignificantly higher risk for spontaneous abortion of a fetus with nontrisomic chromosomal aberration (adjusted RR, 1.2; 95 percent CI, 0.8 to 1.8). The association was not evident among former smokers, and maternal age did not affect the findings. There was no association with loss of a fetus with trisomic chromosomal aberration.

In summary, the available data have been somewhat mixed but have suggested a modest association between cigarette smoking and spontaneous abortion (Hughes and Brennan 1996). The mechanisms underlying the putative association are not known, but they likely involve factors that interfere with normal implantation of a fertilized ovum (Gindoff and Tidey 1989), as discussed previously with regard to ectopic pregnancy (see "Maternal Conditions" earlier in this section). Also, several constituents of cigarette smoke (e.g., nicotine and carbon monoxide [CO]) are toxic for the developing fetus (Lambers and Clark 1996).

Hypertensive Disorders of Pregnancy

Pregnancy-induced hypertensive disorders range from isolated hypertension during pregnancy (gestational hypertension) to preeclampsia (hypertension with proteinuria and edema) and eclampsia

Table 3.36. Relative risks for placental disorders among women smokers

Study	Study type	Population	Study period	Adjustment factors
Voigt et al. 1990	Case-control (population-based)	1,089 women with singleton births with abruption 2,323 women with singleton births without abruption United States	1984–1986	Maternal age, race, marital status, gravidity, income of census tract
Eriksen et al. 1991	Case-control	87 women with singleton births with abruption 5,697 women with singleton births without abruption Denmark	1980–1985	Maternal age, social class, standing at work, congenital malformation, amniocentesis, small-for-gestational-age infant, preeclampsia, hemorrhage
Kramer et al. 1991	Case-control (population-based)	598 women with singleton births with placenta previa 2,422 women with singleton births without placenta previa United States	1984–1987	Maternal age
Williams et al. 1991a,b	Case-control	143 women with singleton births with abruption 1,257 women with singleton births without abruption	1977–1980	Placental abruption: diabetes, late prenatal registration, alcohol intake, cervical incompetence, marijuana use, previous spontaneous or induced abortion, stillbirth, prepregnancy body mass index <18; no adjustment for detailed abruption data
		69 women with singleton births with placenta previa 12,351 women with singleton births without placenta previa United States		Placenta previa: maternal age, payment status, parity, previous spontaneous abortion, previous cesarean section (placenta previa only), previous in utero exposure to diethylstilbestrol (DES), coffee consumption, alcohol intake
Williams et al. 1991c	Case-control	943 women with singleton births with abruption 10,648 women with singleton births without abruption United States	1987–1988	Previous stillbirth, chronic hypertension, maternal age, cervical incompetence, payment status, diabetes, multiparity, education, marital status
Zhang and Fried 1992	Case-control (population-based)	766 women with births with placenta previa 178,953 women with births without placenta previa Both groups without pregnancy-induced hypertension United States	1988–1989	Maternal age, race, gravidity, parity, previous pregnancy termination, previous cesarean section, gestational age

Abruptio placentae		Placenta previa	
Smoking status	**Relative risk (95% confidence interval)**	**Smoking status**	**Relative risk (95% confidence interval)**
Nonsmokers	1.0		
Smokers	1.6 (1.3–1.8)		
Nonsmokers	1.0		
Smokers	2.5 (1.2–5.1)		
		Nonsmokers	1.0
		Smokers	2.1 (1.7–2.5)
Nonsmokers	1.0	Nonsmokers	1.0
Smokers	1.5 (1.0–2.2)	Smokers	2.6 (1.3–5.5)
		1–9 cigarettes / day	3.1 (1.4–6.6)
		≥ 10 cigarettes / day	2.2 (0.9–5.1)
		Never smoked	1.0
		Stopped smoking before conception	1.3 (0.5–3.3)
		Stopped smoking during first trimester	1.9 (0.6–6.7)
		Smoked throughout pregnancy	3.1 (1.2–8.1)
Nonsmokers	1.0		
Smokers	1.7 (1.5–2.0)		
		Nonsmokers	1.0
		Smokers	1.3 (1.1–1.6)
		1–9 cigarettes / day	1.1 (0.8–1.6)
		10–19 cigarettes / day	1.3 (1.0–1.8)
		≥ 20 cigarettes / day	1.4 (1.0–1.9)

Table 3.36. Continued

Study	Study type	Population	Study period	Adjustment factors
Raymond and Mills 1993	Cohort	30,681 women with singleton births 307 women with births with abruption United States	1974–1977	Maternal age, education, parity
Handler et al. 1994	Case-control	304 women with singleton births with placenta previa 2,732 women with singleton births without placenta previa United States	1988–1990	Maternal age, parity, previous cesarean section, previous spontaneous abortion, previous induced abortion
Spinillo et al. 1994a	Case-control	55 women with births with abruption (24–36 weeks' gestation) 726 women with births without abruption (24–36 weeks' gestation) Italy	1985–1991	Maternal age, gestational age, number of clinic visits, abdominal trauma, intravenous drug abuse, hypertension, preeclampsia, diabetes
Monica and Lilja 1995	Case-control	2,345 women with births with placenta previa 825,856 women with births without placenta previa Sweden	1983–1990	Maternal age, year of birth, parity
Ananth et al. 1996	Cohort	87,184 singleton births in 61,667 women 808 women with births with abruption 290 women with births with placenta previa Canada	1986–1993	Hospital type, year of delivery, marital status, maternal age, parity, hypertension, preeclampsia
Chelmow et al. 1996	Case-control	32 women with births with placenta previa at >24 weeks' gestation 96 women with births without placenta previa at >24 weeks' gestation United States	1992–1994	Referral source, maternal age
Cnattingius et al. 1997	Cohort	317,652 women ≤ 34 years old with singleton pregnancies, previously nulliparous	1987–1993	Maternal age, education, country of birth, cohabitating with infant's father
McMahon et al. 1997	Case-control (population-based)	342 women with singleton births with placenta previa 1,082 women with singleton births without placenta previa United States	1990	Maternal age, race, previous spontaneous or induced abortion

Abruptio placentae		Placenta previa	
Smoking status	**Relative risk (95% confidence interval)**	**Smoking status**	**Relative risk (95% confidence interval)**
Nonsmokers	1.0		
Smokers	1.4* (1.1–1.8)		
		Nonsmokers	1.0
		Smokers	1.7 (1.3–2.2)
		1–9 cigarettes / day	0.8 (0.5–1.6)
		10–19 cigarettes / day	1.2 (0.7–5.4)
		20–29 cigarettes / day	2.3 (1.4–3.7)
		30–39 cigarettes / day	1.9 (0.6–6.1)
		40–49 cigarettes / day	3.1 (0.9–10.8)
Nonsmokers	1.0		
Smokers	2.4 (1.3–4.3)		
Stopped smoking during pregnancy	3.6 (1.3–10.1)		
<10 cigarettes / day	2.3 (1.0–4.8)		
≥ 10 cigarettes / day	2.4 (1.1–5.3)		
		Nonsmokers	1.0
		Smokers	1.5 (1.4–1.7)
		<10 cigarettes / day	1.4 (1.3–1.6)
		≥ 10 cigarettes / day	1.7 (1.5–1.9)
Nonsmokers	1.0	Nonsmokers	1.0
Smokers	2.1 (1.8–2.4)	Smokers	1.4 (1.0–1.8)
1–5 cigarettes / day	1.8 (1.3–2.5)	1–5 cigarettes / day	1.5 (0.8–2.7)
6–10 cigarettes / day	1.9 (1.5–2.5)	6–10 cigarettes / day	1.3 (0.8–2.1)
11–15 cigarettes / day	2.2 (1.8–2.8)	11–15 cigarettes / day	1.3 (0.8–2.0)
16–20 cigarettes / day	2.1 (1.5–2.9)	16–20 cigarettes / day	1.8 (1.1–3.1)
≥ 21 cigarettes / day	2.2 (1.8–2.7)	≥ 21 cigarettes / day	1.3 (0.8–2.0)
		Nonsmokers	1.0
		Smokers	4.4 (1.4–14.1)
Nonsmokers	1.0		
Smokers			
1–9 cigarettes / day	2.0 (1.9–2.1)		
≥ 10 cigarettes / day	2.4 (2.3–2.6)		
		Nonsmokers	1.0
		Smokers	
		1–10 cigarettes / day	1.3 (0.9–1.9)
		11–20 cigarettes / day	1.8 (1.2–2.8)
		>20 cigarettes / day	2.0 (0.8–4.8)

Table 3.37. Relative risks for spontaneous abortion among women smokers

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Kline et al. 1977	Case-control	574 cases with spontaneous abortion 320 controls delivering after ≥ 28 weeks' gestation United States	1974–1976	Nonsmokers Smokers	1.0 1.8 (1.3–2.5)	Age at last menses, history of abortion and live births
Ericson and Källén 1986	Case-control	219 cases with spontaneous abortion 1,032 controls with live-born infant without major malformation Sweden	1980–1981	Nonsmokers Smokers	1.0 1.0 (0.6–1.5)	Video screen use, stress
Sandahl 1989	Case-control	610 cases with spontaneous abortion 1,337 controls delivering infant Sweden	1980–1985	Nonsmokers Smokers Any smoking >10 cigarettes / day	1.0 0.9 (0.8–1.0) 0.9 (0.7–1.0)	Maternal age, parity
Armstrong et al. 1992	Cohort	47,146 pregnant women 10,191 women with spontaneous abortion Canada	1982–1984	Nonsmokers Smokers 1–9 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.1 (1.0–1.2) 1.2 (1.1–1.3) 1.7 (1.6–1.8)	Maternal age, education, ethnicity, employment during pregnancy
Windham et al. 1992	Case-control	626 cases with spontaneous abortion at ≤ 20 weeks' gestation 1,300 controls delivering live infant United States	1986–1987	Nonsmokers Smokers 1–10 cigarettes / day >10 cigarettes / day	1.0 0.9 (0.7–1.2) 1.1 (0.8–1.6)	Maternal age, previous fetal loss, marital status, insurance, alcohol intake, intake of bottled water

(hypertension with proteinuria, edema, and seizures). Distinguishing between hypertensive disorders of pregnancy and chronic hypertension is difficult, and accepted classification systems for hypertensive disorders of pregnancy were not established until the late 1980s (Davey and MacGillivray 1988). Gestational hypertension is the most common hypertensive disorder of pregnancy. However, preeclampsia is associated with much greater risks for morbidity and mortality: it is a leading cause of maternal mortality (Berg et al. 1996) and a major contributor to fetal growth retardation and preterm birth (Heffner et al. 1993; Kleigman 1997). Risk factors for preeclampsia include chronic hypertension, multiple fetuses, nulliparity, previous preeclampsia or eclampsia, type 1 diabetes mellitus, previous adverse pregnancy outcomes, high prepregnancy weight and high pregnancy weight gain, working during pregnancy, and black race (Eskenazi et al. 1991).

Smoking has repeatedly been found to be inversely related to the risk for preeclampsia (Marcoux et al. 1989; Eskenazi et al. 1991; Klonoff-Cohen et al.

Table 3.37. Continued

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Dominguez-Rojas et al. 1994	Cohort	711 women with ≥ 1 pregnancy 169 women with spontaneous abortion Spain	1989–1991	Nonsmokers Smokers 1–10 cigarettes / day ≥ 11 cigarettes / day	1.0 1.0 (0.6–1.5) 3.4 (1.7–6.9)	Maternal age, age at menarche, previous spontaneous abortion, marital status
Chatenoud et al. 1998	Case-control	782 cases with spontaneous abortion at ≤ 12 weeks' gestation admitted to hospital 1,543 controls delivering healthy term infants Italy	1990–1997	Never smoked Former smokers Smokers before pregnancy Smokers before and during pregnancy	1.0 0.9 (0.7–1.2) 0.7 (0.5–1.0) 1.3 (1.0–1.6)	Maternal age, education, marital status, history of spontaneous abortion or miscarriage, nausea, alcohol or coffee intake in first trimester
Ness et al. 1999	Case-control	570 cases with spontaneous abortion presenting in hospital emergency department United States	1995–1997	Never smoked Former smokers Current smokers	1.0 0.9 (0.6–1.3) 1.4 (1.0–1.9)	None
Windham et al. 1999b	Cohort	5,342 pregnant women 499 women with spontaneous abortion United States	1990–1991	Nonsmokers Smokers 1–4 cigarettes / day >5 cigarettes / day	1.0 0.9 (0.6–1.5) 1.3 (0.9–1.9)	Maternal age, prior fetal loss, alcohol intake, caffeine intake, gestational age at interview

1993; Spinillo et al. 1994b; Sibai et al. 1995; Mittendorf et al. 1996; Ros et al. 1998; Castles et al. 1999). This finding has persisted even in studies with rigorous diagnostic criteria, adequate adjustment for covariates, and careful assessment of smoking history (Marcoux et al. 1989; Klonoff-Cohen et al. 1993; Sibai et al. 1995; Mittendorf et al. 1996). In one study, the risk for preeclampsia decreased with increasing amount smoked (Marcoux et al. 1989), although in three other studies, no dose-response relationship was observed (Klonoff-Cohen et al. 1993; Spinillo et al. 1994b; Cnattingius et al. 1997; Ros et al. 1998). One investigation reported that the protective effect tended to be confined to women who continued smoking after 20 weeks' gestation (Marcoux et al. 1989); another study reported that the lowest risk for preeclampsia was among women who had stopped smoking at the start of pregnancy (Sibai et al. 1995).

Data on the relationship between cigarette smoking and gestational hypertension or eclampsia have been limited. In one large study, smoking was associated with a moderate reduction in risk for hypertensive disorders of pregnancy as a whole (RR, 0.7; 95 percent CI, 0.6 to 0.8) (Savitz and Zhang 1992). In another investigation, cigarette smoking conferred a modest reduction in risk for gestational hypertension (RR, 0.8; 95 percent CI, 0.5 to 1.1) and a more pronounced inverse association with preeclampsia (RR, 0.5; 95 percent CI, 0.3 to 0.8) (Marcoux et al. 1989). Other studies have also found that smoking during pregnancy was associated with a reduction in the risk for gestational hypertension (Misra and Kiely 1995;

Wong and Bauman 1997). A large, well-conducted study in Sweden found similar inverse associations between smoking and gestational hypertension, preeclampsia, and eclampsia (Cnattingius et al. 1997; Ros et al. 1998). In contrast, smoking was unrelated to eclampsia in one report (Abi-Said et al. 1995).

Thus, epidemiologic evidence has indicated that smoking is inversely related to hypertensive disorders of pregnancy. Little is known, however, about how smoking might exert such an effect (Ros et al. 1998). Despite this apparently beneficial association, other adverse effects make the net impact of smoking strongly detrimental for pregnant women. In a study of 317,652 births, smoking was associated with particularly increased risks in perinatal mortality, abruption, and infants who are small for gestational age (SGA) among women with severe preeclampsia (Cnattingius et al. 1997).

Birth Outcomes

Previous reports of the Surgeon General have provided comprehensive reviews of the association between maternal smoking and fetal, neonatal, and perinatal mortality and morbidity (USDHHS 1980, 1989b). This section describes recent work highlighting the relationship between smoking and those outcomes as well as low birth weight (LBW), SGA (due to intrauterine growth retardation [IUGR]), preterm delivery, birth defects, and SIDS.

Preterm Delivery

Preterm delivery (birth at <37 weeks' gestation) is strongly associated with increased risks for fetal, neonatal, and perinatal mortality. Preterm delivery may spontaneously follow PROM or may occur because of maternal bleeding, preeclampsia, multiple gestation, uterine anomalies, or urinary tract infection (Heffner et al. 1993). The 1979 Surgeon General's report on smoking and health concluded that smoking during pregnancy increases the risk for preterm delivery and that this risk increases with the quantity of cigarettes smoked (USDHEW 1979). The report estimated that 11 to 14 percent of preterm births are attributable to smoking during pregnancy.

Epidemiologic studies have continued to provide evidence for the association between smoking and preterm delivery (Table 3.38). The RRs among smokers compared with nonsmokers have ranged from 1.2 to more than 2.0 after multivariate adjustment (Shiono et al. 1986b; CDC 1990; Ferraz et al. 1990; Wen et al. 1990b; McDonald et al. 1992; Heffner et al. 1993; Olsén et al. 1995). One study showed that smokers had a higher risk for delivery before 32 weeks' gestation than did nonsmokers (RR, 1.9; 95 percent CI, 1.3 to 2.9) but no higher risk for delivery at 32 through 36 weeks' gestation (RR, 0.8; 95 percent CI, 0.6 to 1.2) (Peacock et al. 1995). Shiono and colleagues (1986b) also reported a stronger association between smoking and preterm delivery before 33 weeks' gestation than between smoking and later preterm delivery. A few studies have failed to find any association between smoking and preterm delivery after adjustment for factors such as race (Zhang and Bracken 1995) and other psychosocial indicators (Nordentoft et al. 1996).

Smoking may be associated with premature delivery only in certain circumstances. One investigation found that the RR for smoking was particularly high among women with no other risk factors for premature delivery (Heffner et al. 1993). Two other studies demonstrated a clear involvement of smoking among women whose spontaneous preterm delivery was primarily due to PPROM (see "Preterm Premature Rupture of Membranes" earlier in this section) (Shiono et al. 1986b; Meis et al. 1995).

The association between smoking and preterm birth may differ according to maternal characteristics. For example, the effect of smoking on the risk for premature birth may be more pronounced among older women than among those younger than 20 years old (Cornelius et al. 1995; Olsén et al. 1995). Three studies found that the RR for preterm delivery among smokers compared with nonsmokers increased with maternal age; the association was particularly strong among women older than age 35 years (Wen et al. 1990a; Cnattingius et al. 1993; Olsén et al. 1995). Wen and associates (1990a) reported a mean difference of one-half week in gestational age between infants of smoking and nonsmoking women 35 years old or younger. The mean difference for infants of smokers and nonsmokers older than 35 years was one week. Wisborg and colleagues (1996) did not confirm this pattern of increasing smoking-related risks with increasing maternal age. In one study, the age-related trend in RRs became less significant after an interaction of smoking with parity was included (Cnattingius et al. 1993).

Although most studies have demonstrated an association between maternal smoking and premature delivery, a pattern of increasing risk with increasing amount smoked has not consistently been found. Some studies have demonstrated a clear dose-response relationship between smoking and premature delivery in at least some subpopulations, such as women who

consume high amounts of caffeine (Wisborg et al. 1996) or mothers of infants with placental abnormalities (Shiono et al. 1986b). However, other investigations failed to find a clear dose-response relationship after adjustment for potential confounding factors (McDonald et al. 1992; Cnattingius et al. 1993; Peacock et al. 1995).

Smoking cessation during pregnancy seems to reduce the risk for preterm delivery. In a randomized trial of the effect of smoking cessation on birth weight and gestational age, infants of women who had stopped smoking had a longer gestation than did infants of women who smoked throughout pregnancy (Li et al. 1993). (Smoking cessation was validated by determining salivary cotinine concentrations.) After adjustment for maternal age, race, height, and weight at entry into prenatal care, the mean gestational age was 39.2 weeks among infants delivered to women who had stopped smoking but 38.3 weeks among infants of women who continued to smoke ($p = 0.07$). The risk for preterm delivery among women who had stopped smoking during pregnancy was similar to that among women who had never smoked: the RR was 0.9 (95 percent CI, 0.4 to 2.2). However, simply reducing the amount smoked seemed to have no beneficial effect. According to NHIS data, women who discontinued smoking during the first trimester of pregnancy reduced the risk for preterm delivery to that of nonsmoking women (Mainous and Hueston 1994b). Compared with nonsmokers, women who had stopped smoking during the first trimester had a RR of 0.9 (95 percent CI, 0.6 to 1.5), and women who smoked after the first trimester had a RR of 1.6 (95 percent CI, 1.2 to 2.1).

The association between smoking and preterm delivery is biologically plausible, because nicotine-induced vasoconstriction in the placenta could initiate delivery (Lindblad et al. 1988; Bruner and Forouzan 1991; Wisborg et al. 1996). Furthermore, smoking may cause higher levels of circulating catecholamines that could precipitate premature labor (USDHHS 1980).

Stillbirth

Stillbirth (fetal death after 28 weeks' gestation) is a fairly rare occurrence in developed nations. In the United States, rates of stillbirth are estimated at 3.3 per 1,000 births among white women and 5.5 per 1,000 births among black women (Guyer et al. 1996). A number of risk factors have been identified. Advanced maternal age, nulliparity, previous fetal loss, race, multiple births, and higher maternal BMI all confer increased risks (Kiely et al. 1986; Cnattingius et al. 1988; Ferraz and Gray 1991; Cnattingius et al. 1992; Little and Weinberg 1993; Raymond et al. 1994).

In the past 15 years, cigarette smoking has been repeatedly associated with an increased risk for stillbirth. In early studies, investigators (Lowe 1959; Underwood et al. 1967) examined the effect of cigarette smoking but did not always find a positive relationship. This lack of association may have occurred because these studies were often statistically underpowered or did not control for known risk factors (DiFranza et al. 1995).

More recent studies have found an increased risk for stillbirth among women who smoked during pregnancy (Table 3.39). In one study of 281,808 pregnancies in Sweden, the RR for stillbirth among smokers compared with nonsmokers was 1.4 (95 percent CI, 1.2 to 1.6), after adjustment for maternal age, parity, and type of birth (single vs. multiple) (Cnattingius et al. 1988). Another investigation found that the effect of smoking on stillbirth decreased as gestational age increased but never reached the lower level of stillbirth among nonsmoking women (Raymond et al. 1994). The RRs among women who smoked were 1.6 (95 percent CI, 1.3 to 2.0) at 28 to 31 weeks' gestation and 1.1 (95 percent CI, 0.7 to 1.8) at 42 to 45 weeks' gestation.

A moderate increase in risk for stillbirth has been found with increasing cigarette consumption (Ahlborg and Bodin 1991; Cnattingius et al. 1992; Little and Weinberg 1993; Raymond et al. 1994; Cnattingius and Nordstrom 1996). One large study found that the rate of stillbirth among nonsmokers was 3.5 deaths per 1,000 births (Cnattingius et al. 1992). The rate was 4.4 deaths per 1,000 births among those who smoked 1 to 9 cigarettes per day and 4.9 deaths per 100,000 births among those who smoked more than 9 cigarettes per day. Similarly, another study reported that the RR for stillbirth among women who smoked 1 to 9 cigarettes per day compared with nonsmokers was 1.2 (95 percent CI, 1.02 to 1.4); the RR increased to 1.6 (95 percent CI, 1.4 to 1.8) among women who smoked 10 or more cigarettes per day (Raymond et al. 1994).

Recently, some studies have investigated ways to reduce the risk for stillbirth among women smokers. For example, in one report, the use of multivitamin and mineral supplements significantly reduced the rate of stillbirth among women who smoked (Wu et al. 1998). Schramm (1997) compared smoking patterns in successive pregnancies. Smoking during both the first and second pregnancies was associated with a significant RR for fetal death; however, women who

Table 3.38. Relative risks for preterm delivery among women smokers

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Shiono et al. 1986b	Cohort	30,596 women with preterm births at <37 weeks' gestation United States	1974–1977	Delivery at <37 weeks' gestation Nonsmokers Smokers <1 pack / day ≥ 1 pack / day Delivery at <33 weeks' gestation Nonsmokers Smokers <1 pack / day ≥ 1 pack / day	 1.0 1.1 (0.9–1.2) 1.2 (1.1–1.4) 1.0 1.1 (0.8–1.5) 1.6 (1.2–2.3)	Maternal age, education, ethnicity, marital status, employment, gravidity, induced or spontaneous abortion, gender of infant, time prenatal care began, major malformation of infant, preeclampsia, alcohol use
Centers for Disease Control 1990	Survey of pregnancy history	74,139 women with singleton pregnancies United States	1989	Nonsmokers Smokers	1.0 1.3*	Maternal age, race, prepregnancy weight, weight gain, alcohol use, infant's birth order, education, month prenatal care began, previous termination of pregnancy
Ferraz et al. 1990	Case-control	429 women with preterm births 2,555 controls Brazil	1984–1986	Nonsmokers Smokers	1.0 1.5 (1.2–2.0)	Adjustment factors in final model not stated
Wen et al. 1990b	Cohort	15,539 women with singleton preterm births at <37 weeks' gestation United States	1983–1988	Nonsmokers Smokers Aged ≤ 16 years Aged 17–19 years Aged 20–25 years Aged 26–30 years Aged 31–35 years Aged ≥ 36 years	1.0 1.2 (0.7–2.2) 1.2 (0.9–1.6) 1.1 (0.9–1.3) 1.4 (1.1–1.8) 1.6 (1.0–2.4) 2.0 (0.7–6.3)	Maternal race, marital status, prepregnancy weight, weight gain, parity, alcohol use
McDonald et al. 1992	Survey	40,445 women with singleton births (7.0% delivered at <37 weeks' gestation) Canada	1982–1984	Nonsmokers Smokers <10 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day	1.0 1.2 (1.1–1.4) 1.4 (1.3–1.6) 1.3 (1.2–1.5)	Maternal age, education, pregnancy order, previous spontaneous abortion, previous low-birth-weight infant, prepregnancy weight, ethnic group (white, French, or English), employment at start of pregnancy

*95% confidence interval was not reported.

Table 3.38. Continued

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Cnattingius et al. 1993	Cohort	538,829 women with singleton births 29,937 births at ≤ 36 weeks' gestation Sweden	1983–1988	Nonsmokers Multiparas Aged 20–24 years Aged 25–29 years Aged 30–34 years Aged ≥ 35 years Nulliparas Aged 20–24 years Aged 25–29 years Aged 30–34 years Aged ≥ 35 years Smokers Multiparas Aged 20–24 years Aged 25–29 years Aged 30–34 years Aged ≥ 35 years Nulliparas Aged 20–24 years Aged 25–29 years Aged 30–34 years Aged ≥ 35 years	 1.0 0.9 (0.8–0.9) 1.0 (0.9–1.0) 1.4 (1.3–1.5) 1.5 (1.4–1.6) 1.5 (1.4–1.5) 1.6 (1.5–1.7) 2.1 (1.9–2.2) 1.6 (1.6–1.7) 1.4 (1.3–1.5) 1.6 (1.5–1.7) 2.3 (2.1–2.4) 1.7 (1.6–1.8) 1.6 (1.5–1.7) 1.8 (1.6–1.9) 2.3 (2.1–2.5)	Maternal age, parity
Heffner et al. 1993	Case-control	Women aged 25–35 years 266 cases with birth at 20–26 weeks' gestation 512 controls with term birth United States	1988–1990	Nonsmokers Smokers	1.0 2.0 (1.3–3.2)	Maternal age, race, gravidity, parity, income, third trimester bleeding, placental abruption, multiple gestation, previous preterm delivery, first or second trimester vaginal bleeding, chorioamnionitis, diethylstilbestrol exposure, uterine anomaly
Li et al. 1993	Clinical trial	1,277 women with singleton live births and prenatal care at ≤ 32 weeks' gestation[†] United States	1986–1991	Never smoked Stopped smoking Reduced smoking Did not change smoking habits	1.0 1.0 (0.4–2.2) 1.6 (0.9–2.8) 1.3 (0.8–2.0)	Maternal weight, race

[†]Preterm birth defined as <37 weeks' gestation.

Table 3.38. Continued

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Mainous and Hueston 1994b	Case-control analysis of survey of pregnancy history	305 women with deliveries at ≤ 36 weeks' gestation 4,766 women with term births United States	1988	Nonsmokers Smoked after first trimester Stopped smoking in first trimester	1.0 1.6 (1.2–2.1) 1.0 (0.6–1.5)	Maternal age, race, parity, family income
Meis et al. 1995	Case-control analysis of survey of pregnancy history	26,205 women with singleton births of infant >500 g 1,134 women with births at <257 days' gestation Wales	1970–1979	Induced preterm delivery Nonsmokers Smokers 1–9 cigarettes / day ≥ 10 cigarettes / day Spontaneous preterm delivery (including PPROM‡) Nonsmokers Smokers 1–9 cigarettes / day ≥ 10 cigarettes / day	 1.0 1.0 (0.8–1.4) 1.2 (1.0–1.5) 1.0 1.1 (0.9–1.4) 1.3 (1.1–1.6)	Maternal age, height, weight, parity, social class, employment during pregnancy, previous stillbirth or abortion, maternal hemoglobin at first visit, bacteriuria, bleeding early in pregnancy
Olsén et al. 1995	Cohort	20,363 women with singleton births 1,474 women with births at <37 weeks' gestation Finland	1966, 1985–1986	Nonsmokers Smokers	1.0 1.3 (1.1–1.5)	Maternal age, height, body mass index, rural vs. urban residence, education level, employment status, socioeconomic state, desire for pregnancy, gravidity, previous spontaneous abortion

‡PPROM = Preterm premature rupture of membranes.

smoked during the first pregnancy but not the second had lower rates of fetal death. These results suggested that smoking cessation may reduce the risk for stillbirth.

Although the causes of stillbirth are not completely understood, much of the increased risk is believed to be caused by IUGR, placental complications, or both (Raymond et al. 1994; Cnattingius and Nordstrom 1996; Wong and Bauman 1997). Another etiologic possibility is that nicotine induces a change in central respiratory control mechanism that may elicit fetal hypoxia-ischemia and lead to stillbirth (Slotkin 1998).

Neonatal Mortality

Neonatal death (within 28 days of birth) occurs in about 4.8 of 1,000 live births in the United States (Guyer et al. 1996). The rate of neonatal death has dropped steadily since the early 1970s. However, significant racial differences in neonatal mortality continue to exist between black women and white women: 9.6 deaths per 1,000 live births among black women and 4.0 deaths per 1,000 live births among white women (Guyer et al. 1996). Racial differences in neonatal mortality likely reflect the higher percentage of LBW babies born to black women. Other risk factors for neonatal mortality include advanced maternal

Table 3.38. Continued

Study	Study type	Population	Study period	Smoking status	Relative risk (95% confidence interval)	Adjustment factors
Peacock et al. 1995	Cohort	1,513 white women 113 women with births at <37 weeks' gestation United Kingdom	1982–1984	Delivery at <32 weeks' gestation Nonsmokers Smokers Delivery at 32–36 weeks' gestation Nonsmokers Smokers	 1.0 2.0 (1.3–2.9) 1.0 0.8 (0.6–1.2)	None
Zhang and Bracken 1995	Cohort	3,861 women with singleton live births 205 women with births at <37 weeks' gestation United States	1980–1982	Nonsmokers Smokers (>2 cigarettes / day)	1.0 1.4[§] (1.0–1.9)	None
Nordentoft et al. 1996	Cohort	2,432 women with singleton pregnancies 212 women with deliveries at <37 weeks' gestation Denmark	1990–1992	Nonsmokers Smokers 1–9 cigarettes / day 10–15 cigarettes / day >15 cigarettes / day	1.0 1.1 (0.7–1.7) 1.1 (0.7–1.9) 0.5 (0.2–1.4)	Maternal age, education, cohabitation
Wisborg et al. 1996	Cohort	4,111 nulliparous women with singleton births 178 women with deliveries at <37 weeks' gestation Denmark	1989–1991	Nonsmokers Smokers 1–5 cigarettes / day 6–10 cigarettes / day ≥ 11 cigaretes / day	1.0 1.4 (1.2–1.9) 1.0 (0.6–1.7) 1.5 (1.2–1.9) 1.8 (1.1–3.0)	Maternal age, education, marital status, weight, height, occupational status, alcohol abuse

[§]Tree-based factor analysis. Relative risk was not significant after stratification by race.

age, previous fetal loss, nulliparity, multiple births, greater body mass, and high or low maternal education (Kiely et al. 1986; Cnattingius et al. 1988, 1992; Malloy et al. 1988; Haglund et al. 1993).

In the past decade, the detrimental effects of smoking on neonatal mortality have been well documented (Cnattingius et al. 1988, 1992; Malloy et al. 1988; Walsh 1994; Schramm 1997) (Table 3.39). In an investigation of 305,730 singleton white live births, the multivariate RR for neonatal deaths among smokers compared with nonsmokers was 1.2 (95 percent CI, 1.1 to 1.3) (Malloy et al. 1988). Another study (Cnattingius et al. 1988) reported a RR of 1.2 (95 percent CI, 1.0 to 1.4). Unlike the association of smoking with stillbirth, the dose-dependent effect of smoking on neonatal mortality is not clear (Cnattingius et al. 1992).

Smoking cessation appears to reduce the excess risk for adverse neonatal events. One investigation that compared the RR for neonatal deaths in first and second pregnancies found a significantly higher risk among women who smoked more in the second

Table 3.39. Relative risks for stillbirth or neonatal death among women smokers, cohort studies

Study	Country	Number of pregnancies	Relative risk (95% confidence interval)			
			Stillbirth		Neonatal death	
Cnattingius et al. 1988	Sweden	281,808	Nonsmokers Smokers	1.0 1.4 (1.2–1.6)	Nonsmokers Smokers	1.0 1.2 (1.0–1.4)
Malloy et al. 1988	United States	305,730			Nonsmokers Smokers	1.0 1.2 (1.1–1.3)
Raymond et al. 1994	Sweden	638,242	Nonsmokers Smokers	1.0 1.4 (1.2–1.5)		
Schramm 1997	United States	176,843	Nonsmokers Smokers	1.0 1.2*	Nonsmokers Smokers	1.0 1.4*

*$p < 0.05$.

pregnancy than in the first (Schramm 1997). The study also found a nonsignificant decrease in RR among women who smoked in the first pregnancy but not the second. Another study found that cessation of smoking reduced neonatal morbidity (Ahlsten et al. 1993). Specifically, the authors found that admission for hospital care occurred in 11.4 percent of infants born to mothers who smoked and 8.8 percent of infants born to mothers who did not smoke ($p < 0.05$). The mean birth weight and perinatal morbidity rates among infants of mothers who had stopped smoking during the pregnancy were almost identical to those among infants of nonsmokers.

Perinatal Mortality

Although smoking may have different effects on the risks for stillbirth and neonatal mortality, in many studies the combined end point of perinatal mortality was presented. A meta-analysis of 25 studies of the effects of smoking on perinatal mortality revealed pooled RRs of 1.3 (95 percent CI, 1.2 to 1.3) in cohort studies and 1.2 (95 percent CI, 1.1 to 1.4) in case-control studies (DiFranza and Lew 1995). The authors estimated that 3.4 to 8.4 percent of perinatal deaths could be attributed to maternal smoking during pregnancy. Similarly, others have estimated that elimination of maternal smoking might lead to a 10-percent reduction in all infant deaths and a 12-percent reduction in death from perinatal conditions (Malloy et al. 1988). Not surprisingly, similar results of the effects of maternal smoking have been reported for the combined measure of perinatal mortality (Sachs 1989; Wilcox 1993).

Birth Weight

Because LBW is associated with increased risks for neonatal, perinatal, and infant morbidity and mortality, birth weight has been studied extensively and used as a basic indicator of fetal health. The definition of LBW has varied among studies, but weight less than 2,500 g is a commonly accepted criterion for LBW at term. An SGA infant is one whose weight falls below a defined criterion for gestational age, such as two standard deviations or more below the population mean, or less than the 3rd or 10th percentile of weight (USDHHS 1988; Fanaroff and Martin 1992).

For more than 40 years, it has been known that babies born to mothers who smoke weigh less than babies born to mothers who do not smoke (USDHHS 1980). The effect of smoking is independent of other factors influencing birth weight, including gestational age and gender of the baby and maternal characteristics (e.g., age, parity, race, prepregnancy weight or body mass, socioeconomic status, and prenatal care). More than a dozen studies in the past decade have confirmed that the average difference in birth weight between infants born to smokers and those born to nonsmokers is about 250 g and that the difference increases with the amount smoked (Table 3.40). In a study of 257,698 births, infants of women who smoked were an average of 320 g lighter than infants born to women who did not smoke (Wilcox 1993).

Estimates of adjusted RRs for LBW associated with smoking during pregnancy have ranged from about 1.5 to 3.5, and those for SGA have ranged from about 1.5 to more than 10.0, depending on the amount smoked and other modifying factors (Table 3.41).

Table 3.40. Difference in birth weight between infants born to women nonsmokers and those born to women smokers

Study	Study type	Population	Study period	Number of births	Smoking status	Difference in mean birth weight (g)
Mathai et al. 1990	Cohort	United Kingdom	1987	285	Nonsmokers / smokers	-66
Ahlsten et al. 1993	Cohort	Sweden	1987	3,476	Nonsmokers / smokers	-211
Aronson et al. 1993	Cohort	United States	1991	1,282	Nonsmokers / smokers	-258
Backe 1993	Cohort	Norway	1988–1989	1,827	Nonsmokers / smokers 1–5 cigarettes / day 6–10 cigarettes / day 11–15 cigarettes / day 16–20 cigarettes / day >20 cigarettes / day	-182 -120 -201 -278 -347 +70
Castro et al. 1993	Cohort	United States	1986–1990	7,741	Nonsmokers / smokers	-150
Li et al. 1993	Intervention	United States	1986–1991	803	Smokers* 101–200 ng / mL >200 ng / mL	Blacks / Whites -150 / -103 -76 / -63
Wilcox 1993	Cohort	United States	1980–1984	257,698	Nonsmokers / smokers	-320
English et al. 1994	Cohort	United States	1959–1966	3,343	Nonsmokers / smokers <10 cigarettes / day 10–20 cigarettes / day >20 cigarettes / day	Blacks / Whites -211 / -131 -215 / -151 -277 / -207
Muscati et al. 1994	Cohort	Canada	1979–1989	1,330	Nonsmokers / smokers	-305
Cliver et al. 1995	Cohort	United States	1985–1988	1,205	Nonsmokers / smokers	-130
Conter et al. 1995	Cross-sectional	Italy	1973–1981	12,987	Nonsmokers / smokers 1–9 cigarettes / day ≥ 10 cigarettes / day	Girls / Boys -88 / -107 -168 / -247
Eskenazi et al. 1995b	Cohort	United States	1964–1967	3,529	Nonsmokers / smokers† 0–78 ng / mL 79–165 ng / mL >165 ng / mL	 -78 -191 -233
Murphy et al. 1996	Cohort	Alaska Natives	1989–1991	8,994	Nonsmokers / smokers 1–5 cigarettes / day 6–10 cigarettes / day >10 cigarettes / day	 -142 -239 -311
Zaren et al. 1996	Cohort	Norway and Sweden	1986–1988	933	Nonsmokers / smokers 1–9 cigarettes / day ≥ 10 cigarettes / day	-231 -178 -263

*Smokers with serum levels of cotinine <100 ng / mL after 32 weeks' gestation were compared with smokers who had higher levels.

†Smokers in each category of serum cotinine level were compared with nonsmokers.

Table 3.41. Relative risks for infants with low birth weight (LBW) or small for gestational age (SGA) among women smokers

Study	Study type	Population	Study period	Number of births	Smoking status
Tenovuo et al. 1988	Case-control	Finland	1985	236	Nonsmokers Smokers 1–9 cigarettes / day ≥ 10 cigarettes / day
Cnattingius 1989	Cohort	Sweden	1983–1985	280,809	Nonsmokers Smokers 1–9 cigarettes / day ≥ 10 cigarettes / day
Alameda County Low Birth Weight Study Group 1990	Case-control	United States	1987	1,149	Nonsmokers Smokers
Centers for Disease Control 1990	Survey	United States	1989	74,139	Nonsmokers Smokers <10 cigarettes / day 10–20 cigarettes / day >20 cigarettes / day
Ferraz et al. 1990	Case-control	Brazil	1984–1986	3,406	Nonsmokers Smokers
Wen et al. 1990b	Cohort	United States	1983–1988	17,149	Nonsmokers Smokers Aged ≤ 16 years Aged 17–19 years Aged 20–25 years Aged 26–30 years Aged 31–35 years Aged ≥ 36 years
McDonald et al. 1992	Survey	Canada	1982–1984	40,445	Nonsmokers Smokers <10 cigarettes / day 10–19 cigarettes / day ≥ 20 cigarettes / day
Backe 1993	Cohort	Norway	1988–1989	1,827	Nonsmokers Smokers Aged <25 years Aged 25–34 years Aged ≥ 35 years

*LBW defined as birth weight <2,500 g or ≤ 2,500 g.
†95% confidence interval was not reported.
‡SGA defined as birth weight ≤ 2.5th percentile for gestational age.
§SGA defined as birth weight <5th percentile for gestational age.
ΔSGA defined as birth weight <10th percentile for gestational age.

Relative risk (95% confidence interval)			
LBW*	**SGA**		**Adjustment factors**
	1.0		Matching on gestational age and mode of delivery, adjustment for previous SGAinfant, low social class, low prepregnancy weight
	1.6[†‡]		
	3.4[†‡]		
	Single births	Multiple births	Maternal age, parity, relationship with father
	1.0	1.0	
	2.0 (1.9–2.1)[§]	1.5 (1.3–1.6)[§]	
	2.5 (2.4–2.6)[§]	1.8 (1.6–2.0)[§]	
Whites / Blacks			Maternal age, parity, low prepregnancy weight, low socioeconomic status, alcohol intake, prior LBW infant, prenatal care
1.0 / 1.0			
3.0 (1.7–5.3) / 3.6 (2.4–5.6)			
1.0[†]			Maternal education, maternal age, prepregnancy weight, weight gain, alcohol consumption, infant's birth order, month prenatal care began, previous pregnancy terminations
1.8[†]			
2.2[†]			
2.4[†]			
	1.0		Adjustment factors in final model not stated
	1.5 (1.1–2.0)[Δ]		
	1.0		Race, parity, marital status, weight, weight gain, alcohol use
	1.6 (0.7–3.4)[Δ]		
	2.0 (1.3–3.1)[Δ]		
	2.4 (1.9–3.2)[Δ]		
	2.4 (1.7–3.3)[Δ]		
	2.3 (1.3–4.0)[Δ]		
	5.1 (1.3–20.5)[Δ]		
1.0	1.0		Age, ethnic group, education, pregnancy order, previous spontaneous abortion or LBW infant, prepregnancy weight, employment, alcohol consumption, coffee consumption
1.6 (1.4–1.9)	2.0 (1.7–2.3)[§]		
2.4 (2.1–2.7)	2.6 (2.3–2.9)[§]		
2.9 (2.5–3.2)	3.2 (2.8–3.6)[§]		
	1.0		None
	1.3 (0.8–2.0)[Δ]		
	1.6 (1.1–2.3)[Δ]		
	3.8 (1.4–10.2)[Δ]		

Table 3.41. Continued

Study	Study type	Population	Study period	Number of births	Smoking status
Bakketeig et al. 1993	Cohort	Norway and Sweden	1986–1988	5,722	No other risk factors Nonsmokers Smokers Previous LBW infant Nonsmokers Smokers Maternal weight <50 kg Nonsmokers Smokers Previous LBW infant and maternal weight <50 kg Nonsmokers Smokers
Castro et al. 1993	Cohort	United States	1986–1990	7,741	Nonsmokers Smokers
Lieberman et al. 1994	Cohort	United States	1977–1980	11,177	Nonsmokers Smokers 1–5 cigarettes / day 6–10 cigarettes / day >10 cigarettes / day
Spinillo et al. 1994c	Case-control	Italy	1988–1993	1,041	Nonsmokers Smokers 1–10 cigarettes / day 11–20 cigarettes / day >20 cigarettes / day
Cornelius et al. 1995	Cohort	Black adolescents United States	1990–1993	310	Nonsmokers Smokers
Eskenazi et al. 1995b	Cohort	United States	1964–1967	3,529	Nonsmokers (0–1.9 ng / mL) Smokers[¶] 0–78 ng / mL 79–165 ng / mL >165 ng / mL
Zhang and Bracken 1995	Cohort	United States	1980–1982	3,861	Nonsmokers Smokers
Nordentoft et al. 1996	Cohort	Denmark	1990–1992	2,432	Nonsmokers Smokers 0–9 cigarettes / day 10–15 cigarettes / day >15 cigarettes / day
Cnattingius 1997	Cohort	Sweden	1983–1992	1,057,711	Nonsmokers Smokers 1–9 cigarettes / day ≥ 10 cigarettes / day

*LBW defined as birth weight <2,500 g or ≤ 2,500 g.
[Δ]SGA defined as birth weight <10th percentile for gestational age.
[¶]Smokers in each category of serum cotinine concentration were compared with nonsmokers.

Relative risk (95% confidence interval)			
LBW*	**SGA**		**Adjustment factors**
			Adjustment factors not stated
	1.0 1.8 (1.4–2.3)[Δ] 2.5 (1.7–3.8)[Δ] 6.9 (5.1–9.4)[Δ] 1.3 (0.6–2.6)[Δ] 4.7 (3.2–6.9)[Δ] 2.6 (0.6–10.4)[Δ] 8.8 (4.9–16.0)[Δ]		
	1.0 2.0 (1.5–2.7)[Δ]		Race and ethnicity, nulliparity, insurance status, marital status
	1.0 1.7 (1.3–2.1)[Δ] 2.2 (1.7–2.7)[Δ] 2.5 (2.1–3.0)[Δ]		Maternal age, education, race, marital status, body mass index, height, weight gain, late prenatal care, parity, exposure to diethylstilbestrol, hypertension, urinary tract infection, payment source
	1.0 2.9 (2.1–3.9)[Δ] 1.5 (0.99–2.3)[Δ] 4.1 (2.7–6.3)[Δ] 9.9 (4.0–24.4)[Δ]		Maternal age, marital status, nulliparity, low prepregnancy weight, body mass index <20 kg/m^2, weight gain <5 kg, previous LBW infant, female infant, first trimester hemorrhage, hypertension, hypertensive disorders of pregnancy, maternal education <6th grade, manual (nonskilled) social class, alcohol consumption, coffee consumption
1.0 3.1 (1.2–8.0)			Adjustment factors in final model not stated
1.0 1.2 (0.7–1.9) 1.6 (1.1–2.4) 3.3 (2.4–4.6)			None
	Whites**	Blacks**	None
	1.0 2.0 (1.2–3.0)	1.0 1.5 (1.0–2.4)	
	1.0 2.4 (1.5–3.8)[Δ] 2.7 (1.5–4.7)[Δ] 2.9 (1.4–6.1)[Δ]		Maternal age, education, social network, psychosocial stress
	1.0 2.1 (2.1–2.2)[††] 2.7 (2.6–2.8)[††]		Parity, maternal cohabitation with infant's father

**SGAdefined as in Brenner et al. 1976.

[††]SGA defined as birth weight ≤ 2 standard deviations below mean for gestational age.

Twenty percent or more of the incidence of LBW and SGAcan be attributed to cigarette smoking (Alameda County Low Birth Weight Study Group 1990; CDC 1990; Backe 1993; Roquer et al. 1995; Muscati et al. 1996; Cnattingius 1997). Numerous studies have demonstrated a statistically significant dose-response relationship between the number of cigarettes smoked by the mother and higher RRs for LBW or SGA (Kleinman and Madans 1985; Bell and Lumley 1989; Brooke et al. 1989; CDC 1990; McDonald et al. 1992; Lieberman et al. 1994; Spinillo et al. 1994c). In most of these studies, adverse effects of smoking were apparent even among the lightest smokers (e.g., less than one-half pack of cigarettes per day). In a study examining the type of cigarettes smoked, Peacock and colleagues (1991) compared birth weights of infants born to women who smoked low-yield cigarettes (<12 mg of CO per cigarette) with those born to women who smoked high-yield cigarettes. They reported that women who smoked a low number (<15 cigarettes per day) of low-yield cigarettes had infants with birth weights comparable to those of nonsmokers' infants. However, women who smoked a low number of high-yield cigarettes had infants with an average birth weight 8 percent lower than that of nonsmokers' infants.

Studies that used cotinine or other nicotine metabolites as a measure of exposure to cigarette smoke also showed an increased risk for LBW among infants of smokers, as shown in Table 3.40 (Mathai et al. 1990; Li et al. 1993; Eskenazi et al. 1995b), in Table 3.41 (Eskenazi et al. 1995b), and in other studies (Bardy et al. 1993; English et al. 1994; Ellard et al. 1996; Wang et al. 1997b; Peacock et al. 1998). These studies are especially important because some women who smoke may report themselves as nonsmokers. This misreporting results in misclassification of smokers and nonsmokers and underestimation of the true effect of smoking (Bardy et al. 1993). Among 3,529 pregnant women who had serum cotinine concentration measured at approximately 27 weeks' gestation, smokers had infants weighing an average of 78, 191, and 233 g less than infants of nonsmokers for the first, second, and third tertiles of increasing cotinine concentration, respectively (Eskenazi et al. 1995b). Similar trends of decreasing birth weight with increasing urine cotinine concentration were found in several other studies (Mathai et al. 1990; Bardy et al. 1993; Ellard et al. 1996; Wang et al. 1997b; Peacock et al. 1998).

A number of investigations have found that the effects of smoking on birth weight become more pronounced as maternal age increases (Cnattingius et al. 1985, 1993; Cnattingius 1989; Wen et al. 1990a; Aronson et al. 1993; Backe 1993; Fox et al. 1994). For example, in a large study from Sweden, the RRs for delivering an SGAinfant among women who smoked 10 or more cigarettes per day compared with nonsmokers were 1.9 (95 percent CI, 1.7 to 2.1) for mothers 15 through 19 years old and 3.4 (95 percent CI, 3.0 to 3.8) for mothers 40 through 44 years old (Cnattingius 1989). The reasons for this pattern of findings are not clear (Fox et al. 1994). The smoking-related risks for LBW and SGAmay be higher among women who have had no live births than among those who have had at least one live birth (Cnattingius et al. 1993).

The effects of smoking on birth weight appear to be similar among various racial groups in the United States (e.g., whites and blacks) (Alameda County Low Birth Weight Study Group 1990; CDC 1990; Castro et al. 1993; USDHHS 1998), but the findings from one study suggested stronger effects among black women than among white women (English et al. 1994). Lower average birth weight has also been reported among infants of Alaska Native smokers (Murphy et al. 1996) and Mexican American smokers (Wolff et al. 1993) compared with nonsmokers of the same race or ethnicity. However, in these studies, no comparisons were made with other racial or ethnic groups.

Cliver and colleagues (1995) found that birth weight, crown-to-heel length, and chest circumference were significantly less affected among infants whose mothers had stopped smoking during pregnancy than among infants born to women who continued to smoke. It is unclear exactly how early in pregnancy smoking cessation must occur to avoid the adverse effects of smoking on fetal growth. The longer the mother smokes during pregnancy, the greater the effect on the infant's birth weight (Adriaanse et al. 1996). Most studies suggested that infants of women who stop smoking by the first trimester have weight and body measurements comparable to those of nonsmokers' infants and that smoking in the third trimester is particularly detrimental (MacArthur and Knox 1988; Frank et al. 1994; Lieberman et al. 1994; Mainous and Hueston 1994a; Zaren et al. 1996). In one study, even women who were heavy smokers in the first trimester but who had stopped smoking before the second trimester had only an insignificantly higher risk for delivering an LBW infant than did women nonsmokers (RR, 1.2; 95 percent CI, 0.7 to 2.1) (McDonald et al. 1992). Reducing the amount smoked by the mother seems to be associated with infant birth weights higher than those among infants of mothers

who do not reduce the amount smoked, but the benefits are considerably smaller than for complete smoking cessation (McDonald et al. 1992; Li et al. 1993). Women nonsmokers who smoked during a previous pregnancy seem to have babies whose birth weights and risks for LBW and SGA are comparable to those of infants born to women who had never smoked (Nordstrom and Cnattingius 1994; Schramm 1997).

In principle, the apparent benefit of smoking cessation in observational studies could simply reflect other differences between women who stop smoking and those who continue to smoke. For example, women who stop smoking tend to be lighter smokers than those who continue to smoke (Lieberman et al. 1994; Nordstrom and Cnattingius 1994). However, the reported effects of cessation are probably not due to uncontrolled confounding. Even after consideration of the numbers of cigarettes smoked, cessation confers a benefit over continued smoking (McDonald et al. 1992; Li et al. 1993; Frank et al. 1994; Lieberman et al. 1994; Adriaanse et al. 1996). Randomized clinical trials of smoking cessation programs provided even stronger evidence of the benefit of cessation with regard to birth weight (Dolan-Mullen et al. 1994).

Smoking may lower birth weight by causing premature birth at less than 37 weeks' gestation (see "Preterm Delivery" earlier in this section), fetal growth retardation, or both. The nicotine and CO in cigarette smoke could cause fetal growth retardation (USDHHS 1988; Lambers and Clark 1996). Impairment of uteroplacental circulation, caused by the vasoconstrictive effect of nicotine, results in fetal hypoxia and impaired fetal nutrition, both of which may disrupt normal growth (Nash and Persaud 1988). Fetal hypoxia due to elevated carboxyhemoglobin levels from the CO in cigarette smoke may also retard fetal growth. Another mechanism contributing to the reduced birth weight associated with maternal smoking may be that pregnant women who smoke gain less weight than do nonsmokers (Ellard et al. 1996; Muscati et al. 1996). A study of more than 3,000 women reported that smokers gained an average of 9.9 kg (21.8 pounds) during pregnancy and that nonsmokers gained an average of 11.6 kg (25.5 pounds) (Ellard et al. 1996). The lower weight gain among women who smoke during pregnancy and the lower birth weight among their infants may not be explained by lower energy intake: in one investigation, smokers consumed significantly more calories per day than did nonsmokers but gained less weight (Muscati et al. 1996). Increased weight gain during pregnancy and higher prepregnancy weight among women who smoke may partially mitigate the negative effects of smoking on fetal growth (Muscati et al. 1996), but even after adjustment for pregnancy weight gain, maternal smoking is associated with SGA(Wen et al. 1990b; Lieberman et al. 1994; Spinillo et al. 1994c; Zaren et al. 1997).

Congenital Malformations

Congenital malformations (birth defects) encompass a wide variety of structural malformations that occur during gestation. Common categories of birth defects include central nervous system (CNS) malformations, such as neural tube defects, circulatory and respiratory (e.g., cardiac) anomalies, chromosomal anomalies, gastrointestinal malformations, musculoskeletal and integumental anomalies (e.g., oral clefts and limb reductions), and urogenital malformations. Risk factors for congenital malformations are difficult to assess as a group, because different defects have distinct etiologies. However, in general, advanced maternal age, previous perinatal death, and radiation (Seidman et al. 1990; Pradat 1992) confer an increased risk for birth defects to the developing fetus. Folic acid intake appears to reduce the risk for some malformations, particularly neural tube defects (Medical Research Council Vitamin Study Research Group 1991; Shaw et al. 1991). In this section, recent literature highlighting the relationship between smoking and risk for congenital malformations is reviewed.

Overall Risk

To date, most studies have found no association between cigarette smoking during pregnancy and the overall risk for birth defects (Shiono et al. 1986a; Malloy et al. 1989; Seidman et al. 1990; Van den Eeden et al. 1990; McDonald et al. 1992; Werler 1997) (Table 3.42). For example, one study of 33,434 live births in California found a RR of 1.0 (95 percent CI, 0.8 to 1.2) for "major" malformations among smokers compared with nonsmokers (Shiono et al. 1986a). The risk among smokers for "minor" malformations was lower than that among nonsmokers (RR, 0.9; 95 percent CI, 0.8 to 0.9). Similarly, in a case-control study among 3,284 singleton live births with at least one malformation and 4,500 controls, RR was 1.0 (95 percent CI, 0.9 to 1.1) among smokers (Van den Eeden 1990). These results suggested that, as a whole, maternal cigarette smoking during pregnancy does not have teratogenic effects on live-born infants. Some investigators have suggested that this lack of effect on the risk for birth defects can be explained by the increased risk

Table 3.42. Relative risks for congenital malformations among infants of women smokers

Study	Study type	Country	Number of infants	Relative risk (95% confidence interval) of malformations	
Shiono et al. 1986a	Cohort	United States	33,434	Nonsmokers	1.0
				Smokers	
				Major malformation of infant	1.0 (0.8–1.2)
				Minor malformation of infant	0.9 (0.8–0.9)
Malloy et al. 1989	Cohort	United States	288,067	Nonsmokers	1.0
				Smokers	
				All birth defects	0.98 (0.94–1.03)
Seidman et al. 1990	Cohort	Israel	17,152	Nonsmokers	1.0
				Smokers	
				Major malformation of infant	0.9 (0.6–1.4)
				Minor malformation of infant	1.1 (0.9–1.3)
Van den Eeden et al. 1990	Case-control	United States	3,284 cases 4,500 controls	Nonsmokers	1.0
				Smokers	
				Any birth defect	1.0 (0.9–1.1)

for spontaneous abortion, stillbirth, or both among smokers (Shiono et al. 1986a; Van den Eeden et al. 1990; Li et al. 1996; Källén 1998). These outcomes would prevent a deformed fetus from being born alive and recognized as having a birth defect. Nonetheless, smoking may be modestly related to an increased risk for certain birth defects, such as oral clefts, limb reductions, and urogenital or gastrointestinal defects (see below). CO and nicotine from the cigarette smoke may increase the risks for fetal hypoxia and vascular disruption, which can cause birth defects (Czeizel et al. 1994; Li et al. 1996; Werler 1996). Other possible mechanisms by which cigarette smoke may produce birth defects include toxic effects on the fetus from metabolites present in the smoke (Li et al. 1996), decreased use of folate (Alderman et al. 1994), or mutagenic effects (Seidman et al. 1990).

Central Nervous System Malformations

CNS defects occur at a rate of about 100 per 100,000 live births (Ventura et al. 1997). Neural tube defects (anencephaly, spina bifida, and encephalocele) are the most common form of neurologic malformations (Werler 1997). Several studies have shown that maternal smoking during pregnancy is not related to an increased risk for neural tube defects (Van den Eeden et al. 1990; Wassermann et al. 1996; Källén 1998). After adjusting for year of birth, maternal age, parity, education level, and other possible risk factors, an investigator in Sweden found a protective effect of smoking for all neural tube defects (RR, 0.8; 95 percent CI, 0.6 to 0.9) (Källén 1998). On the other hand, some findings suggested a positive association of smoking with other CNS malformations (e.g., microcephaly) (Van den Eeden et al. 1990).

Craniosynostosis (premature closure of one or more suture joints in the skull) is not primarily a CNS defect, but it does have implications for the CNS. In one study, maternal smoking was found to confer an increased risk for craniosynostosis (Alderman et al. 1994).

Cardiac Defects

Heart malformations are relatively common birth defects and occur in about 124 of 100,000 live births (Ventura et al. 1997). No strong evidence has appeared for an association between maternal smoking and the risk for cardiac malformation (Malloy et al. 1989; Van den Eeden et al. 1990; Pradat 1992). A case-control study of major congenital heart defects found a RR of 0.9 (95 percent CI, 0.8 to 1.1) among women smokers compared with nonsmokers (Pradat 1992). However, another study that examined the effect of smoking on conotruncal malformations found a higher risk when both parents smoked than when neither parent smoked (RR, 1.9; 95 percent CI, 1.2 to 3.1) (Wassermann et al. 1996). No effect was found for maternal smoking only.

Oral Clefts

Oral clefts are estimated to occur in 82 of 100,000 live births (Ventura et al. 1997) and are categorized as cleft lip (with or without cleft palate) and cleft palate (Wyszynski et al. 1997). These defects have been the subject of several epidemiological investigations. For cleft lip with or without cleft palate, one investigation found a RR of 1.5 (95 percent CI, 1.0 to 2.1) among smokers after adjustment for maternal age and parity (Van den Eeden et al. 1990). In three large studies (Shaw et al. 1996; Christensen et al. 1999; Lorente et al. 2000), investigators noted an increasing risk for cleft lip with or without cleft palate with increasing amount of maternal smoking. However, a third large study did not find a dose-effect relationship (Werler et al. 1990).

For cleft palate only, one investigation found a RR of 1.4 (95 percent CI, 1.1 to 1.6) among smokers (Källén 1997b). Others found the risk for cleft palate to be increased among women who smoked 20 or more cigarettes per day (RR, 2.2; 95 percent CI, 1.1 to 4.5) (Shaw et al. 1996). No effect of smoking was found among women who smoked fewer than 20 cigarettes per day. Other investigators reported no effect of smoking on the risk for cleft palate (Van den Eeden 1990; Werler et al. 1990; Christensen et al. 1999). A meta-analysis reported an overall RR of 1.3 (95 percent CI, 1.2 to 1.4) for cleft lip with or without cleft palate and an overall RR of 1.3 (95 percent CI, 1.1 to 1.6) for cleft palate (Wyszynski et al. 1997). This association does not appear to be due to confounding by alcohol intake (Källén 1997b).

Recent evidence suggested that the inconsistency among reports may be, in part, explained by an interaction between smoking and genetic factors (Hwang et al. 1995; Shaw et al. 1996; Werler 1997). Two studies (Hwang et al. 1995; Shaw et al. 1996) reported that women with the uncommon allele for transforming growth factor alpha and who smoke during pregnancy are at significantly greater risk for delivering an infant with cleft lip with or without cleft palate or an infant with cleft palate than are nonsmoking women with the common allele.

Limb Reductions

Limb reductions (the absence or severe underdevelopment of proximal or distal limbs) are reported to occur in 60 per 100,000 live births (Källén 1997c). Most studies have found no effect of maternal smoking on the risk for overall limb reductions (Shiono et al. 1986a; Van den Eeden et al. 1990; McDonald et al. 1992; Wassermann et al. 1996), although a case-control study among Swedish infants found a RR of 1.3 (95 percent CI, 1.1 to 1.5) for any maternal smoking and the risk for limb reduction (Källén 1997c).

Two studies reported significant associations between certain limb reductions and maternal smoking. Källén (1997c) reported a RR of 1.3 (95 percent CI, 1.01 to 1.6) for transverse reductions. Other investigators found RRs of 2.1 (95 percent CI, 1.3 to 3.6) for terminal transverse deficiencies among infants of smokers compared with infants of nonsmokers; a significant dose-response relationship was found after multivariate adjustment (Czeizel et al. 1994). The association between transverse limb reductions and maternal smoking is biologically plausible, because these defects are believed to result from vascular interruption (Werler 1997).

Down Syndrome

Down syndrome affects about 45 per 100,000 live births (Ventura et al. 1997), and the risk increases sharply among older women (Chard and Macintosh 1995). A few studies have found a protective effect of maternal smoking on the risk for giving birth to a child with Down syndrome (Hook and Cross 1985, 1988; Shiono et al. 1986a). Most investigations, however, have reported no effect of smoking (Cuckle et al. 1990a; Seidman et al. 1990; Van den Eeden 1990; Källén 1997a), particularly after careful control for maternal age (Chen et al. 1999).

Digestive and Urinary Tract Malformations

Urogenital abnormalities have been reported to occur at a rate of 121 per 100,000 live births (Ventura et al. 1997). Three large case-control studies found no effect of smoking on the risk to the offspring for developing urogenital anomalies (Shiono et al. 1986a; Seidman et al. 1990; Van den Eeden et al. 1990). More recent investigations that have examined individual defects have reported cases of smoking-related malformations of urinary organs. For example, one study reported a weak association (RR, 1.2; 95 percent CI, 1.0 to 1.5) between maternal smoking and kidney malformations (Källén 1997d). Smoking was also found to be a risk factor for congenital urinary tract abnormalities (RR, 2.3; 95 percent CI, 1.2 to 4.5), but no dose-response relationship could be substantiated (Li et al. 1996).

Gastrointestinal abnormalities are much less frequent and occur in about 82 per 100,000 live births (Ventura et al. 1997). Maternal smoking during pregnancy has sometimes been associated with increased

risks for gastroschisis (Werler et al. 1992; Torfs et al. 1994) and anal atresia (Yuan et al. 1995). However, three case-control studies did not find any affect of smoking on the risk for gastrointestinal abnormalities (Shiono et al. 1986a; Seidman et al. 1990; Van den Eeden et al. 1990).

Breastfeeding

Breastfeeding is widely recognized to have nutritional benefits and preventive effects against infectious diseases, such as respiratory tract infections and diarrhea, among infants (Victora et al. 1987). These conditions are the leading causes of death among infants in developing countries, where infant mortality is high. Duration of lactation differs among societies, but studies have generally shown a positive association with maternal age, education, and socioeconomic class (Andersen et al. 1982a).

Because the definitions of breastfeeding, weaning, and smoking differ greatly among studies, summarizing information about the relationship between smoking and breastfeeding is difficult. Nevertheless, studies have consistently shown that women who smoke are less likely to start breastfeeding than are nonsmokers (Yeung et al. 1981) and tend to wean an infant earlier than do nonsmokers (Lyon 1983; Counsilman and Mackay 1985; Feinstein et al. 1986; Woodward 1988; Matheson and Rivrud 1989; Rutishauser and Carlin 1992; Ever-Hadani et al. 1994). Maternal milk production of smokers is more than 250 mL/day less than that of nonsmokers (Vio et al. 1991; Hopkinson et al. 1992); the number of cigarettes smoked per day and the duration of breastfeeding are negatively associated (Horta et al. 1997). In most epidemiologic studies, these associations are evident even after careful adjustment for indicators of social class (Lyon 1983; Nylander and Matheson 1989; Horta et al. 1997). A study from southern Brazil is typical: 28 percent of mothers who smoked at least 20 cigarettes per day were still breastfeeding at 6 months after delivery, whereas 40 percent of mothers who did not smoke were still breastfeeding then (Horta et al. 1997). Findings from this study have also suggested that exposure to ETS may be associated with shorter duration of breastfeeding.

Initiation and maintenance of lactation require maternal secretion of the hormone prolactin (Akre 1989). One group of investigators found that among lactating women, basal prolactin levels were lower for smokers than for nonsmokers (Andersen and Schiöler 1982; Andersen et al. 1982a). This effect could provide a physiologic basis for an association between smoking and early weaning. Several studies of men and nonlactating women also reported lower prolactin levels among smokers than among nonsmokers (Andersen and Schiöler 1982; Andersen et al. 1984; Baron et al. 1986a; Fuxe et al. 1989), but other studies have not found this pattern (Wilkins et al. 1982; Jernström et al. 1992). These discrepancies may relate to differences across studies in the pattern of smoking before blood sampling. In rats, isolated exposure to nicotine has increased prolactin levels (Sharp and Beyer 1986), whereas repeated exposure has inhibited secretion (Terkel et al. 1973; Andersson et al. 1985; Fuxe et al. 1989).

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is the sudden death of an infant younger than 1 year of age that remains unexplained after a thorough investigation, including a complete autopsy, examination of the death scene, and a review of the clinical history (Willinger et al. 1991). In the United States, SIDS is the leading cause of death among infants 1 to 12 months of age and affects more than 0.1 percent of live births. Although the causes of SIDS are unknown, several risk factors have been identified. Black infants and American Indian infants have SIDS mortality rates two to three times higher than do white infants. Prone sleeping position and not having been breastfed are also associated with increased risk (Willinger et al. 1994).

In many studies, maternal smoking during pregnancy has been associated with SIDS (Bergman and Wiesner 1976; Avery and Frantz 1983; Malloy et al. 1988, 1992; Kraus et al. 1989; McGlashan 1989; Bulterys et al. 1990; Haglund and Cnattingius 1990; Li and Daling 1991; Mitchell et al. 1991; Schoendorf and Kiely 1992; Scragg et al. 1993; DiFranza and Lew 1995; Klonoff-Cohen et al. 1995; Golding 1997; MacDorman et al. 1997). The association has persisted after adjustment for covariates such as infant sleeping position, birth weight, and race as well as maternal age, marital status, education, and parity (Malloy et al. 1988; Bulterys et al. 1990; Li and Daling 1991; Schoendorf and Kiely 1992; Scragg et al. 1993). However, because smoking during and after pregnancy are highly correlated, it is difficult to separate the effects of these two exposures (Spiers 1999).

Few studies of SIDS obtained data to distinguish between the effects of maternal smoking during pregnancy and the effects of passive smoking on the infant after delivery. Schoendorf and Kiely (1992) compared the risk for SIDS among infants of mothers who did not smoke, infants of mothers who smoked during

pregnancy and after delivery, and infants of mothers who smoked only after delivery. After adjustment for demographic risk factors, infants whose mothers smoked both during pregnancy and after delivery had three times the risk for SIDS as infants born to mothers who did not smoke. Among infants of mothers who smoked only after delivery, the adjusted RR for SIDS was about 2.0. A case-control study from southern California also reported an independent effect of passive exposure to smoke after delivery on the risk for SIDS (Klonoff-Cohen et al. 1995).

Several case-control and cohort studies reported a dose-response relationship between the number of cigarettes smoked during pregnancy and the risk for SIDS (Kraus et al. 1989; Bulterys et al. 1990; Haglund and Cnattingius 1990; Malloy et al. 1992; Scragg et al. 1993; Klonoff-Cohen et al. 1995; MacDorman et al. 1997). For example, in a study that included 636 infants who died of SIDS, the RR for SIDS among infants whose mothers smoked less than one pack of cigarettes per day was 2.0 (95 percent CI, 1.6 to 2.4), and the RR among infants whose mothers smoked at least one pack per day was 2.9 (95 percent CI, 2.3 to 3.5) (Malloy et al. 1992).

In summary, maternal smoking during pregnancy has been repeatedly associated with SIDS, and the risk increases with the number of cigarettes smoked daily. A meta-analysis of studies that compared the incidence of SIDS among the offspring of women who smoked during pregnancy and those who did not yielded a pooled RR of 3.0 (95 percent CI, 2.5 to 3.5) (DiFranza and Lew 1995). The mechanism by which smoking affects the risk for SIDS is not clear. One possibility is that tobacco smoke interferes with neuroregulation of breathing and causes apneic spells that lead to sudden infant death (Avery and Frantz 1983).

Conclusions

1. Women who smoke have increased risks for conception delay and for both primary and secondary infertility.
2. Women who smoke may have a modest increase in risks for ectopic pregnancy and spontaneous abortion.
3. Smoking during pregnancy is associated with increased risks for preterm premature rupture of membranes, abruptio placentae, and placenta previa, and with a modest increase in risk for preterm delivery.
4. Women who smoke during pregnancy have a decreased risk for preeclampsia.
5. The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy.
6. Infants born to women who smoke during pregnancy have a lower average birth weight and are more likely to be small for gestational age than are infants born to women who do not smoke.
7. Smoking does not appear to affect the overall risk for congenital malformations.
8. Women smokers are less likely to breastfeed their infants than are women nonsmokers.
9. Women who quit smoking before or during pregnancy reduce the risk for adverse reproductive outcomes, including conception delay, infertility, preterm premature rupture of membranes, preterm delivery, and low birth weight.

Body Weight and Fat Distribution

Body Weight

The term “obesity” is most often understood to refer to a high body weight in relation to height. BMI is the most commonly used measure of body size and is defined as weight (in kilograms) divided by the square of height (in meters) (Bray 1998). Beside the effects on health, body weight may be a focus of concern about attractiveness and body image. The association between smoking and low body weight has been recognized by the lay public (USDHHS 1988, 1990; Klesges et al. 1989), and concern about weight may encourage smoking initiation and impede cessation (see “Factors Influencing Initiation of Smoking” in Chapter 4 and “Weight Control” in Chapter 5). Smoking cessation may result in weight gain, yet

smoking may promote a harmful pattern of body fat distribution. These aspects of the relationship between smoking and weight are discussed here.

Cross-sectional studies generally have found that smokers weigh less than former smokers and those who had never smoked (Klesges et al. 1989; Grunberg 1990). The weight differences increase with age—a finding that suggested smoking may inhibit weight gain over relatively long periods of time (Klesges et al. 1989, 1991a). Among current smokers, there tends to be a U-shaped curve for the relationship between smoking and body mass: typically, moderate smokers (approximately 10 to 20 cigarettes per day) weigh less than light smokers (<10 cigarettes per day), and heavy smokers (≥ 20 cigarettes per day) weigh more than moderate smokers (Albanes et al. 1987; Klesges et al. 1989, 1991b; Klesges and Klesges 1993). Most of the data on this association have been generated by research among whites. One study, however, reported that this relationship was particularly pronounced among black women, in contrast to a regular inverse relationship in that study between the number of cigarettes smoked and weight among white women, white men, and black men who smoked (Klesges and Klesges 1993).

Body Weight and Smoking Initiation

Because of the negative relationship between smoking and body weight and the common finding that weight gain occurs after smoking cessation, the public and several reviews of the literature (USDHHS 1988, 1990; Klesges et al. 1989) concluded, perhaps prematurely, that persons who start smoking lose weight. Concern about body weight appears to be related to smoking initiation (see "Other Issues" in Chapter 2 and "Concerns About Weight Control" in Chapter 4). Most adolescents believe that smoking controls body weight (Camp et al. 1993), and women, in particular, report that they smoke to keep body weight down (USDHHS 1988; Gritz et al. 1989; Grunberg 1990). However, more recent studies indicated that smoking initiation may not be related to short-term changes in body weight.

Only four prospective studies that included women examined changes in body weight after smoking initiation, and three of these were among women aged about 30 through 60 years, after the age of smoking initiation for most women. Results from these studies were conflicting. Data on more than 3,500 women (mean age at baseline, 38 years) showed that weight gain over two years did not differ significantly among women and men who started smoking or among those who did not (French et al. 1994). Similar results were reported for the 55,000 women in the U.S. Nurses' Health Study after eight years of follow-up (Colditz et al. 1992). The nurses who began smoking gained an average of 9.2 pounds over the eight years, whereas those who had never smoked gained 8.2 pounds on average. Among current smokers of 1 to 24 cigarettes per day, the mean weight gain was 11.2 pounds; that among women who currently smoked 25 or more cigarettes per day was 11.9 pounds. In contrast, in a cohort of women followed for an average of six years, the women who started smoking lost 0.37 BMI units and the women who had never smoked gained 0.62 BMI units ($p < 0.01$) (Lissner et al. 1992).

One prospective study examined the relationship between smoking initiation and body weight among adults aged 18 through 30 years (Klesges et al. 1998). The investigators evaluated 5,115 women and men at three time points during a seven-year period. Continuing smokers, persons who began smoking between the first and second evaluations, and those who had never smoked were compared with persons who had stopped smoking. Although persons in all groups gained weight, no significant differences in body weight among the groups emerged during the follow-up period; those who began smoking did not lose weight or have an attentuated weight gain. At least over a seven-year period, smoking initiation did not affect body weight and continued smoking did not have anorectic effects or suppress weight.

No prospective studies of smoking initiation and body weight have been conducted among adolescents, who are the most likely age group to start smoking (see "Smoking Initiation" in Chapter 2). Such studies should be a high priority for future research because concerns about body weight appear to be associated with smoking initiation among adolescents (see "Smoking Initiation" in Chapter 2). However, the anorectic effect of smoking is small, and smoking may affect body weight only after decades of smoking (Klesges et al. 1989). Because most cross-sectional studies of body weight differences between smokers and nonsmokers focused on middle-aged persons, the anorectic qualities of smoking may have been overestimated. For example, if the average weight difference between smokers and nonsmokers in middle age (e.g., 45 years of age) is about 5.5 pounds after about 30 years of smoking (Klesges et al. 1989), then on average, each year of smoking would contribute less than two-tenths of a pound to the weight difference.

Body Weight and Smoking Cessation

Smoking cessation has been shown to result in weight gain among both women and men, but the magnitude of the gain and the mechanisms involved are not clear (Klesges et al. 1989; Williamson et al. 1991). In a review of 43 longitudinal studies that examined the effects of smoking cessation on body weight (USDHHS 1988), the average weight gain was 6.2 pounds (range, 1.8 to 18.1 pounds) during the first year after cessation. A1990 review of the most methodologically rigorous studies (USDHHS 1990) showed that the weight gain among persons who had stopped smoking was greater than that among persons who continued to smoke (mean, 4.6 vs. 0.8 pounds). This summary also invalidated the commonly reported, but empirically unsupported, estimate that one-third of persons who stop smoking gain weight, one-third have stable weight, and one-third lose weight (USDHEW 1977). The 1990 review concluded that 79 percent (range, 58 to 87 percent) of persons who had stopped smoking gained weight and that 56 percent (33 to 62 percent) of persons who continued to smoke gained weight. A major weight gain (>10 pounds) also was found to be more common among persons who had stopped smoking (20.3 percent) than among persons who continued to smoke (0.8 percent).

Findings similar to those in the 1990 review were reported from a prospective study of 121,700 female nurses who had eight years of follow-up (Colditz et al. 1992). The mean weight gain attributable to smoking cessation was 3.1 pounds among women who had smoked fewer than 25 cigarettes daily and 6.2 pounds among women who had smoked 25 or more cigarettes daily. A weight gain of 11 pounds or more occurred within two years among 24.3 percent of women who had stopped smoking but among only 8.4 percent of women who continued to smoke. Weight gain after cessation was positively associated with the amount smoked before cessation, younger age, and lower initial weight.

The actual weight gain after smoking cessation may be greater than the 4 to 8 pounds suggested by the 1990 review (USDHHS 1990). Few studies were designed to prospectively assess the effects of smoking cessation on weight gain, and most relied on self-reported smoking status and weight (USDHHS 1990), which are subject to systematic error (bias). Weight is typically underreported (Klesges 1983; Crawley and Portides 1995), and smokers are more likely to state that they had stopped smoking than are nonsmokers to describe themselves as smokers (Klesges et al. 1992). Moreover, many of the estimates of weight changes were based on studies conducted during the 1970s and 1980s. Thus, women who have stopped smoking in more recent years may have been more nicotine dependent and may have smoked more cigarettes daily than did women who had stopped smoking in earlier decades. These two factors may increase the risk for postcessation weight gain (Williamson et al. 1991; Colditz et al. 1992). Investigators also have typically used point prevalence rather than sustained smoking cessation to determine smoking status, and sustained cessation may be associated with greater weight gain.

Large-scale follow-up studies have avoided several of these limitations (Williamson et al. 1991; O'Hara et al. 1998). More than 9,000 respondents in the first National Health and Nutrition Examination Survey (NHANES) were interviewed during 1971–1975 and reinterviewed during 1982–1984 (Williamson et al. 1991). Consistent with previous reports, women who had stopped smoking tended to gain more weight than did men who had stopped smoking. A major weight gain (>29 pounds) occurred among 13.4 percent of women and among 9.8 percent of men who sustained cessation for more than 1 year. The RR for major weight gain among women who had stopped smoking compared with those who continued to smoke was 5.8 (95 percent CI, 3.7 to 9.1). Risk for major weight gain was higher among women who were initially underweight, younger (25 to 54 years vs. 55 to 74 years), physically inactive, and parous. Average weight gains were 12.1 pounds among women who had stopped smoking for more than 1 year and 3.7 pounds among women who continued to smoke. The average weight gain attributable to smoking cessation was greater among both women and men than that in previous reviews (USDHHS 1988, 1990). This finding was possibly due to the longer follow-up period (10 years). Despite the high overall weight gain among these women, the mean body weight of women former smokers after follow-up was similar to that of women who had never smoked. Similarly, in the Lung Health Study (O'Hara et al. 1998), women who sustained cessation for 5 years gained an average of 19.1 pounds during that interval, whereas women who continued to smoke gained an average of 4.3 pounds. During the first year of cessation, weight gain was strongly associated with the number of cigarettes formerly smoked. In subsequent years, weight gain was less strongly associated with baseline smoking.

Other studies have also suggested that the magnitude of postcessation weight gain is higher than

previous estimates. In one investigation, sustained smoking cessation resulted in a weight gain almost double the average reported in earlier studies of women (11.7 pounds at 1-year follow-up) (Nides et al. 1994). Another analysis examined self-reported weight change in the previous 10 years among participants in the third NHANES, which was conducted from 1988 through 1991 (Flegal et al. 1995). The age-adjusted increase in weight during the previous 10 years was 8.46 ± 0.91 kg (18.6 pounds) among women who had quit smoking during that 10-year period, 4.75 ± 1.20 kg (10.5 pounds) among those who had quit smoking 10 or more years before, 2.96 ± 0.61 kg (6.5 pounds) among current smokers, and 3.75 ± 0.41 kg (8.3 pounds) among those who had never smoked. When the difference in weight gain between those who had quit smoking and continuing smokers was taken into account and when age and other factors were adjusted for, the estimated weight gain due to smoking cessation was 5.0 kg (95 percent CI, 2.0 to 8.0 kg) (11.0 pounds) among women and 4.4 kg (95 percent CI, 2.5 to 6.3 kg) (9.7 pounds) among men. In another study, women abstinent at 1-year follow-up, but not abstinent at one or more of the previous follow-ups, had gained an average of 6.7 pounds, a figure similar to previous estimates. However, women who achieved sustained abstinence had gained almost twice this amount—13.0 pounds (Klesges et al. 1997).

Weight gain after smoking cessation occurs largely in the first few years of abstinence. Thereafter, the rate of excess weight gain slows. In the follow-up of the first NHANES (Williamson et al. 1991), the RR for major weight gain (>29 pounds) did not increase as a function of duration of cessation. In the U.S. Nurses' Health Study, women who had stopped smoking within the past two years gained 4.7 pounds more than did continuing smokers. This excess weight gain fell to 1.2 pounds during subsequent two-year intervals (Colditz et al. 1992). In the Lung Health Study, women who sustained smoking cessation for five years gained more weight in the first year of abstinence than in the next four years (O'Hara et al. 1998).

Thus, more recent estimates of RR indicated that weight gain may be higher than previous estimates, but the health benefits of smoking cessation still far outweigh the health risk from the extra body weight, unless the weight gain is extraordinarily large (USDHHS 1990).

Distribution of Body Fat and Smoking

Abdominal obesity refers to a pattern of body fat distribution characterized by excess subcutaneous or visceral fat in the abdominal region. This pattern is sometimes referred to as a male pattern, whereas gluteal obesity (excess fat in the hips and buttocks) is more typical of women. However, abdominal obesity can occur among both women and men (Tarui et al. 1991). This type of obesity is a risk factor for several conditions, including type 2 diabetes mellitus (Hartz et al. 1984; Ohlson et al. 1985; Cassano et al. 1992), dyslipidemia or hyperinsulinemia (Kissebah et al. 1982; Krotkiewski et al. 1983; Evans et al. 1984; Marti et al. 1989; Landsberg et al. 1991; Ward et al. 1994), sympathetic overactivity and hypertension (Evans et al. 1984; Hartz et al. 1984; Cassano et al. 1990; Landsberg et al. 1991; Ward et al. 1994), stroke (Lapidus et al. 1984; Larsson et al. 1984), coronary artery disease (Lapidus et al. 1984; Larsson et al. 1984; Donahue et al. 1987; Terry et al. 1992), and possibly breast cancer (Folsom et al. 1990). Abdominal obesity is also associated with increased total mortality among both women and men (Lapidus et al. 1984; Larsson et al. 1984; Stevens et al. 1992a,b; Folsom et al. 1993), possibly because of its association with such metabolic abnormalities.

Because overall obesity is positively associated with abdominal obesity (Haffner et al. 1987), smokers might be expected to have less abdominal fat than do nonsmokers. However, many studies reported a positive association of smoking with a high waist-to-hip ratio (WHR) among women (Table 3.43). The relationship between smoking and WHR may be stronger among women than among men. Barrett-Connor and Khaw (1989) reported that among women, WHR was 2.9 percent higher for current smokers than for those who had never smoked, but only 1.8 percent higher among men. In another study, WHR among white women was 2.3 percent higher among current smokers than among those who had never smoked and 2.0 percent higher among comparable groups of black women (Kaye et al. 1993). WHR was also higher among current smokers than among those who had never smoked, for women and men, black or white (Duncan et al. 1995). However, the difference in WHR for current smokers and those who had never smoked was one-third higher among white women than among white men and twice as high among black women as among black men.

The mechanisms underlying the positive relationship between smoking and increased WHR are unknown, but at least two plausible explanations exist. First, smoking may not directly influence WHR but may be part of several adverse health behaviors that together directly increase WHR. Several studies

have documented that WHR is positively associated with physical inactivity and with increased intake of total calories, alcohol, and fat (Troisi et al. 1991; Rodin 1992; Slattery et al. 1992; Randrianjohany et al. 1993; Duncan et al. 1995). Because cigarette smoking has been associated with all these behaviors, the observed relationship between smoking and WHR could be due to these factors. No study has investigated whether this is the case.

Second, smoking could directly promote deposition of fat in the abdominal area by increasing the relative balance of androgenic and estrogenic sex hormones. Patterns of fat deposition among both women and men are known to be determined partly by sex steroid hormones (Kirschner et al. 1990; Bouchard et al. 1993). These hormones are involved in the regulation of lipoprotein lipase (LPL) in adipose tissue, the key enzyme regulating deposition of triglyceride in fat cells (Bouchard et al. 1993). Before menopause, when estrogen levels are high, LPL activity is higher in femoral fat depots than in abdominal depots, which promotes deposition of femoral fat (Rebuffé-Scrive et al. 1985). After menopause, when the ovarian production of sex hormones slows or ceases, LPL activity decreases in the femoral region and becomes similar to activity in the abdominal depots, which promotes deposition of abdominal fat. Compared with women with femoral obesity, premenopausal and postmenopausal women who develop high WHR have elevated production rates and serum levels of testosterone, as well as lower levels of sex hormone-binding globulin. These findings suggested that increased androgenicity promotes high WHR among women (Evans et al. 1983; Seidell et al. 1989; Kirschner et al. 1990; Kirschner and Samojlik 1991). The antiestrogenic effect of smoking, together with the increases in adrenal androgens seen among smokers, could thus contribute to their high WHR.

Conclusions

1. Initiation of cigarette smoking does not appear to be associated with weight loss, but smoking does appear to attenuate weight gain over time.
2. The average weight of women who are current smokers is modestly lower than that of women who have never smoked or who are long-term former smokers.
3. Smoking cessation among women typically is associated with a weight gain of about 6 to 12 pounds in the year after they quit smoking.
4. Women smokers have a more masculine pattern of body fat distribution (i.e., a higher waist-to-hip ratio) than do women who have never smoked.

Bone Density and Fracture Risk

Bone fractures are a common health problem among women: about 16 percent of 50-year-old white women and 5.5 percent of 50-year-old black women will have a hip fracture in their remaining lifetime (Cummings et al. 1989). Risk rises steeply with age (Melton 1988); most patients who sustain a hip fracture are older than 70 years. The mortality after hip fracture is also high; more than 10 percent of patients die within six months of injury (Magaziner et al. 1989; Lu-Yao et al. 1994). Some of the mortality after hip fracture seems to be due to the debilitated state of the patient sustaining the fracture (Poór et al. 1995). Nonetheless, the event often is devastating, and the fracture imposes a significant burden of morbidity and mortality.

Compared with men, women are at increased risk for virtually all types of fractures; among women older than 65 years, the risk for fracture at most anatomic sites is about twice the risk among men the same age (Griffin et al. 1992; Baron et al. 1994a, 1996a). The incidence of fracture of the vertebrae or distal forearm increases among women around the time of menopause; among women younger than about age 70 years, both types of fractures occur more frequently than do hip fractures. Fractures of the ankle are fairly common among middle-aged women but appear to become less common later in life (Griffin et al. 1992; Baron et al. 1994a).

Osteoporosis, the state of having low bone density, impairs the structural integrity of the bone and heightens its susceptibility to trauma. Low bone density (measured at the wrist) is associated with an increased risk for fracture at most bone sites (Seeley et al. 1991). Data on the relationships between smoking and bone density and between smoking and fracture risk are presented here.

Table 3.43. Findings regarding the relationship between smoking and abdominal obesity as measured by waist-to-hip ratio (WHR)

Study	Population	Smoking status	Relationship with WHR	Covariate adjustment factors
Haffner et al. 1986	388 women, 563 men Aged 25–64 years	Cigarettes / day	Positive association for both women and men	BMI,* age, physical activity level, alcohol intake, ethnicity
Barrett-Connor and Khaw 1989	1,112 women, 836 men Aged 50–79 years	Never smoked Former smokers Current smokers	Positive linear trend across smoking categories for both women and men Positive linear trend for women within BMI tertiles Nonsignificant positive trend for men within BMI tertiles	Age, BMI
den Tonkelaar et al. 1989	152 premenopausal women, 300 postmenopausal women Aged 41–75 years	Nonsmokers Current smokers	WHR higher for smokers than for nonsmokers among premenopausal women only	BMI
Lapidus et al. 1989	1,462 women Aged 38–60 years	Cigarettes / day	Positive association	Age, BMI
den Tonkelaar et al. 1990	5,923 premenopausal women, 3,568 postmenopausal women Aged 40–73 years	Never smoked Former smokers, >20 cigarettes / day Current smokers, <10, 10–20, or >20 cigarettes / day	Positive linear trend across categories of number of cigarettes smoked for both premenopausal and postmenopausal women Positive linear trend within BMI tertiles for current smokers	BMI, BMI^2, age
Kaye et al. 1990	40,980 postmenopausal women Aged 55–69 years	Never smoked Former smokers Current smokers	Positive linear trend across smoking categories	Age, BMI

*BMI = Body mass index.

Smoking and Bone Density

The technology of bone density measurement is evolving rapidly, and several radiographic techniques were used to generate the data summarized here. Single photon absorptiometry was used in many studies of the peripheral skeleton, generally the radius (forearm) or the calcaneus (heel). Dual photon absorptiometry can be used for assessing those sites, as well as the hip and the axial skeleton, generally the spine. Dual X-ray absorptiometry, a refinement of the dual photon technique, offers higher resolution, shorter scanning times, and increased precision (Mazess and Barden 1989).

The growth of the skeleton continues until peak bone mass is reached, probably before age 30 years (Sowers and Galuska 1993). A slow decrease in bone density then begins and accelerates for several years after menopause (Riggs and Melton 1986; Resnick and Greenspan 1989). Because of these age-related patterns, studies of bone density are considered here by menopausal status of participants. Cross-sectional studies reporting mean bone density for at least 100 smokers and nonsmokers are summarized in Tables 3.44 and 3.45.

It is not clear whether environmental factors such as smoking affect bone differently at different anatomic sites. One large study reported similar effects of

Table 3.43. Continued

Study	Population	Smoking status	Relationship with WHR	Covariate adjustment factors
Marti et al. 1991	2,756 women, 2,526 men Aged 25–64 years	7-point scale 1 = never smoked 7 = current smokers of ≥ 25 cigarettes / day	No statistically significant independent association across smoking index in women or men	Age, education, heart rate, dietary fat, alcohol consumption, exercise
Wing et al. 1991	487 women Aged 42–50 years	Never smoked Former smokers Current smokers	Positive linear trend across smoking groups Positive association with number of cigarettes smoked	BMI
Daniel et al. 1992	56 women Aged 20–35 years	Nonsmokers Never smoked Former smokers Current smokers	WHR higher for smokers than for nonsmokers	None
Armellini et al. 1993	307 women, 294 men Outpatients Aged 20–60 years	Never smoked Current smokers, <10, 10–15, or >15 cigarettes / day	WHR and number of cigarettes smoked not significantly associated for women or men	Age, BMI, alcohol intake, physical activity level, menopausal status
Kaye et al. 1993	1,464 black women, 1,142 black men 1,300 white women, 1,159 white men Aged 18–30 years	Never smoked Former smokers Current smokers	Positive linear trend across smoking categories for both genders and races	Age, BMI
Duncan et al. 1995	2,366 black women, 1,444 black men 5,872 white women, 5,293 white men Aged 45–64 years	Never smoked Former smokers Current smokers	WHR higher for current smokers than for those who never smoked for both genders and races	Age, education, BMI, physical activity, menopausal status, alcohol intake

smoking at the radius and the calcaneus (Bauer et al. 1993). However, another large investigation found more pronounced effects for measurements at the hip than at the spine or radius (Hollenbach et al. 1993). Several investigators also reported greater differences in bone density between smokers and nonsmokers at the hip than at other sites (Hansen et al. 1991; Nguyen et al. 1994; Ortego-Centeno et al. 1994), but others reported more marked effects at the radius (Krall and Dawson-Hughes 1991; Bauer et al. 1993; Kiel et al. 1996; Orwoll et al. 1996).

Cross-Sectional Studies

Some studies of premenopausal women have suggested a lower bone density at various sites among smokers than among nonsmokers (Stevenson et al. 1989; McCulloch et al. 1990; Mazess and Barden 1991; Ortego-Centeno et al. 1994; Jones and Scott 1999) (Table 3.44). However, other investigations did not find a substantial effect (Sowers et al. 1985a,b; Bilbrey et al. 1988; Picard et al. 1988; Davies et al. 1990; Cox et al. 1991; Laitinen et al. 1991; Turner et al. 1992; Hansen 1994; Välimäki et al. 1994; Daniel and Martin 1995;

Table 3.44. Relative bone density among premenopausal women, for smokers compared with nonsmokers, cross-sectional studies

Study	Population	Smoking status	Relative bone density* (%)
Davies et al. 1990	Patients with amenorrhea Aged 16–40 years England	39 current smokers 93 never smoked	Lumbar spine: -3.4
McCulloch et al. 1990	Hospital employees Mean age 28.5 years Canada	25 daily smokers 76 nondaily smokers	Calcaneus: -6.7
Mazess and Barden 1991	Volunteers Aged 20–39 years United States	39 smokers 261 nonsmokers	Lumbar spine: -3.9† Mid-radius: -1.4 Distal radius: 0.0 Femoral neck: -4.0
Daniel et al. 1992	Volunteers Aged 20–35 years Canada	25 smokers 27 nonsmokers	Lumbar spine: +2.3 Femoral neck: +3.8 Trochanter: +3.2 Ward's triangle: +3.3
Ortego-Centeno et al. 1994	Healthy volunteers Mean age 28.2 years Spain	47 current smokers 54 former smokers or never smoked	Lumbar spine: -1.3 Femoral neck: -5.0‡ Trochanter: -3.8 Ward's triangle: -5.6‡
Law et al. 1997a	Healthy volunteers Aged ≥ 35 years England	142 current smokers 350 never smokers	Distal radius: +1.0
Jones and Scott 1999	Participants in follow-up study Mean age 32.7 years for smokers, 34.0 years for nonsmokers Australia	118 smokers 158 nonsmokers	Lumbar spine: -3.7 Femoral neck: -4.7

*Relative bone density = (bone density in smokers – bone density in nonsmokers)/bone density in nonsmokers, based on unadjusted bone density means.
†Statistically significant at $p < 0.05$.
‡Statistically significant, but statistical significance lost after adjustment for age and weight.

McKnight et al. 1995; Franceschi et al. 1996; Law et al. 1997a; Fujita et al. 1999), and one study from China reported a statistically significant trend of increasing bone density with number of cigarettes smoked (Hu et al. 1994). In many of these studies, no adjustment was made for potentially important covariates such as age and body weight, which hampered interpretation of the findings.

Results from cross-sectional studies of perimenopausal women have been similar to findings from studies of premenopausal women: an effect of smoking on bone density was not consistently seen (Johnell and Nilsson 1984; Jensen and Christiansen 1988; Elders et al. 1989; Slemenda et al. 1989; Cheng et al. 1991; Spector et al. 1992; Kröger et al. 1994; Leino et al. 1994; McKnight et al. 1995).

Among postmenopausal women, an association of lower bone density with smoking has generally been reported (Law and Hackshaw 1997). The majority of cross-sectional studies found a lower bone mass among smokers (Table 3.45) (Holló et al. 1979; Rundgren and Mellström 1984; Jensen 1986; Hansen et al. 1991; Krall and Dawson-Hughes 1991; Bauer et al. 1993; Cheng et al. 1993; Johansson et al. 1993; Nguyen

et al. 1994; Ward et al. 1995; Orwoll et al. 1996; Grainge et al. 1998). Nonetheless, several other such studies reported no substantial effect (Sowers et al. 1985a,b; Nordin and Polley 1987; Bilbrey et al. 1988; Cauley et al. 1988; Hunt et al. 1989; Stevenson et al. 1989; Ho et al. 1995), and a study from China reported a positive correlation between cigarette smoking and bone mass (Hu et al. 1994). In the Framingham study, bone density was lower only among smokers who took oral estrogen (Kiel et al. 1996). Findings among men in cross-sectional studies have not been entirely consistent, but men who smoke seem to have lower bone density than do nonsmokers, with a reduction in bone mass similar to that reported among postmenopausal women smokers (Holló et al. 1979; Suominen et al. 1984; Johansson et al. 1992; Kröger and Laitinen 1992; Cheng et al. 1993; Hollenbach et al. 1993; May et al. 1994; Kiel et al. 1996).

Longitudinal and Twin Studies

Few substantial differences in bone loss between smokers and nonsmokers have emerged among premenopausal women (Mazess and Barden 1991; Sowers et al. 1992) or perimenopausal women (Slemenda et al. 1989; Spector et al. 1992) who were studied longitudinally. Some studies of postmenopausal women have also reported statistically similar bone loss among smokers and nonsmokers (Aloia et al. 1983; Hansen et al. 1991; Jones et al. 1994), but most investigations of these women reported a higher rate of bone loss among smokers (Lindsay 1981; Krall and Dawson-Hughes 1991; Writing Group for the PEPI Trial 1996; Burger et al. 1998). One longitudinal study of male twins supported an association between smoking and bone loss (Slemenda et al. 1992), but another longitudinal study of men found no differences in bone loss between smokers and nonsmokers (Jones et al. 1994). All these longitudinal studies faced substantial statistical impediments. Changes in bone density over a few years are small, and the analyses typically have only limited statistical power to detect differences that would be substantial if cumulated over a longer period.

A potentially important aspect of the relationship between smoking and bone density among perimenopausal women emerged from studies in Denmark. Among women receiving oral estrogen, bone loss was more rapid for smokers than for nonsmokers (Jensen and Christiansen 1988). In contrast, smoking had no effect among women who were not taking estrogens or who were taking them percutaneously. This estrogen-related variation in the effect of smoking on bone density mirrors the variation in fracture risk found in one cohort study of hip fracture (Kiel et al. 1992). In one clinical trial, however, HRT affected the change in bone density similarly among smokers and nonsmokers (Writing Group for the PEPI Trial 1996).

Studies of twins provided additional information on the relationship between smoking and bone density. In these studies, adjustment can be made for known and unknown genetic factors, as well as early-life exposures such as diet. In the largest of these studies of adults, 41 pairs of twins discordant for amount of smoking had measurements of bone density at several anatomic locations, including the lumbar spine, the femoral neck, and the femoral shaft (Hopper and Seeman 1994). At each site, bone density was lower for the heavier smoker. Similar findings were reported from an earlier, smaller analysis (Pocock et al. 1989). A study of female twins aged 10 to 26 years showed no differences in bone mass by smoking status, but the analysis lacked statistical power (Young et al. 1995).

Effects of Covariates

Only a few studies presented both adjusted and unadjusted data from analyses of smoking and bone density (Lindsay 1981; Rundgren and Mellström 1984; Bauer et al. 1993; Nguyen et al. 1994; Ortego-Centeno et al. 1994; Välimäki et al. 1994). In general, any association found was shown both in crude analyses (or those adjusted for age only) and in those adjusted for factors such as body weight and exercise. However, adjustment, particularly for weight, lowers the magnitude of the association. For example, in the Study of Osteoporotic Fractures, the age-adjusted bone mass was 5.8 percent (95 percent CI, 5.0 to 7.7 percent) lower among current smokers than among nonsmokers (Bauer et al. 1993). After further adjustment for multiple factors, including weight, WHR, age at menopause, calcium intake, lifetime activity, and estrogen use, the reduction was 2.1 percent (95 percent CI, 0.2 to 4.0 percent).

Data on the effect of smoking cessation on bone density are scant. In most studies, bone density of women former smokers was intermediate between that of women current smokers and women who had never smoked (Rundgren and Mellström 1984; Davies et al. 1990; Bauer et al. 1993; Cheng et al. 1993; Hollenbach et al. 1993).

Table 3.45. Relative bone density among postmenopausal women for smokers compared with nonsmokers, cross-sectional studies

Study	Population	Smoking status	Relative bone density* (%)	Comments
Hollóʹ et al. 1979	Volunteers Aged 61–75 years Hungary‡	41 smokers 125 nonsmokers	Radius: -6.0†	
Rundgren and Mellström 1984	Population sample Aged 70, 75, 79 years Sweden	111 current smokers 825 never smoked	Calcaneus: -13.6 to -31.4†§	
Sowers et al. 1985b	Population sample Aged 55–80 years United States	72 ever smoked 252 never smoked	Distal radius: +1.6	Adjustment for age, muscle mass
Jensen 1986	Population sample Aged 70 years Denmark§	77 current smokers 103 never smoked	Radius: -5.2	
Jensen and Christiansen 1988	Clinical trial participants Aged 45–54 years Denmark§	56 smokers 54 nonsmokers	Distal forearm: -1.3	
Hansen et al. 1991	Clinical trial participants Menopause in past 3 years Denmark	61 current smokers 117 nonsmokers	Lumbar spine: -3.4 Radius: +1.0 Femoral neck: -5.8† Trochanter: -8.1† Ward's triangle: -8.2†	Findings similar after adjustment for multiple factors
Krall and Dawson-Hughes 1991	Clinical trial participants Low-to-moderate calcium intake Aged 40–70 years United States§	35 current smokers 285 nonsmokers	Lumbar spine: +0.4 Radius: -0.5 Femoral neck: -0.8 Calcaneus: -2.4	Multiple regression: pack-years significant predictor of bone density of radius
Bauer et al. 1993; Orwoll et al. 1996	Volunteers Aged ≥ 65 years United States	970 current smokers 8,734 nonsmokers	Distal radius: -5.8† Femoral neck: -4.5†	Age-adjusted estimates Multivariate-adjusted estimate for radius, -2.1% Age- and weight-adjusted estimate for hip, -1.9%†
Cheng et al. 1993	Responders to population survey Aged 75 years Finland	10 current smokers 161 nonsmokers	Calcaneus: -15	Estimate adjusted for body mass Analysis of variance: statistically significant differences among former and current smokers and persons who never smoked

*Relative bone density = (bone density in smokers – bone density in nonsmokers)/bone density in nonsmokers, based on unadjusted bone density means, unless otherwise noted in comments.
†Statistically significant at $p < 0.05$.
‡Dates of subject recruitment not stated.
§Different age groups.

Table 3.45. Continued

Study	Population	Smoking status	Relative bone density* (%)	Comments
Hollenbach et al. 1993	Responders to population survey Aged 60–100 years United States	181 current smokers 573 nonsmokers	Lumbar spine: -0.3 Mid-radius: -2.6 Ultradistal radius: -1.3 Total hip: -5.0†	Estimates adjusted for multiple factors
Nguyen et al. 1994	Responders to population survey Australia	1,080 participants	Lumbar spine: -5.9† Femoral neck: -7.6†	Estimates adjusted for age, weight
Egger et al. 1996	Responders to study of long-term residents Aged 63–73 years England	23 current smokers 99 never smoked	Lumbar spine: -8.2 Femoral neck: -3.9	Estimates adjusted for multiple factors
Kiel et al. 1996	Participants in cohort study Aged ≥ 70 years United States	51 current smokers 222 never smoked	Never used menopausal estrogen Radial shaft: 0 Ultradistal radius: -5.8 Femoral neck: -0.7 Trochanter: -2.4 Ward's area: -3.4 L2–L4 spine: +4.1	Estimates adjusted for multiple factors
			Ever used menopausal estrogen Radial shaft: -4.4 Ultradistal radius: -19.0† Femoral neck: -3.2 Trochanter: -8.0† Ward's area: -7.3 L2–L4 spine: +2.2	Estimates adjusted for multiple factors
Law et al. 1997a	Healthy volunteers Aged <65 years England	105 current smokers 288 never smokers	Distal radius: 0	

*Relative bone density = (bone density in smokers – bone density in nonsmokers) / bone density in nonsmokers, based on unadjusted bone density means, unless otherwise noted in comments.
†Statistically significant at $p < 0.05$.

Mechanisms

Smoking could affect osteoporosis and osteoporotic fractures through several mechanisms (Law and Hackshaw 1997). A lower bone density in smokers may partially explain associations of smoking with fracture risk. If smoking increases the risk for trauma, it could be a risk factor for fractures through other mechanisms as well.

Body weight tends to be lower among smokers than among nonsmokers (see "Body Weight and Fat Distribution" earlier in this chapter), and this weight difference may itself lead to lower bone density and higher risk for fracture (Cummings et al. 1995). In several analyses, weight explains much of the increased risk associated with smoking (e.g., Lindsay 1981; Bauer et al. 1993). This effect may be derived from

lower estrogen production in relatively thin postmenopausal women; reduced padding of bones, which results in less protection from fracture during falls; and decreased physical loading of weight-bearing bones, which reduces the stimulus for bone growth. The antiestrogenic effect of smoking may also contribute to osteoporosis among women (see "Sex Hormones" earlier in this chapter).

Clinical evidence is consistent with the hypothesis that smoking is associated with increased bone resorption. Levels of parathyroid hormone and 25-hydroxy vitamin D_3 are lower among smokers than among nonsmokers (Gudmundsson et al. 1987; Mellström et al. 1993; Hopper and Seeman 1994), an expected consequence of increased release of calcium from resorbed bone. Perhaps because of this hormonal milieu, smoking leads to decreased absorption of calcium or decreased retention of calcium in the gut (Aloia et al. 1983; Krall and Dawson-Hughes 1991; Clement and Fung 1995).

Other possible mechanisms have been proposed but remain to be confirmed. Vascular effects of smoking may adversely affect bone (Daftari et al. 1994), and the excess exposure to cadmium associated with smoking may be deleterious (Bhattacharyya et al. 1988). A smoking-related resistance to calcitonin has also been described (Holló et al. 1979), but smoking seems to lead to increased calcitonin levels (Tabassian et al. 1988; Eliasson et al. 1993). Finally, smoking probably results in a modest chronic elevation of cortisol levels (Baron et al. 1994a), which may adversely affect bone, and nicotine may have direct effects on osteoblasts (Fang et al. 1991).

Smoking and Fracture Risk

The relationship between smoking and risk for bone fracture has been investigated intensively for fracture of the hip (Law and Hackshaw 1997). A few studies have also addressed fractures of the vertebrae, distal forearm, proximal humerus, ankle, and foot.

Hip Fracture

Six cohort studies that included at least 50 women with hip fracture reported the effect of smoking (Table 3.46). Most of these studies focused on white women, and most of the fractures were observed at older ages, although one investigation from Norway included only middle-aged women (Meyer et al. 1993). In these studies, the age-adjusted RR was consistently elevated, although often only modestly; among current smokers compared with women who had never smoked, the age-adjusted RR varied between 1.2 and 2.1. Risk estimates adjusted for multiple covariates were lower than those adjusted for age only. One study found no overall effect (RR, 1.2) but reported a substantially increased risk associated with smoking among women who took menopausal estrogen (Kiel et al. 1992). Other studies, however, did not find a similar interaction of smoking with estrogen use (Williams et al. 1982; Cauley et al. 1995).

In several cohort studies, the risk for hip fracture was higher among heavy smokers than among light smokers, but statistical tests for trend by amount smoked were not reported (Kiel et al. 1992; Meyer et al. 1993). In the one study that considered the effect of duration of smoking, the number of years of smoking did not affect risk for hip fracture (Meyer et al. 1993). In the cohort studies, the risk among women former smokers was not substantially higher than that among women who had never smoked (Paganini-Hill et al. 1991; Kiel et al. 1992; Meyer et al. 1993; Forsén et al. 1998).

Ten case-control studies that included at least 75 women with hip fracture reported the effect of smoking (Table 3.47). Again, most of the studies focused on older white women. The RRs were fairly consistent: generally elevated but less than 2.0 after adjustment for age, and 1.0 to 1.5 after adjustment for body mass and other factors. Few of the RR estimates were statistically significant. The risk for hip fracture among former smokers was about the same as that among current smokers (La Vecchia et al. 1991b; Grisso et al. 1994; Michaëlsson et al. 1995). In one large multicenter study, however, the RR was lower among women former smokers than among women who had never smoked, after adjustment for age, BMI, and center (0.8; 95 percent CI, 0.6 to 0.97) (Johnell et al. 1995).

The epidemiology of fractures has been more extensively studied among women than among men, probably because of the greater susceptibility of women to fractures. Two cohort studies showed similar relationships between smoking and risk for hip fracture among women and men (Paganini-Hill et al. 1991; Meyer et al. 1993), and one small case-control study reported an effect of smoking on risk for hip fracture among men (Grisso et al. 1991). In contrast, one cohort study and one case-control study of hip fracture—both with limited statistical power—found no association among men (Felson et al. 1988; Hemenway et al. 1994).

In the literature as a whole, the age-adjusted RR for current smoking and hip fracture among women appears to be between 1.5 and 2.0. Adjustment for the lower body weight or BMI of smokers tends to reduce

Table 3.46. Relative risks for hip fracture among women, among current smokers, cohort studies

Study	Study description	Population	Age-adjusted relative risk (95% confidence interval)	Multivariate analysis	
				Relative risk (95% confidence interval)	Adjustment factors
Paganini-Hill et al. 1991	281 cases over 7 years	Retirement community residents Median age 73 years United States	1.8 (1.3–2.0)	1.6 (1.2–2.3)	Age at menarche, parity, body mass, exercise
Kiel et al. 1992	207 cases over 38 years	Framingham study participants Aged 28–62 years United States	1.2 (0.8–1.7)	1.2 (0.8–2.0)	Age, body mass, alcohol use, estrogen use
Scott et al. 1992	218 cases over 6 years	Population sample Aged ≥ 65 years United States	Not reported	1.9	Estrogen use, residence, disability, milk consumption, use of sleeping pills
Meyer et al. 1993	146 cases over 13 years	Population sample Aged 35–49 years Norway	1.5 (0.8–2.6)*	1.4 (0.8–2.5)	Multiple factors, including body mass, height, physical activity
Forsén et al. 1994	421 fractures over 4 years	Population sample Aged >20 years Norway	Not reported	1.8 (1.2–2.6)	Body mass, physical activity, self-reported health status
Cummings et al. 1995	192 fractures over 4.1 years (mean)	White volunteers Aged ≥ 65 years United States	2.1 (1.4–3.3)	1.4 (0.9–2.3)	Multiple factors, including weight change, health status

*Current smoking was defined as smoking ≥ 15 cigarettes / day.

the magnitude of the effect of smoking. This finding suggested that the effect of smoking on hip fracture may act at least partly through the association of smoking with reduced body weight (see "Body Weight and Fat Distribution" earlier in this chapter).

Other Fractures

Some studies have reported an increased prevalence of vertebral fractures among women who smoke (Aloia et al. 1985; Spector et al. 1993), but other investigations have reported no association (Kleerekoper et al. 1989; Cooper et al. 1991; Santavirta et al. 1992) (Table 3.48). Santavirta and colleagues (1992) conducted a large-scale, population-based investigation—by far the largest published survey of the prevalence of vertebral fractures. Among the 27,278 females aged 15 years or older, only 105 had fractures of the thoracic spine. Because no separate risk estimate was given for postmenopausal women, the lack of an effect of smoking in these data does not provide much evidence against an association between smoking and osteoporotic vertebral fractures among older women. Findings in three studies suggested that male smokers are at increased risk for fractures of the vertebrae (Seeman et al. 1983; Santavirta et al. 1992; Scane et al. 1999).

Data are also sparse on the association of smoking with the risk for fractures at other sites among women. The one published study of fractures of the proximal humerus found no association of risk with

Table 3.47. Relative risks for hip fracture among women smokers, case-control studies

Study	Population	Smoking status	Age-adjusted relative risk (95% confidence interval)	Multivariate analysis: Relative risk (95% confidence interval)	Multivariate analysis: Adjustment factors
Paganini-Hill et al. 1981	83 community cases, 166 community controls Postmenopausal, aged <80 years	Postmenopausal smokers 1–10 cigarettes / day ≥ 11 cigarettes / day	 0.9* 1.7*	 1.1* 2.0*	Age, estrogen use, oophorectomy
Williams et al. 1982	160 hospital cases, 567 community controls Aged 50–74 years		Risk elevated in smokers		
Kreiger and Hilditch 1986	98 hospital cases, 884 hospital controls Aged 45–74 years	Ever smoked	1.5† 1.8*	1.3† 1.3*	Age, body mass, lactation, ovariectomy, estrogen use
La Vecchia et al. 1991b	209 hospital cases, 1,449 hospital controls Median age 62 years	Current smokers	1.6 (1.0–2.3)	1.5 (1.0–2.1)	Age, body mass, education, menopausal status, estrogen use, alcohol use
Kreiger et al. 1992	102 hospital cases, 277 hospital controls Mean age 74 years	Current smokers	2.7 (1.5–4.8)	1.7 (0.9–3.3)	Age, body mass, ovariectomy, estrogen use
Jaglal et al. 1993	381 hospital cases, 1,138 controls from population Aged 55–84 years	≥ 60 pack-years	1.4 (0.7–2.8)†	1.2 (0.6–2.5)	Multiple variables, including age, body mass, estrogen use, physical activity
Yamamoto et al. 1993	100 cases, 100 controls Population sample Aged ≥ 35 years	Habitual smokers	1.5 (0.5–4.7)		
Grisso et al. 1994	144 hospital cases, 218 controls from population Aged ≥ 45 years	Current smokers	Not reported	1.3 (0.7–2.6)	Age, body mass, residence area
Johnell et al. 1995	2,086 cases from population, 3,532 controls from population or neighbors Mean age 78 years	Current smokers	0.9 (0.7–1.2)	1.1 (0.8–1.5)	Body mass; mental score; intake of tea, coffee, alcohol, calcium; physical activity
Michaëlsson et al. 1995	247 cases, 893 controls Population sample	Current smokers, >20 pack-years	1.8 (1.0–3.2)‡	1.6 (0.9–3.0)	Multiple variables, including body mass, height, estrogen use, physical activity

*95% confidence interval was not reported.
†Two control groups.
‡Not adjusted for age.

smoking (Kelsey et al. 1992) (Table 3.48). The same investigation showed that smoking was also unrelated to risk for ankle or foot fractures (Seeley et al. 1996). Another study, based on a one-time survey of fractures during the previous 10 years, did not find a significant association between smoking and wrist fractures but did report that smoking was associated with increased risk for ankle fractures (Honkanen et al. 1998). The data on fracture of the distal forearm also indicated that the relationship with smoking is modest at most (Table 3.48). No association with cigarette smoking was found in the only study of distal forearm fractures among men (Hemenway et al. 1994).

Conclusions

1. Postmenopausal women who currently smoke have lower bone density than do women who do not smoke.
2. Women who currently smoke have an increased risk for hip fracture compared with women who do not smoke.
3. The relationship among women between smoking and the risk for bone fracture at sites other than the hip is not clear.

Gastrointestinal Disease

Gallbladder Disease

Gallstones are common in most Western countries. In the United States, autopsy series showed gallstones in 20 percent of women and 8 percent of men older than age 40 years (Johnston and Kaplan 1993). Risk for gallstones increases with age and is higher among women than among men (Johnston and Kaplan 1993). Weight gain and obesity increase risk; alcohol intake appears to be protective (Friedman et al. 1966; Maclure et al. 1989). Because smoking is associated with low body mass (see "Body Weight" earlier in this chapter) and alcohol use (Schoenborn and Benson 1988; Willard and Schoenborn 1995), it is necessary to consider these factors in studies of the relationship between smoking and gallstones.

Several population surveys presented information on the association of cigarette smoking and gallbladder disease. In a sample of 3,418 women and men aged 30, 40, 50, or 60 years who lived in western Copenhagen County, Denmark, ultrasonography of the gallbladder showed a higher prevalence of gallstones among smokers than among persons who had never smoked, particularly men. After adjustment for other risk factors, including family history, BMI, and alcohol intake, the RR for gallstones among women smokers was 1.2 ($p > 0.20$) (Jorgensen 1989) and the RR among male smokers was 1.9 ($p > 0.10$). Among 70-year-olds, the RR was 3.3 among men and 1.6 among women (both $p > 0.05$) (Jorgensen et al. 1990). Ultrasonography of pregnant women in Ireland also showed a positive relationship between smoking and gallstones (Basso et al. 1992). An Italian survey found that the prevalence of gallstones increased with the number of cigarettes smoked per day among men but not among women (Rome Group for Epidemiology and Prevention of Cholelithiasis 1988). No statistically significant overall association was observed between smoking and the presence of gallstones. A survey from Germany found an increased risk among smokers that was not statistically significant (Kratzer et al. 1997).

Several cohort studies reported an association between smoking and gallbladder disease. The Oxford Family Planning Contraceptive Study, which followed up more than 17,000 women and observed 227 cases, found an increased risk for hospitalization for gallstones or cholecystectomy among smokers (Layde et al. 1982). The RR was 1.6 among women who smoked fewer than 15 cigarettes per day and 1.4 among women who smoked 15 or more cigarettes per day. Results were controlled for multiple factors, including age, parity, and BMI. These findings remained unchanged after additional follow-up (Vessey and Painter 1994). In a second British follow-up study of 46,000 women, 1,087 reported a first episode of symptomatic cholelithiasis (Murray et al. 1994). In a comparison of all smokers with nonsmokers, the RR was 1.2 (95 percent CI, 1.1 to 1.3) after adjustment for age, socioeconomic level, and parity. Risk increased with the number of cigarettes smoked per day.

Table 3.48. Relative risks for fractures other than hip fractures among women smokers

Site of fracture/study	Study type	Population	Results (95% confidence interval)
Vertebrae			
Aloia et al. 1985	Age-matched, case-control study	58 cases, 58 controls Volunteer women Mean age 64 years United States	Percentage of smokers; $p < 0.01$ Cases: 59% Controls: 30%
Kleerekoper et al. 1989	Case-control study	266 cases, 263 controls Postmenopausal women screened for osteoporosis trial Aged 45–75 years United States	Percentage of current smokers; $p > 0.05$ Cases: 27% Controls: 20%
Cooper et al. 1991	Survey of general practice patients	1,012 women 79 fractures Aged 48–81 years United Kingdom	Smoking >10 cigarettes / day for >10 years not related to fracture risk
Santavirta et al. 1992	Population-based survey	27,278 girls and women 105 fractures Aged ≥ 15 years Finland	RR* = 1.1 (0.6–2.0) for current smokers Adjusted for age, history of trauma, tuberculosis, peptic ulcer, BMI,† occupation
Distal forearm			
Williams et al. 1982	Population-based, case-control study	184 cases, 567 controls Aged 50–74 years United States	Higher fracture risk in women smokers using estrogens
Kelsey et al. 1992	Cohort study	9,704 women 171 fractures over 2.2 years (mean) Aged ≥ 65 years United States	RR = 1.0 (0.96–1.0) for current smokers (10 cigarettes / day) vs. never smoked
Kreiger et al. 1992	Hospital case-control study	54 fractures Aged 50–84 years Canada	RR = 1.5 (0.9–2.6) for current smokers vs. former smokers or never smoked Adjusted for age, BMI

*RR = Relative risk.
†BMI = Body mass index.

In the U.S. Nurses' Health Study II, 425 of the 96,211 women (aged 25 through 42 years) who were followed up for two years had a diagnosis of gallstones (Grodstein et al. 1994). After adjustment for established risk factors, current cigarette smokers were at a slightly higher risk for gallstones than were nonsmokers (RR, 1.3; 95 percent CI, 1.0 to 1.7). No evidence was found for a dose-response relationship. Former smokers were not at higher risk than those who had never smoked. In a more detailed analysis of incident cases of symptomatic gallstones and of cholecystectomies during six years of follow-up of the U.S. Nurses' Health Study cohort, Stampfer and colleagues (1992) observed an increase in risk with increasing number of cigarettes smoked per day. Women who smoked 25 to 34 cigarettes per day had a RR of 1.3 (95 percent CI, 1.1 to 1.6) compared with women who had never smoked; those who smoked 35 or more cigarettes per day had a RR of 1.5 (95 percent CI, 1.2 to 1.9). These results are consistent with findings from a study of 868 female twins; the RR among smokers compared with persons who had never smoked was 1.8 (95 percent CI, 1.0 to 3.3) (Petitti et al. 1981). Smoking was also a risk factor for the

Table 3.48. Continued

Site of fracture/study	Study type	Population	Results (95% confidence interval)
Mallmin et al. 1994	Population-based, case-control study	385 cases, 385 controls Aged 40–80 years Sweden	RR = 0.9 (0.5–1.6) for current smokers Adjusted for multiple factors, including age, BMI, physical activity, hormone use
Honkanen et al. 1998	Retrospective survey	12,192 women 345 fractures Aged 47–56 years Finland	Current smoking RR = 0.9 (0.6–1.4) Any smoking RR = 0.6 (0.3–1.1) for 1–10 cigarettes / day RR = 1.4 (0.9–2.3) for >10 cigarettes / day Adjusted for age, BMI, menopausal status, chronic health disorders
Proximal humerus			
Kelsey et al. 1992	Cohort study	9,704 women 79 fractures over 2.2 years (mean) Aged ≥ 65 years United States	RR = 1.2 (0.9–1.6) for current smokers (10 cigarettes / day)
Ankle			
Seeley et al. 1996	Cohort study	9,704 women 191 fractures over 5.9 years (mean) Aged ≥ 65 years	No association for current smokers
Honkanen et al. 1998	Retrospective survey	12,192 women 210 fractures Aged 47–56 years Finland	Current smoking RR = 2.2 (1.6–3.2) Any smoking RR = 1.6 (0.9–2.8) for 1–10 cigarettes / day RR = 3.0 (1.9–4.6) for >10 cigarettes / day Adjusted for age, BMI, menopausal status, chronic health disorders
Foot			
Seeley et al. 1996	Cohort study	9,704 women 204 fractures over 5.9 years (mean) Aged ≥ 65 years	No association for current smokers

development of gallstones among women and men in a population followed up with repeat ultrasonography (Misciagna et al. 1996). Finally, an Australian case-control study suggested an adverse effect of smoking on the risk for gallbladder disease among women younger than age 35 years (McMichael et al. 1992).

In contrast with these positive findings, another cohort study reported no relationship between smoking and gallbladder disease among 1,303 women in a California retirement community (Mohr et al. 1991). A case-control study from Italy also found no substantial association between smoking and surgery for gallstone disease among women and men (La Vecchia et al. 1991a). Data from the Framingham study suggested lower risk for cholelithiasis or cholecystitis among female smokers than among female nonsmokers, but the difference in risk was not statistically

significant and no adjustment was made for alcohol intake (Friedman et al. 1966). Unadjusted analyses from a small population survey in Italy also suggested an inverse association between smoking and gallbladder disease among women and men (Okolicsanyi et al. 1995), as did a small case-control study in Greece (Pastides et al. 1990). Another retrospective study also showed that smoking was associated with a lower risk for symptomatic gallbladder disease among both women and men (Rhodes and Venables 1991). However, the low response rate for cases (62 percent) and the procedures for selection of the control subjects raise concerns about the validity of these findings.

Peptic Ulcer Disease

Peptic ulcer disease comprises a group of chronic ulcerative conditions that primarily affect the proximal duodenum and the gastric mucosa. The 1979 Surgeon General's report on smoking and health noted a strong association between peptic ulcer and smoking (USDHEW 1979). This conclusion was reaffirmed in the 1990 Surgeon General's report on the health benefits of smoking cessation, which also concluded that smoking impairs the healing of ulcers and causes an increased risk for recurrence that decreases after smoking cessation (USDHHS 1990).

Several studies have demonstrated an increased prevalence of peptic ulcers among women who smoke compared with women who do not smoke (Higgins and Kjelsberg 1967; Alp et al. 1970; Friedman et al. 1974). In a Norwegian case-control study of patients with radiographic diagnosis of a first gastric or duodenal ulcer and no family history of peptic disease, the RR among women smokers compared with women nonsmokers was 2.0 for duodenal ulcers and 1.3 for gastric ulcers (no CIs were provided). A population survey in Göteborg, Sweden, reported similar findings (Schöön et al. 1991). Women former smokers tended to have RRs between those among women current smokers and women who had never smoked. Women who smoked also had an increased risk for incident ulcers.

Prospective studies provided strong support for a relationship between smoking and incident peptic ulcer among women. The NHANES Epidemiologic Followup Study (Anda et al. 1990b) found 140 incident cases of peptic ulcer during 12.5 years of follow-up among 2,851 women. After adjustment for age, education, regular use of aspirin, number of cups of coffee or tea consumed per day, and alcohol use, the RR among current smokers was 1.8 (95 percent CI, 1.2 to 2.6). The RR increased with the number of cigarettes smoked per day. Among former smokers, the RR was 1.3 (95 percent CI, 0.7 to 2.9). An estimated 20 percent of incident cases of peptic ulcer during the study period was attributable to current smoking.

A prospective study from Norway also found an elevated risk for incident peptic ulcer among women who smoked; effects were similar for gastric and duodenal ulcers and were similar among women and men (Johnsen et al. 1994). Likewise, in a large cohort study in the United Kingdom, women who smoked had an increased risk for reported gastric and duodenal ulcers (Vessey et al. 1992). However, in a Finnish twin study, smoking was a clear risk factor for incident peptic ulcer disease only among men; risks were not significantly elevated among women smokers (Räihä et al. 1998).

Thus, data for women—like data for men—support a relationship between smoking and the incidence of peptic ulcer. At comparable levels of smoking, the mortality from this disorder is equivalent for women and men (Kurata et al. 1986). In a meta-analysis, the RR for peptic ulcer among women smokers compared with women nonsmokers was 2.3 (95 percent CI, 1.9 to 2.7); about 23 percent of the peptic ulcers in the populations studied could be attributed to smoking (Kurata and Nogawa 1997).

Little research has been conducted on the effects of smoking or smoking cessation on the healing or recurrence of peptic ulcer among women. Breuer-Katschinski and associates (1995) reported findings on the influence of smoking patterns on relapse of duodenal ulcers among female and male patients taking ranitidine. They observed that 18.0 percent of patients who had never smoked and 23.4 percent of patients who were smoking at the start of the trial had relapse of duodenal ulcers during the two-year study period. Patients who had stopped smoking had significantly fewer relapses than did continuing smokers ($p < 0.001$), and those who had stopped smoking before study entry had relapse significantly more often than did those who had never smoked ($p < 0.001$). In an earlier double-blind trial of the effects of cimetidine and ranitidine on the healing and relapse of peptic ulcer, women who smoked (42 percent) tended to have lower healing rates than did women nonsmokers (83 percent); no p value was given (Peden et al. 1981). Similar findings among women and men combined have also documented the deleterious effects of smoking on ulcer relapse (Berndt and Gütz 1981; Sonnenberg et al. 1981; Korman et al. 1983; Kratochvil and Brandstätter 1983; Lee et al. 1984; Sontag et al. 1984; Bertschinger et al. 1987; Van Deventer et al.

1989). One study of self-reported peptic ulcers that was based on data from a national survey found a strong association of smoking with chronic ulcers but no association with incident ulcers (Everhart et al. 1998). No gender-specific results were presented.

These findings emphasize the importance of smoking in perpetuating ulcers that develop, at least with treatment regimens used in the early 1990s. However, in studies conducted largely among men, smoking has not been a risk factor for ulcer recurrence after eradication of *Helicobacter pylori* (Borody et al. 1992; Graham et al. 1992; Bardhan et al. 1997; Chan et al. 1997). Smoking may thus have a smaller impact on ulcer healing under newer treatment regimens.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) includes three chronic gastrointestinal diseases: ulcerative colitis, ulcerative proctitis, and Crohn's disease. These three diseases affect about 1 per 1,000 persons in the United States (Everhart 1994).

Ulcerative Colitis and Ulcerative Proctitis

The first published investigation of the relationship between smoking and IBD demonstrated a much lower prevalence of smoking among patients with ulcerative colitis than among control subjects (Harries et al. 1982). Since then, both case-control and prospective studies have addressed the relationship between smoking and risk for ulcerative colitis. The results are summarized in Table 3.49. All except one of the studies in the table reported decreased risk associated with current smoking compared with never smoking, and all studies except one showed increased risk with former smoking.

The relationship between smoking and ulcerative colitis appears to be present among both genders. Seven studies reported RRs separately for women and men and found similar results among both genders (Gyde et al. 1984; Logan et al. 1984; Benoni and Nilsson 1987; Franceschi et al. 1987; Tobin et al. 1987; Persson et al. 1990; Nakamura et al. 1994). Moreover, the cohort studies that included women only reported findings similar to those of the case-control studies that included both women and men (Vessey et al. 1986; Logan and Kay 1989).

Two relatively small, randomized controlled trials of transdermal administration of nicotine as treatment for active ulcerative colitis symptoms showed benefit after four weeks (Sandborn et al. 1997) and six weeks (Pullan et al. 1994) of treatment. One of these studies reported that effects were similar among women and men (Pullan et al. 1994).

Crohn's Disease

In contrast to the risk for ulcerative colitis, the risk for Crohn's disease seems to be increased by cigarette smoking (Table 3.50). Both case-control and cohort studies found higher risks among current smokers and, less markedly, among former smokers than among persons who had never smoked. Of the five studies that presented gender-specific results, all showed higher RRs for current smoking among women than among women and men combined (Table 3.50).

For several reasons, the clinical course of Crohn's disease in relation to smoking has been studied more successfully than that of ulcerative colitis. The higher prevalence of smoking among patients with Crohn's disease facilitates the study of its effects on the clinical severity of the disease. Also, because severe Crohn's disease often leads to surgical resection, the number and extent of surgical resections provide a convenient proxy measure for disease severity.

Five retrospective studies and one prospective study examined the association between smoking and severity of Crohn's disease; the findings were fairly consistent. Patients who smoked tended to have more frequent hospital admissions (Holdstock et al. 1984), early treatment with surgery rather than drugs alone (Lindberg et al. 1992), and repeated surgical treatment (Sutherland et al. 1990; Lindberg et al. 1992). Moreover, smokers have a higher risk for disease recurrence than do nonsmokers, and they tend to need immunosuppressive therapy more often (Duffy et al. 1990; Cottone et al. 1994; Cosnes et al. 1996; Timmer et al. 1998).

Conclusions

1. Some studies suggest that women who smoke have an increased risk for gallbladder disease (gallstones and cholecystitis), but the evidence is inconsistent.
2. Women who smoke have an increased risk for peptic ulcers.
3. Women who currently smoke have a decreased risk for ulcerative colitis, but former smokers have an increased risk—possibly because smoking suppresses symptoms of the disease.
4. Women who smoke appear to have an increased risk for Crohn's disease, and smokers with Crohn's disease have a worse prognosis than do nonsmokers.

Table 3.49. Relative risks for ulcerative colitis among former and current smokers, case-control and cohort studies

Study	Number of cases	Time in relation to diagnosis	Relative risk (95% confidence interval)*	
			Former smokers	Current smokers
Case-control				
Harries et al. 1982	230	A[†]	Increased risk	Decreased risk
Jick and Walker 1983	239	A	1.2 (0.8–1.8)	0.3 (0.2–0.4)
Gyde et al. 1984	74	A	Decreased risk[‡]	Decreased risk[§]
	31[Δ]	A	Decreased risk[‡]	Decreased risk[§]
Logan et al. 1984[¶]	120	D**	NR[††]	Decreased risk[‡‡]
	64[Δ]	D	NR	Decreased risk[‡‡]
Thornton et al. 1985	30	D	Increased risk[§]	Decreased risk[§]
Burns 1986	63	A	Increased risk[§]	Decreased risk[‡‡]
Benoni and Nilsson 1987[¶]	173	D	1.6	0.3[§]
	80[Δ]	D	1.8	0.3[§]
Boyko et al. 1987[¶]	212	D	1.9 (1.1–3.5)	0.6 (0.4–1.0)
Franceschi et al. 1987	124	D	2.7 (1.5–4.9)	0.5 (0.3–1.0)
	49[Δ]	D	2.6 (1.0–7.2)	1.1 (0.4–2.2)
Tobin et al. 1987	143	D	1.5 (0.8–2.8)	0.2 (0.1–0.3)[‡‡]
	81[Δ]	D	NR	Decreased risk
Lindberg et al. 1988[¶]	258	D	2.3 (1.4–3.9)	0.7 (0.4–1.0)
Lorusso et al. 1989	84	D	3.0 (0.9–10.3)	Decreased risk[‡]
Persson et al. 1990[¶]	145	D	2.2 (0.9–5.0)	0.8 (0.5–1.3)
	63	D	1.6 (0.6–4.2)	0.7 (0.4–1.4)
Samuelsson et al. 1991	167	A	1.1 (0.6–2.3)	0.5 (0.3–0.9)
Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan 1994	76	D	2.4 (1.0–6.0)	0.7 (0.2–2.0)[§§]

*Compared with those who never smoked, unless otherwise indicated.
[†]A = Smoking status ascertained after diagnosis.
[‡]Statistically significant differences in relative risk by smoking status, $p < 0.05$.
[§]Percentage of smokers differed significantly between cases and controls; $p < 0.05$.
[Δ]Number of women.
[¶]Population-based study.
**D = Smoking status ascertained before or soon after diagnosis.
[††]NR = Not reported.
[‡‡]Compared with former smokers and those who never smoked.
[§§]≥ 20 cigarettes / day.

Table 3.49. Continued

Study	Number of cases	Time in relation to diagnosis	Relative risk (95% confidence interval)*	
			Former smokers	Current smokers
Case-control (continued)				
Nakamura and Labarthe 1994;	384[Δ]	D	1.7 (1.0–2.9)	0.3 (0.2–0.5)
Nakamura et al. 1994	199		2.3 (0.9–5.7)	0.4 (0.2–1.0)
Rutgeerts et al. 1994	174	A	NR	Decreased risk[‡‡]
Silverstein et al. 1994	100	D	1.2 (0.5–3.0)	0.1 (0.1–0.4)
Reif et al. 1995	54	A	No difference	No difference
Corrao et al. 1998	594	D	3.0 (2.1–4.3)	0.9 (0.7–1.2)
Cohort				
Vessey et al. 1986	24[Δ]	D	Increased risk	Decreased risk[‡‡]
Logan and Kay 1989	78	D	NR	Decreased risk[‡‡]

*Compared with those who never smoked, unless otherwise indicated.
[Δ]Number of women.
[‡‡]Compared with former smokers and those who never smoked.

Arthritis

Arthritic diseases are a diverse group of disorders that can lead to considerable morbidity among women (Lawrence et al. 1989b). These disorders prominently affect the joints but may also affect other organs. In this section, the three most common arthritic disorders are discussed: rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE). RA and SLE are systemic immune diseases characterized by the production of antibodies that participate in the disease process (Firestein 1997; Lahita 1997). OA, on the other hand, is largely a degenerative joint disorder (Solomon 1997). RA and SLE are more common among women than among men; OA occurs with similar frequency in both genders (Firestein 1997; Harris 1997; Lahita 1997; Solomon 1997).

Rheumatoid Arthritis

The prevalence of RA in the United States is approximately 1 percent, and it is three times higher among women than among men. Characteristic clinical features include bilateral symmetric inflammation of small and large joints in both upper and lower extremities.

Several cohort studies reported findings on the relationship between smoking and RA. In a study of 17,000 women recruited from family-planning clinics in the United Kingdom, the age-adjusted risk for RA among women who smoked was significantly increased (Vessey et al. 1987). Those who smoked 15 or more cigarettes per day had more than twice the risk among nonsmokers. The analysis was based on only 78 cases, however, and few details were provided. In contrast to these findings, data from the U.S. Nurses' Health Study cohort suggested no relationship between smoking and RA (Hernandez-Avila et al. 1990), and a study of 24,445 women in Finland found that women who smoked 1 to 14 cigarettes per day did not have an increased risk for either seropositive or seronegative RA compared with nonsmokers (Heliovaara et al. 1993).

Table 3.50. Relative risks for Crohn's disease among former and current smokers, case-control and cohort studies

Study	Number of cases	Time in relation to diagnosis	Relative risk (95% confidence interval)*	
			Former smokers	Current smokers
Case-control				
Somerville et al. 1984[†]	81	D[‡]	NR[§]	4.8 (2.4–9.7)[Δ¶]
	52**	D	NR	8.2 (2.8–24.0)[Δ¶]
Thornton et al. 1985	30	D	Increased risk	Increased risk[††]
Burns 1986	25	A[‡‡]	Decreased risk	Increased risk[††]
Benoni and Nilsson 1987	155	D	0.7	2.2[‡]
	90**	D	0.2	2.7[‡]
Franceschi et al. 1987	109	D	3.5 (1.5–8.0)	4.2 (2.3–7.7)
	49**	D	3.0 (0.9–10.6)	4.8 (2.0–11.3)
Tobin et al. 1987	132**	D	1.6 (0.6–4.1) NR	3.1 (1.6–6.0)[¶]
Lindberg et al. 1988[†]	144	D	1.9 (0.8–4.3)	2.0 (1.3–3.1)
Silverstein et al. 1989	115		1.5 (0.7–2.9)	3.7 (1.9–7.1)
Persson et al. 1990[†]	60	D	1.2 (0.5–3.1)	1.3 (0.7–2.6)
	89**	D	1.0 (0.3–4.0)	5.0 (2.7–9.2)
Katschinski et al. 1993	83	D	1.1 (0.3–4.3)	3.8 (1.5–9.5)
Reif et al. 1995	33	A	Increased risk	Decreased risk[††]
Corrao et al. 1998	225	D	1.7 (0.9–3.3)	1.7 (1.1–2.6)
Cohort				
Vessey et al. 1986	18**	D	Decreased risk[§§]	Increased risk[††]
Logan and Kay 1989	42**	D	NR	Increased risk[¶]

*Compared with those who never smoked, unless otherwise indicated.
[†]Population-based study.
[‡]D = Smoking status ascertained before or soon after diagnosis.
[§]NR = Not reported.
[Δ]$p < 0.05$.
[¶]Compared with former smokers and those who never smoked.
**Number of women.
[††]Percentage of smokers differed significantly between cases and controls; $p < 0.05$.
[‡‡]A = Smoking status ascertained after diagnosis.
[§§]$p > 0.05$.

Several case-control studies addressed the relationship between smoking and risk for RA. Voigt and colleagues (1994) identified 349 patients with RA through Group Health Cooperative of Puget Sound, Washington. The investigators reported a RR of 1.5 (95 percent CI, 1.0 to 2.0) among women with 20 or more pack-years of smoking compared with women who had never smoked. RRs were similar in premenopausal and postmenopausal groups. In a case-control analysis of 120 female twins, current smokers

were at much higher risk than were nonsmokers for developing RA (RR, 3.8; 95 percent CI, 1.4 to 13.0) (Silman et al. 1996). The RR among males was similar. A population-based study from England also reported findings consistent with an increased risk among smokers (Symmons et al. 1997). A study from Norway suggested an increased risk for seronegative RA among women who smoked (RR, 1.5; 95 percent CI, 0.99 to 2.4), but no association was found for seropositive RA(RR, 0.7; 95 percent CI, 0.4 to 1.2) (Uhlig et al. 1999). The RRs among men were higher. In contrast to these reports, a clinic-based, case-control study found a reduced risk for RA among women smokers compared with nonsmokers (Hazes et al. 1990). The use of controls drawn from rheumatology outpatient clinics may account for the discrepancy between these results and those from other published studies.

Osteoarthritis

Osteoarthritis, a degenerative joint disease, is the most common form of arthritis and the leading cause of rheumatic disability in the United States (Lawrence et al. 1989b). Body weight, which is lower among smokers, must be taken into account when interpreting epidemiologic data on smoking and OA.

Cross-sectional data from the first NHANES showed an inverse relationship between cigarette smoking and the risk for OAof the knee, as diagnosed by radiography among 2,765 women. In age-adjusted analyses, the RR among female smokers compared with nonsmokers was 0.7 (95 percent CI, 0.5 to 0.99); the association was similar after adjustment for BMI and other risk factors, although not statistically significant (Anderson and Felson 1988). The RRs among men were similar. Extending this work, the investigators analyzed follow-up data from the Framingham Heart Study (Felson et al. 1989) and reported an inverse association between smoking and the prevalence of radiographically diagnosed OA of the knee. The RR per 20 cigarettes smoked per day was 0.7 (95 percent CI, 0.6 to 0.95). This association persisted after adjustment for age, gender, weight, physical activity, and participation in sports. These investigators confirmed this finding in a subsequent longitudinal analysis (Felson et al. 1997), in which women smokers had reduced risk for incident OA diagnosed by radiography. Similarly, in a survey conducted in North Carolina, female and male smokers had a lower prevalence of OAof the knee diagnosed by radiography, even after adjustment for factors such as obesity and race (RR, 0.7; 95 percent CI, 0.6 to 0.9) (Jordan et al. 1995).

An inverse association between smoking and clinical OA of the knee was also observed in a British clinic-based study of women: for ever smoking, the RR was 0.3 (95 percent CI, 0.1 to 0.6) (Samanta et al. 1993). Also, in a Swedish radiographic survey of 79-year-old women and men, RR was 0.7 (95 percent CI, 0.4 to 0.7) for current smoking compared with never smoking, after adjustment for gender and BMI (Bagge et al. 1991). However, findings in a detailed British study of OA among 985 women were contrary (Hart and Spector 1993). After adjustment for age and BMI, no reduction in risk for OA of the knee was found among smokers compared with nonsmokers, but the number of cases was small and the CIs for the estimated RRs were wide.

Data on OAof the hip have not consistently suggested a relationship with cigarette smoking. One study reported that women who smoked had a lower prevalence of hip OA than did those who did not smoke (Samanta et al. 1993); another investigation found a lower risk among men who smoked than among those who did not, but no association was found among women (Cooper et al. 1998). Other studies reported no association of hip OAwith smoking among women and men (Jordan et al. 1995) or even suggested an increased risk among women who smoked (Vingard et al. 1997). Small-joint OA (e.g., of the hand) appears to be unrelated to smoking (Bagge et al. 1993; Hart and Spector 1993).

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterized by disturbances of the immune system that lead to increased production of antibodies, formation of immune complexes, and tissue injury.

Some studies suggested an increased risk for SLE among women who smoke, but overall the data on smoking and SLE have been somewhat inconsistent. In a case-control study that included 50 female patients, the RR among current smokers compared with women who had never smoked was 2.0 (95 percent CI, 0.5 to 4.8) (Benoni et al. 1990). In a larger Japanese case-control study of SLE among women, the RR for SLE among current smokers compared with those who had never smoked was 2.3 (95 percent CI, 1.3 to 4.0) (Nagata et al. 1995). In a case-control study in England with 150 women and men with SLE, risk among current smokers was increased compared with those who had never smoked (RR, 2.0; 95 percent CI, 1.1 to 3.3) (Hardy et al. 1998). However, the

prospective U.S. Nurses' Health Study found no significant relationship between smoking and the risk for SLE (Sanchez-Guerrero et al. 1996). On the basis of data from 85 cases of SLE that met established criteria for diagnosis, the age-adjusted RR was 1.1 (95 percent CI, 0.7 to 1.8) among women current smokers compared with women who had never smoked. Furthermore, no substantial relationship was observed between the number of cigarettes smoked per day and risk for SLE among current smokers.

Conclusions

1. Some but not all studies suggest that women who smoke may have a modestly elevated risk for rheumatoid arthritis.
2. Women who smoke have a modestly reduced risk for osteoarthritis of the knee; data regarding osteoarthritis of the hip are inconsistent.
3. The data on the risk for systemic lupus erythematosus among women who smoke are inconsistent.

Eye Disease

Cataract

Cataract (opacity in the lens of the eye) is a major health concern among older adults in the United States. However, only a few studies have specifically addressed the relationship between smoking and the risk for cataract among women. In the Beaver Dam (Wisconsin) Eye Study, a cross-sectional analysis of 2,762 women showed a strong relationship between smoking and cataract (Klein et al. 1993b). The age-adjusted RR for each 10 pack-years of smoking was significantly elevated for nuclear sclerosis (RR, 1.1; 95 percent CI, 1.0 to 1.2), posterior subcapsular cataract (RR, 1.1; 95 percent CI, 0.98 to 1.1), and a history of cataract surgery (RR, 1.1; 95 percent CI, 1.03 to 1.2) but not for cortical opacity (RR, 1.02; 95 percent CI, 0.96 to 1.1).

Prospective data from the U.S. Nurses' Health Study also showed a strong relationship between smoking and cataract extraction (Hankinson et al. 1992). A total of 493 cases were reported in the cohort of 121,700 women who were followed up since 1976. The multivariate RR was 1.6 (95 percent CI, 1.2 to 2.3) among women with more than 65 pack-years of smoking compared with women who had never smoked. Risk was generally lower among women former smokers than among women who continued to smoke, although those who had formerly smoked more than 35 cigarettes per day had a higher risk than did those who had never smoked (RR, 1.7; 95 percent CI, 1.0 to 2.7).

Several studies that included both women and men reported a relationship between smoking and risk for cataract (Klein et al. 1985; Flaye et al. 1989; Leske et al. 1991; Cumming and Mitchell 1997; Hiller et al. 1997; Leske et al. 1998), but others found no significant association after adjustment for other factors (Bochow et al. 1989; Mohan et al. 1989; Italian-American Cataract Study Group 1991). In studies of this association among men, findings were generally similar to those reported among women (West et al. 1989; Christen et al. 1992; Klein et al. 1993b).

Age-Related Macular Degeneration

Age-related macular degeneration is a relatively common disorder among older adults. In its mildest forms, it may affect more than one-fourth of the U.S. population older than 75 years. Advanced macular degeneration is an important cause of visual impairment and blindness (Klein and Klein 1996).

In a cohort study of more than 30,000 women, smoking was associated with an increased risk for macular degeneration (Seddon et al. 1996). Women who smoked 25 or more cigarettes daily were 2.4 times as likely to have macular degeneration (adjusted RR of 2.4; 95 percent CI, 1.4 to 4.0) as were women who had never smoked. The RR increased with the number of pack-years of smoking and did not decline even after 15 years of cessation. In a related cohort investigation, similar findings were reported among men (Christen et al. 1996).

A population-based, cross-sectional analysis reported a higher risk for exudative age-related macular degeneration among women current smokers than among women who had never smoked (RR, 2.5; 95 percent CI, 1.0 to 6.2) (Klein et al. 1993c). The RR

among men smokers was similar. However, no association was found between smoking and less advanced age-related maculopathy among either women or men. In the follow-up phase of the study, current smoking at baseline was associated with an increased risk for some lesions associated with early, age-related macular degeneration and with progression to advanced disease. In general, the associations were stronger among men than among women (Klein et al. 1993c). Another investigation reported that men smokers had an increased risk for macular degeneration with visual impairment, but no association was found among women smokers (Hyman et al. 1983). In contrast, a similar study from Australia found risk to be increased among both women and men who smoked (Smith et al. 1996): women current smokers were 5.4 times as likely as women who had never smoked to have macular degeneration (RR of 5.4; 95 percent CI, 2.4 to 12.4). Studies in which data for women and men were combined have generally reported that smoking is a risk factor for macular degeneration or that smokers with a diagnosis of this condition have a worse prognosis than do nonsmokers (Macular Photocoagulation Study Group 1986; Eye Disease Case-Control Study Group 1992; Tsang et al. 1992; Vinding et al. 1992; Holz et al. 1994; Hirvelä et al. 1996).

Open-Angle Glaucoma

Open-angle glaucoma is a progressive optic neuropathy often associated with high intraocular pressure (ocular hypertension). A series of population surveys have investigated the relationship between cigarette smoking and the risk for open-angle glaucoma. All reported that smoking was unrelated to this disease (Klein et al. 1993a; Ponte et al. 1994; Stewart et al. 1994; Leske et al. 1995).

Conclusions

1. Women who smoke have an increased risk for cataract.
2. Women who smoke may have an increased risk for age-related macular degeneration.
3. Studies show no consistent association between smoking and open-angle glaucoma.

HIV Disease

Smoking has been associated with infection with human immunodeficiency virus type 1 (HIV-1) among women, but it is unclear whether this association is due to an underlying relationship between smoking and high-risk sexual behavior, biological effects of smoking, or both. An association between smoking and increased risk for HIV-1 infection among women was first identified in a longitudinal study of pregnant women in Haiti (Boulos et al. 1990). The association persisted after adjustment for marital status, age, number of sexual partners in the year before pregnancy, and serologic evidence of syphilis. The risk for HIV-1 infection also appeared to increase with the number of cigarettes smoked. A nested case-control study was subsequently performed in the same population to more fully assess the contribution of sexual practices, other substance use, parenteral exposures, and other potential confounders (Halsey et al. 1992). This study also reported an independent association between smoking and HIV-1 infection.

Smoking also has been associated with HIV-1 infection among homosexual and heterosexual men (Newell et al. 1985; Burns et al. 1991; Penkower et al. 1991; Siraprapasiri et al. 1996) and with other STDs among both women and men (Daling et al. 1986; Aral and Holmes 1990; Willmott 1992). Whether these associations are causal or a coincidence of high-risk sexual behavior is unclear (Aral and Holmes 1990). The influence of smoking on progression of HIV-1 infection and on survival among women has not been examined in cohorts sufficiently large for meaningful interpretation.

Conclusion

1. Limited data suggest that women smokers may be at higher risk for HIV-1 infection than are nonsmokers.

Facial Wrinkling

Wrinkling of the facial skin occurs with age and with long-term exposure to sunlight. Except for these two recognized factors, little is known about the causes of wrinkling. Four studies reported that smoking is associated with prominent skin wrinkling, particularly in the lateral periorbital "crow's foot" area of the face. Ippen and Ippen (1965) defined "cigarette skin" as pale, grayish, and wrinkled, especially on the cheeks, and thickened between the wrinkles. In a study of women 35 through 84 years old, 66 of 84 smokers (79 percent) and 27 of 140 nonsmokers (19 percent) had cigarette skin. Because no adjustment was made for differences between smokers and nonsmokers in age or sun exposure, the independent effect of smoking in that study cannot be assessed (Ippen and Ippen 1965).

One researcher examined facial wrinkles and smoking status among 589 women aged 30 through 70 years (Daniell 1971). Skin wrinkling was assessed in the crow's foot area and the adjacent forehead and cheeks and was graded in six categories of increasing severity. Ratings of 4 to 6 (more severe wrinkling) were more prevalent among smokers than among nonsmokers and were also more common with increasing age and sun exposure. According to calculations from the published data, smokers were significantly more likely than nonsmokers to be evaluated as having prominent wrinkling (categories 4 to 6 vs. categories 1 to 3). All women with ratings in the most severe wrinkling category were smokers. Severity of wrinkling increased with duration of smoking and number of cigarettes smoked daily. The occurrence of prominent wrinkling was as common among women smokers aged 40 through 49 years as among women nonsmokers 20 years older. The association of smoking with prominent wrinkling was found in each age, sex, and sun-exposure group. Although these findings suggested that smoking is associated with skin wrinkling among women, the measurement of wrinkling was not precise. An attempt was made to use a blinded procedure in the assessment of wrinkling, but participants were patients and friends of the investigator, who may have known the smoking status of many of them.

Two subsequent studies of the effect of smoking on facial wrinkling and other facial changes did not provide adequate data to assess the effect among women (Allen et al. 1973; Model 1985). In another study, Kadunce and colleagues (1991) used Daniell's categories of wrinkling in a blinded procedure to evaluate wrinkling shown in standardized photographs of the right temple area of the face for 59 white women aged 35 through 59 years. After adjustment for age, sun exposure, and skin pigmentation, smoking was associated with an increased risk for prominent wrinkling of the temple area of the face, but the study included only 12 nonsmokers and the result was not statistically significant (RR, 4.7; 95 percent CI, 0.2 to 89.1).

Other investigators studied 463 white women aged 40 through 69 years enrolled in an HMO in northern California (Ernster et al. 1995). Smoking status, pack-years of smoking, age, and sun exposure were assessed by questionnaire. Examiners who were blinded to the smoking status of the women visually evaluated several areas of the face by using standardized procedures. The examiners determined facial wrinkle category, a dichotomous variable, and facial wrinkle score, a continuous variable based on number, length, and depth of wrinkles. Adjustment for age, sun exposure, and BMI indicated that women current smokers were three times as likely as women who had never smoked to have moderate or severe facial wrinkling (RR, 3.1; 95 percent CI, 1.6 to 5.9). Former smokers were also more likely to have moderate or severe wrinkling than were women who had never smoked (RR, 1.8; 95 percent CI, 1.0 to 3.1). Risk for wrinkling increased with pack-years of smoking.

Smoking has been shown to produce short-term decreases in capillary and arteriolar blood flow in the skin (Reus et al. 1984; Richardson 1987) and in oxygen tension in subcutaneous wound tissue (Jensen et al. 1991). These findings suggest that chronic ischemia of the dermis may contribute to wrinkling. In the lung, cigarette smoke damages collagen and elastin, which are connective tissue elements that help to maintain the integrity of the skin. Facial wrinkling may also be promoted by chronic squinting caused by the irritating effects of smoke on the nostrils and eyes.

Conclusion

1. Limited but consistent data suggest that women smokers have more facial wrinkling than do nonsmokers.

Depression and Other Psychiatric Disorders

Depression, anxiety disorders, and bulimia and binge eating are considerably more prevalent among women than among men (Halmi et al. 1981; Pyle et al. 1983; Killen et al. 1987; Patton et al. 1990; Timmerman et al. 1990; Weissman et al. 1991; Johnson et al. 1992). Thus, these psychiatric disorders, in their own right, constitute a public health problem among women and take a large toll in terms of lost productivity and diminished quality of life. To the extent that they are associated with an increased likelihood of smoking or greater difficulty in stopping, the health-related consequences of these disorders are magnified. A recent analysis of data from the National Comorbidity Survey, a nationally representative study conducted from 1991 through 1992, compared smoking prevalence among respondents with no mental illness (22.5 percent), those who had been mentally ill at any time in their lives (34.8 percent), and those with active mental illness in the past month (41.0 percent) (Lasser et al. 2000). The RR for being a current smoker among those with mental illness in the past month, adjusted for age, sex, and region of the country, was 2.7 (95 percent CI, 2.3 to 3.1). The mental illness category grouped together many of the psychiatric disorders considered individually below, and gender-specific results were not presented. Still, the authors estimated that persons with a diagnosable mental disorder in the past month consume nearly half of the cigarettes smoked in the United States, and they underscored the importance of addressing smoking prevention and cessation efforts to the mentally ill.

Smoking and Depression

Hughes and associates (1986) reported an excess of both female and male smokers among psychiatric outpatients with major depression compared with local and national population-based samples. Glassman and colleagues (1988) observed that 61 percent of the 71 participants in a smoking cessation trial had a history of clinical depression, even though they were not currently depressed. Subsequently, in analyses of a community database, Glassman and colleagues (1990) confirmed their clinical observation of an excess of depressed persons among smokers. Using the St. Louis, Missouri, node of the Epidemiological Catchment Area survey, they obtained information on psychiatric diagnosis and smoking for 3,213 respondents. The lifetime prevalence of major depressive disorder (MDD) among smokers (6.6 percent) was more than double that among nonsmokers (2.9 percent), and smokers with a lifetime history of clinical depression (14.0 percent) were one-half as likely as smokers without such a history (28.0 percent) to succeed in attempts to stop smoking.

Since 1990, the relationship between smoking and depression or dysphoric mood has been confirmed in numerous clinical studies and population-based surveys (e.g., Anda et al. 1990a; Breslau et al. 1991, 1992; Hall et al. 1991; Lee and Markides 1991; Kendler et al. 1993). In one study the association was found among girls throughout the teenage years, but only among younger teenage boys (Patton et al. 1996). Some studies among adults also suggested that the relationship may be even stronger for women than for men (Anda et al. 1990a; Glassman et al. 1990; Pérez-Stable et al. 1990), but a stronger link between smoking and depression among women has not been universally observed (Breslau 1995; Breslau et al. 1998). (See also "Beliefs About Mood Control and Depression" in Chapter 4, and "Depression" in Chapter 5.)

Inferential evidence supports the hypothesis that persons with depression smoke as a form of self-medication. Nicotine has been described as having antidepressant effects (Rausch et al. 1989; Balfour 1991). It is known to have important effects on several neurotransmitter systems in the CNS (Pomerleau and Pomerleau 1984) that contribute to depression (Janowsky and Risch 1987; Siever 1987) and to affect brain regions that influence mood and well-being (Gilbert and Spielberger 1987; Carmody 1989; Pomerleau and Rosecrans 1989). Studies found that smoking a single cigarette can cause mood elevations and transient pleasurable effects among smokers (Jasinski et al. 1984; Henningfield et al. 1987). Investigators also have reported that these effects were more intense after abstinence from smoking than during smoking ad libitum and were more pronounced as nicotine dose increased (Pomerleau and Pomerleau 1992).

Studies of the effects of nicotine replacement products in reducing postcessation dysphoric mood have produced inconsistent results; some studies showed a reduction in dysphoric mood (see West 1984; Fagerström et al. 1993), but others did not (see

Fiore et al. 1994). A study by Kinnunen and colleagues (1996), showing a significant reduction in depressive symptoms only among depressed smokers, suggested a possible explanation for these discrepancies and raises the possibility that depressed smokers are particularly sensitive to the mood-enhancing effects of nicotine.

Because several large studies suggested that smoking precedes the onset of depression or that the relationship is bidirectional, self-medication is clearly not an exhaustive explanation for the link. Choi and colleagues (1997) found that cigarette smoking was the strongest predictor of the development of depressive symptoms among adolescents and that the effect was more pronounced among girls than among boys. A longitudinal study by Breslau and colleagues (1998) among 1,007 young adults showed that a history of daily smoking at study entry significantly increased the risk for major depression five years later and that a history of major depression at baseline increased risk for progression to daily smoking; no interaction with gender was detected. Patton and colleagues (1998) showed that depression and anxiety symptoms among adolescents are associated with a higher risk for smoking initiation through increased susceptibility to the influence of peer smoking. This effect was significant among both girls and boys when most peers smoked but only among girls when some peers smoked. A study of 1,731 young persons aged 8 through 14 years in Atlanta, who were assessed at least twice from 1989 through 1994, found that previous smoking was associated with an increased risk for subsequent depressed mood but that previous depressed mood was not associated with risk for subsequent smoking initiation (Wu and Anthony 1999). Findings were not presented separately by gender. Finally, in an analysis of data from the National Longitudinal Study of Adolescent Health, Goodman and Capitman (2000) found, in a sample of 8,704 adolescents who were not depressed at baseline, that current cigarette smoking was the strongest predictor of developing high depressive symptoms at one-year follow-up. However, in a companion analysis of 6,947 teens from the same study who were not smokers at baseline, high depressive symptoms at baseline did not predict moderate-to-heavy smoking (≥ 1 pack per week) at follow-up in multivariate analysis. Results were not presented separately by gender.

Hughes (1988) proposed that there may be a common predisposition to both smoking and depression, either because of cognitive factors such as low self-efficacy and low self-esteem or because of a common genetic defect. Kendler and associates (1993) likewise minimized the causal element, arguing that the strong association they observed between smoking and major depression among women was most likely the result of inherited, neurobiological factors that predispose to both conditions. The researchers based this hypothesis on the best-fitting bivariate twin model in an elegant study of 1,566 dizygotic and monozygotic female twin pairs who were either concordant or discordant for a history of depression or for smoking.

Finally, in an early molecular genetic study of smoking, Lerman and associates (1998) reported an interaction of the gene for the D_4 dopamine receptor (*DRD4*) and depression. They suggested that self-medication of depression may occur—but only in a subgroup of smokers with depression who are homozygous for the short alleles of the gene *DRD4*.

Antidepressant drugs have been tested with some success as adjuncts to smoking cessation therapy in clinical trials, but the explanation for their effects in promoting smoking cessation is unclear (Benowitz 1997). In a placebo-controlled trial of sustained-release bupropion, investigators reported significantly higher rates of abstinence among bupropion-treated smokers with or without a history of depression, but treatment-related effects were noted for postcessation depression (Hurt et al. 1997). In another study, nortriptyline produced significantly higher abstinence rates than the placebo, regardless of history of depression. Postcessation increases in negative affect also were alleviated by nortriptyline (Hall et al. 1998). Even though improvement in symptoms has been demonstrated, it remains to be determined whether treatment of depression improves the outcome of smoking cessation treatment among persons with current depression or with a history of depression (e.g., Dalack et al. 1995). (See "Depression" in Chapter 5).

Psychiatric Disorders Other than Depression

Anxiety Disorders, Bulimia Nervosa, and Attention Deficit Disorder

Hughes and associates (1986) observed increased smoking prevalence among patients with anxiety disorders, and these findings have been supported by a number of other investigations. Breslau and associates (1991) studied a sample of more than 1,000 young adults and reported a relationship between anxiety disorders and severity of nicotine dependence based on *Diagnostic and Statistical Manual of Mental Disorders,*

third edition (revised) criteria (American Psychiatric Association [APA] 1987). This relationship was noted after adjustment for gender. Similar findings among children and adolescents were reported by Kandel and colleagues (1997), who observed that effects were more pronounced among girls than among boys. Covey and colleagues (1994) showed an association of smoking with generalized anxiety disorder among both women and men. Women with anxiety disorders, however, were more likely than men with anxiety disorders to stop or reduce smoking. Pohl and associates (1992) noted a higher prevalence of smoking among women with panic disorder (40 vs. 25 percent in control group) but not among men. Thus, although study findings support a relationship between smoking and anxiety disorders, the evidence is less consistent than that for depression (Glassman 1997).

A high prevalence of smoking has been observed among patients with bulimia nervosa (Weiss and Ebert 1983; Bulik et al. 1992; Welch and Fairburn 1998) and among dieters and binge eaters in school- and community-based populations (Killen et al. 1986; Krahn et al. 1992; Pomerleau and Krahn 1993). In contrast, no association has been observed between smoking and anorexia nervosa (Bulik et al. 1992; Wiederman and Pryor 1996).

Attention deficit disorder (ADD), an impairment in "the capacity to receive, hold, scan, and selectively screen out stimuli in a sequential order" (Clements and Peters 1962, p. 20), has been studied extensively as a disorder of childhood and adolescence (Barkley 1990). Although prevalence of adult ADD is higher among men than among women and most available data on smoking are largely based on samples of men, the validity of the diagnosis also has been supported for women, and little evidence exists of gender-specific differences in the expression of adult ADD or in the distribution of subtypes (Biederman et al. 1994). Both children and adults with ADD are significantly more likely to be smokers than are non-ADD controls (Borland and Heckman 1976; Hartsough and Lambert 1987; Barkley et al. 1990; Pomerleau et al. 1995).

Schizophrenia

Smoking is highly prevalent and, in some studies, close to universal among persons with schizophrenia (O'Farrell et al. 1983; Masterson and O'Shea 1984; Hughes et al. 1986; Goff et al. 1992; Lohr and Flynn 1992), more so than other types of substance dependence (Schneier and Siris 1987). Moreover, persons with schizophrenia are extremely heavy smokers and show higher levels of cotinine (a metabolite of nicotine) than do those in control groups with similar smoking patterns (Olincy et al. 1997). The mechanism for this association is unknown, but dopaminergic effects of nicotine in the brain have frequently been implicated (Lohr and Flynn 1992). Although evidence is mixed, case reports suggested that nicotine withdrawal leads to exacerbation of both negative and positive symptoms of schizophrenia (Dalack and Meador-Woodruff 1996) and that smoking reduces negative symptoms (Lohr and Flynn 1992).

Although the occurrence of schizophrenia is generally thought to be about equal among women and men, especially as evidenced in community-based surveys (APA 1994), marked gender-specific differences in the presentation and course of this disorder do exist. Women are likely to have later onset of schizophrenia (median age in late 20s for women and early 20s for men), more prominent mood symptoms, and more favorable prognosis (APA 1994). Although conflicting evidence exists (e.g., Hughes et al. 1986), smoking prevalence may also be lower among women than among men with schizophrenia (de Leon et al. 1995).

Dependence on Alcohol and Other Drugs

The high prevalence of smoking among persons with alcoholism has long been recognized (Istvan and Matarazzo 1984) and is similar among women and men (Bobo 1989). Possible mechanisms for this relationship are that nicotine may increase tolerance to the deleterious effects of alcohol on behavior, may directly enhance the reinforcing effects of alcohol, or may act in both ways (Pomerleau 1995). Because of the high rate of comorbidity of alcohol dependence and major depression (Weissman and Myers 1980; Helzer et al. 1988; Ross et al. 1988; Merikangas and Gelernter 1990; Regier et al. 1990), coexisting depression may contribute to or mediate the association between alcohol dependence and smoking. In a study of women and men smokers with a history of alcohol dependence, those who currently consumed alcohol had significantly higher self-ratings of depression than those who did not consume alcohol (Pomerleau et al. 1997). Another study showed that the occurrence of depression together with alcohol dependence exerted a detrimental effect on the ability to stop smoking among men but not among women (Covey et al. 1993).

Conclusions

1. Smokers are more likely to be depressed than are nonsmokers, a finding that may reflect an effect of smoking on the risk for depression, the use of smoking for self-medication, or the influence of common genetic or other factors on both smoking and depression. The association of smoking and depression is particularly important among women because they are more likely to be diagnosed with depression than are men.
2. The prevalence of smoking generally has been found to be higher among patients with anxiety disorders, bulimia, attention deficit disorder, and alcoholism than among individuals without these conditions; the mechanisms underlying these associations are not yet understood.
3. The prevalence of smoking is very high among patients with schizophrenia, but the mechanisms underlying this association are not yet understood.
4. Smoking may be used by some persons who would otherwise manifest psychiatric symptoms to manage those symptoms; for such persons, cessation of smoking may lead to the emergence of depression or other dysphoric mood states.

Neurologic Diseases

Parkinson's Disease

Parkinson's disease (PD), an idiopathic neurodegenerative disorder, is characterized clinically by muscular rigidity, slowness of movement, and a characteristic tremor (Yahr 1985). A major cause of disability in the United States, PD may affect half a million to one million people nationally; it has been estimated that as many as 50,000 new cases occur each year (Yahr 1985). The incidence of PD among both women and men increases exponentially with age after about 55 years until about age 75 years. The incidence among women and men is generally similar, but some data have suggested a higher incidence of PD among men (Zhang and Román 1993).

Cigarette smoking is inversely related to the development of PD (Baron 1986; Morens et al. 1995). This association was first observed in follow-up studies of mortality in two cohorts of men. The standardized mortality ratio (SMR) was 0.23 among men current smokers in the study by Kahn (1966) and 0.72 among men who had ever smoked in the study by Hammond (1966). Similar inverse associations were also noted in prospective mortality studies of men in England (SMR, 0.43) (Doll and Peto 1976) and of women and men in Japan (SMR, 0.57) (Hirayama 1985). Results of prospective cohort studies by investigators who actively sought incident cases of PD (Wolf et al. 1991; Grandinetti et al. 1994) support these findings. Numerous case-control studies have also found that PD occurs less often among smokers than among persons who had never smoked (Baron 1986; Morens et al. 1995).

The inverse association between PD and smoking appears to be present among both women and men. In the only cohort study with data for both genders, Hirayama (1985) reported similarly reduced risks for PD mortality among women and men. Case-control studies that presented data separately for women and men are summarized in Table 3.51. These findings showed similar inverse associations among women and men. Thus, no compelling evidence exists that gender modifies the relationship between smoking and development of PD.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment and shortened life expectancy (for review, see Terry et al. 1994). An estimated four million U.S. residents have AD (National Institute on Aging 1992). Because age is a strong risk factor for AD and women have a longer life expectancy than do men, more women than men develop this disease. Even after adjustment for age, however, many studies found the prevalence of AD to be higher among women (e.g., Jorm et al. 1987; Rocca et al. 1991; Bachman et al. 1992; Canadian Study of Health and Aging Working Group 1994). Reports of longer survival among women with AD than among affected men (e.g., Heyman et al.

Table 3.51. Relative risks for Parkinson's disease among smokers, women and men, case-control studies

Study	Smoking status	Relative risk		Comments
		Women	Men	
Kessler and Diamond 1971	Ever vs. never smoked	0.7	0.6*	
		0.7	0.7*	Adjusted for hospitalization diagnoses
Kessler 1972	Ever vs. never smoked	0.6	0.4†	Adjusted for age
Haack et al. 1981	Ever vs. never smoked	0.2‡	0.7	
Godwin-Austen et al. 1982		0.6*	0.5*	
Ogawa et al. 1984	Smokers vs. nonsmokers	0.5§	0.3*	Hospital control (adjusted)
		0.6§	0.4	Neighborhood control (adjusted)
Hofman et al. 1989	Ever vs. never smoked	0.3§	0.8	
Hellenbrand et al. 1997	Ever vs. never smoked	0.6§	0.4§	

*$p < 0.01$.
†$p < 0.001$.
‡$p < 0.0001$.
§$p < 0.05$.

1996; Kokmen et al. 1996) suggested another reason that prevalence is higher among women. Differences in the incidence of AD by gender are less clear. Some studies reported the incidence of AD to be similar among women and men after adjustment for age (Schoenberg et al. 1987; Bachman et al. 1993; Letenneur et al. 1994a). In other studies, however, incidence was substantially higher among women, although the differences were not statistically significant (Brayne et al. 1995; Yoshitake et al. 1995; Aevarsson and Skoog 1996). One study reported that age-specific incidence rates were consistently higher among women, significantly so in one age group (Fratiglioni et al. 1997). Another report found a higher age-adjusted incidence among women than among men (RR, 1.7; 95 percent CI, 1.0 to 2.6) (Ott et al. 1998a).

Although results are inconsistent, many studies have found an inverse association between smoking and AD. This association is evident in the meta-analyses by Graves and associates (1991) and by van Duijn and Hofman (1992). The RRs for AD decreased with increasing number of pack-years of smoking, from 0.7 (95 percent CI, 0.5 to 1.1) for less than 15.5 pack-years to 0.6 (95 percent CI, 0.4 to 0.95) for 15.5 to 37.0 pack-years and to 0.5 (95 percent CI, 0.3 to 0.8) for more than 37.0 pack-years.

The inverse relationship between smoking and AD reported in these studies and meta-analyses needs to be interpreted in the light of the potential limitations discussed here. For example, a significant protective effect of smoking shown in one study disappeared after adjustment for appropriate confounding factors (Tyas 1998). This pattern was consistent with that of another investigation (Letenneur et al. 1994b) and suggested that failure to adjust for confounders may have contributed to the variation in the findings for the effects of smoking on AD (Tyas 1998). In another example, a protective association reported in one case-control study was based on unadjusted analyses of data obtained from proxy respondents for case subjects but not for control subjects (Ferini-Strambi et al. 1990).

Another meta-analysis included data from 19 investigations, primarily case-control studies, of the relationship between AD and smoking (Lee 1994). Of the 19 studies analyzed, 4 showed a statistically significant protective effect of smoking, 11 showed a nonsignificantly lower risk for AD among smokers, 3 reported a nonsignificantly increased risk among smokers, and 1 found no significant effect and did not describe the direction of the association. Case-control studies published after the meta-analyses by Graves and colleagues (1991), van Duijn and Hofman (1992),

and Lee (1994) have reported statistically significant inverse associations (Brenner et al. 1993; van Duijn et al. 1995; Callahan et al. 1996) or no association (Canadian Study of Health and Aging Workshop 1994; Letenneur et al. 1994b; Forster et al. 1995; Wang et al. 1997a).

Cohort studies have been less supportive of an inverse association. Katzman and colleagues (1989) noted that persons who developed AD were less likely to have been smokers than were those who did not have AD. Other investigators reported a nonsignificantly reduced risk for incident AD among smokers (Hebert et al. 1992; Yoshitake et al. 1995), no association (Wang et al. 1999), or an increased risk (Ott et al. 1998b; Launer et al. 1999). A significant protective effect of smoking was reported in a case-control study (Mayeux and Tang 1993), but a significantly higher risk for AD was reported among smokers in an associated cohort study (Merchant et al. 1999). Failure to adequately adjust for confounders and other methodological problems may have contributed to some of the variation in the findings across studies (Tyas 1998).

Because smokers are more likely than nonsmokers to die before developing AD, the issue of selective mortality has been used to argue against a causal protective association between smoking and AD (Riggs 1993; Graves and Mortimer 1994). The higher mortality among smokers compared with nonsmokers would create an apparent lower risk for AD among smokers if those who died were more likely than nonsmokers to have developed AD if they had lived. Some researchers have argued against such an explanation (e.g., Plassman et al. 1995; van Duijn et al. 1995). Nonetheless, the possibility that a protective effect of smoking could be attributable to survival bias is plausible, particularly when prevalent cases are studied (Wang et al. 1999).

Most studies have not presented findings on cigarette smoking and AD separately for women and men. Those that have examined the interaction between gender and smoking on AD have reported inconsistent results (Ferini-Strambi et al. 1990; Graves et al. 1991; Hebert et al. 1992; Letenneur et al. 1994a; Salib and Hillier 1997; Launer et al. 1999).

Conclusions

1. Women who smoke have a decreased risk for Parkinson's disease.
2. Data regarding the association between smoking and Alzheimer's disease are inconsistent.

Nicotine Pharmacology and Addiction

The 1988 Surgeon General's report on the health consequences of smoking focused on nicotine addiction (USDHHS 1988). The report concluded that cigarettes and other tobacco products are addicting and that nicotine causes the addiction. Primary criteria for addiction included (1) psychoactive effects that involve alterations in mood, behavior, and/or cognition; (2) reinforcing effects that maintain self-administration of the drug; and (3) highly controlled or compulsive use driven by strong urges to use the drug. Additional criteria included (4) development of physical dependence on the drug, which is characterized by tolerance and withdrawal symptoms; (5) continued use despite negative consequences; (6) difficulty in maintaining abstinence or in reducing the quantity consumed; and (7) recurrent cravings for the drug (*British Journal of Addiction* 1982; APA 1994).

USDHHS (1995) summarized studies documenting addiction among smokers. The report indicated that approximately 90 percent of cigarette smokers smoke daily. Of those who smoke one pack of cigarettes per day, 80 percent have unsuccessfully tried to reduce the number of cigarettes smoked. About 50 percent of those who stop smoking experience nicotine withdrawal syndrome. Of those making a serious attempt to stop, fewer than 3 percent have long-term success. Data from the 1991 and 1992 National Household Survey on Drug Abuse showed that three-fourths of women current smokers reported feeling dependent on cigarettes; about 80 percent reported experiencing at least one of four indicators of nicotine addiction (CDC 1995) (see "Nicotine Dependence Among Women and Girls" in Chapter 2).

The pharmacology of nicotine was discussed in depth in the 1988 Surgeon General's report on smoking and health (USDHHS 1988) and in several subsequent reviews (Le Houezec and Benowitz 1991; Benowitz 1992; Henningfield et al. 1995). This discussion emphasizes those aspects for which gender-specific differences have been explored. The pharmacologic processes relevant to drug addiction include absorption, distribution, elimination, and dosing of nicotine in the body (pharmacokinetics); pharmacologic effects on target organs (pharmacodynamics); and behavorial manifestations of the pharmacologic effects.

Absorption, Distribution, and Metabolism of Nicotine

When tobacco burns during smoking, nicotine is distilled and carried into the lungs, where it is absorbed rapidly through the pulmonary alveoli. After absorption, nicotine is distributed to various body tissues. Evidence from animal studies showed that tissues with the highest affinity for nicotine are the kidney, liver, lung, brain, and heart, in that order. Skeletal muscle has moderate affinity for nicotine, and adipose tissue has the lowest affinity (Benowitz et al. 1990). Women in general have a higher percentage of fat than do men (average, 34 percent vs. 20 percent of total body weight) (Watson et al. 1980). Because nicotine has a relatively low affinity for fat, it is largely distributed in lean tissues. The lower lean body weight of women might then suggest that, for a nicotine dose normalized to total weight, women would have higher concentrations in blood and other organs than would men. Animal studies have reported gender-specific differences in nicotine concentrations in the brain, and these differences support the hypothesis that there are differences in nicotine distribution among females and males (Rosecrans 1972; Rosecrans and Schechter 1972; Hatchell and Collins 1980). Such differences have not been investigated in clinical studies with humans.

Nicotine is broken down to several metabolites in the liver. Beckett and associates (1971) suggested that the extent of nicotine metabolism is different among women and men, reporting that women nonsmokers excreted more nicotine and less cotinine in urine than did men nonsmokers. This early study involved a small number of participants and was based on 24-hour urine collections, but 24 hours is an insufficient period for complete excretion of metabolites. Gender-specific patterns of urinary excretion of nicotine metabolites have not been described in more recent research. Indeed, a study involving administration of labeled nicotine and cotinine, which permits quantification of nicotine metabolic pathways, found essentially identical conversion of nicotine to cotinine (72 to 73 percent) among 10 women and 10 men (Benowitz and Jacob 1994).

In a study of men, Armitage and colleagues (1975) used ^{14}C-labeled nicotine to measure absorption of nicotine from cigarette smoke. Regular smokers generally absorbed 80 to 90 percent of the nicotine that was inhaled. Comparisons between women and men were not made. However, a study of nicotine absorption from ETS among nonsmoking women compared the nicotine content of inspired versus expired air (Iwase et al. 1991). On average, 71 percent (range, 60 to 80 percent) of the nicotine inhaled was absorbed.

Studies of gender-specific differences in nicotine clearance among humans have shown varying results. An early study reported that the total clearance of nicotine, when normalized for body weight, was significantly greater among 11 men than among 11 age-matched women (20.5 ± 5.0 vs. 15.7 ± 4.7 mL/[min x kg]) (Benowitz and Jacob 1984). However, a more recent study of 10 women and 10 men found no difference in normalized clearance (Benowitz and Jacob 1994). Thus, it is not known whether drug metabolic activity, expressed as clearance per kilogram of body weight, differs between women and men. Nonetheless, because men tend to weigh more than do women, total body clearance (body weight x clearance normalized by body weight) is consistently greater among men than among women. One study compared the clearance of cotinine among women and men (Benowitz and Jacob 1994). Both total clearance of cotinine and clearance normalized for body weight tended to be higher among men than among women, but the differences were not statistically significant.

Nicotine Levels and Dosing

The daily dose of nicotine from cigarette smoking is strongly related to the number of cigarettes smoked per day but only weakly related to the machine-determined nicotine yield of cigarettes (Benowitz et al. 1983; Gori and Lynch 1985; Höfer et al. 1991a). The dose of nicotine from a cigarette also depends on the efficiency of systemic absorption and how the cigarette is smoked (i.e., number of puffs, intensity of puffing, volume of smoke inhaled, and whether the filter holes are blocked). No data are available on gender-specific differences in the efficiency of pulmonary absorption of nicotine, but cigarette-puffing behavior has been studied by using cigarette-holder flowmeter devices. The results of such studies must be interpreted

with caution, because in general, single cigarettes are tested in laboratory settings with unfamiliar cigarette holders, which could influence a smoker's puffing behavior.

Several investigators testing in such a laboratory setting found gender-specific differences in smoking behavior. One study reported that among hospitalized smokers, men took puffs of larger volume and longer duration than did women but that the number of puffs taken per cigarette was similar (Moody 1980). Bättig and coworkers (1982) also observed that men had larger puff volume and longer puff duration than did women but that women tended to have a greater increase in expired CO after smoking a cigarette. Women took an average of one extra puff per cigarette, which partially offset the difference in volume per puff. Höfer and colleagues (1991a) reported similar results and noted that the increase in plasma nicotine levels after smoking a cigarette was greater among men than among women. Epstein and coworkers (1982) found that men had greater total puff duration than did women, but no significant differences were found in the number of puffs taken per cigarette or in puff volume. Because men generally inhale more smoke from each cigarette, the increase in plasma nicotine concentration and the amount of nicotine absorbed after smoking would be expected to be greater among men than among women. These predictions have been confirmed in two laboratory studies (Höfer et al. 1991a; Benowitz and Jacob 1994). However, comparison of the increase in plasma nicotine concentration after dosing with nicotine nasal spray showed no gender-specific difference (Perkins et al. 1995).

With regular use of tobacco in any form, blood nicotine concentrations are determined by the dose of nicotine delivered and by the rates of absorption and clearance. Some studies reported that concentrations of nicotine and cotinine in plasma during smoking ad libitum were similar among women and men, even though women, on average, smoked fewer cigarettes than did men (Russell et al. 1980, 1986; Höfer et al. 1991a). These data suggested that the lower daily dose of nicotine from cigarettes among women may be balanced by their lower total body clearance and may result in similar average concentrations of plasma nicotine. In several more recent studies, women smokers had lower salivary or serum concentrations of cotinine than did men smokers, as might be expected from the lower number of cigarettes smoked by women (Wagenknecht et al. 1990; Woodward and Tunstall-Pedoe 1993; Bjornson et al. 1995). These findings suggested that the number of cigarettes smoked per day is the major determinant of nicotine exposure and that, in general, women are exposed to less nicotine than are men because they smoke fewer cigarettes per day (Benowitz and Hatsukami 1998).

Psychoactive and Rewarding Effects of Nicotine

Nicotine produces a variety of subjective, cognitive, and physiologic effects in humans. Gender-specific differences in these effects can be determined by comparing the extent of nicotine self-administration, the ability to discriminate nicotine as a stimulus, and responsiveness to the rewarding effects of nicotine.

Nicotine self-administration has been demonstrated among both animals and humans, providing evidence that nicotine is itself reinforcing (USDHHS 1988). Few studies have closely examined differences by gender in the self-administration of nicotine. In general, women smoke fewer cigarettes and inhale less than do men (Grunberg et al. 1991; Perkins 1996), but as previously noted, the circulating concentrations of nicotine may be the same among both genders. In a laboratory study that examined the reinforcing value of smoking, women and men had a similar response pattern in working for puffs on a cigarette (Perkins et al. 1994b). In another experimental study, however, women self-administered nicotine nasal spray at a lower rate than did men, even when the dose was corrected for body weight (Perkins et al. 1996a). Lower concentrations of plasma nicotine reflected this lower rate of nicotine self-administration among women. Furthermore, men self-administered nicotine nasal spray to a greater extent than a placebo spray, whereas no difference was observed among women in self-administration of nicotine versus placebo. These results suggested that nicotine administered via nasal spray is reinforcing among men but not among women. Whether this difference in self-administration reflects reduced reinforcement from nicotine as a result of differential sensitivity to nicotine is not known.

The limited data available suggested that women are less effective than men in maintaining a particular concentration of nicotine in the body by changing nicotine self-administration (Benowitz and Hatsukami 1998). For example, studies of male smokers reported significant declines in the number of cigarettes smoked after self-administration of nicotine, whereas studies that showed little or no compensation in smoking in response to nicotine self-administration predominantly involved women (Perkins 1996). Only one study directly compared

smoking behavior of women and men after self-administration of various doses of nicotine via nasal spray (Perkins et al. 1992). In this study, women did not compensate for nicotine self-administration to the same extent by smoking less as did men. Further evidence for less-effective nicotine regulation among women was provided by a study that observed women to have increasing serum cotinine and alveolar CO with use of cigarette brands with higher nicotine yields, whereas men had similar CO and cotinine levels regardless of machine-determined yield (Woodward and Tunstall-Pedoe 1993). This finding suggested that men smoked cigarettes to obtain the same dose of nicotine from all brands, whereas women smoked different cigarettes in a similar fashion, irrespective of nicotine delivery. However, an earlier study provided contradictory findings; it showed better nicotine regulation among women than among men (Bättig et al. 1982). Less effective nicotine regulation among women is consistent with data indicating that women are less able than men to distinguish nicotine from placebo or to distinguish different doses of nicotine in blind comparisons (Perkins 1995; Perkins et al. 1996b; Benowitz and Hatsukami 1998).

Nicotine produces variable effects on mood. Depending on the dose and the state (withdrawal or tolerance) or initial mood of the individual, nicotine can enhance arousal and alertness or can relax and calm (USDHHS 1998; Parrott 1994). Few data on gender-specific differences in nicotine's mood-altering effects have been available. Most studies showed no differences between women and men in subjective responses to nicotine (Perkins et al. 1993, 1994c). However, one investigation reported more dizziness among women than among men after smoking cigarettes (Perkins et al. 1994a), and another found that women reported greater increase in comfort and relaxation after smoking (Perkins et al. 1994d). No such differences by gender were observed across doses of nicotine delivered via nasal spray. Because no gender-specific differences in response to nicotine were found (Perkins 1996), these results indicated that influences independent of nicotine may be more important determinants of mood responses to smoking among women than among men.

An important area in understanding the reinforcing influence of nicotine is its effect among smokers who are confronted with a stressful situation or who are experiencing negative affect. Smokers report a greater desire for cigarettes (Perkins and Grobe 1992) and demonstrate increased intensity of smoking during periods of stress (e.g., Schachter 1978; Dobbs et al. 1981; Rose et al. 1983; Pomerleau and Pomerleau 1987, 1989). It is more common for women than for men to smoke in response to negative affect or stress (Frith 1971; Ikard and Tomkins 1973; Karasek et al. 1987; Sorensen and Pechacek 1987; Livson and Leino 1988; Bjornson et al. 1995), and women report smoking for sedative effects (Russell et al. 1974). In contrast, men report that they smoke more for stimulation (Gilbert 1995). Even in an adolescent population, smoking to relax or cope with stress or depression was significantly more common among girls than among boys (Oakley et al. 1992). For example, young women who reported on a questionnaire that they needed more information about how to cope with stress or depression were more likely to be smokers than were young men who reported needing this information. It is possible that women have a greater propensity to smoke in a state of negative affect or stress because they have fewer coping strategies or that women more commonly use strategies that alter emotional arousal without addressing the source of stress (Pomerleau et al. 1991; Solomon and Flynn 1993). Another explanation may be that nicotine has a greater effect on stress or negative affect among women than among men, which would increase the potential for nicotine to be reinforcing among women.

Nicotine may have beneficial effects on several aspects of human performance, including improved attention, learning and memory functioning, and enhanced sensory and motor performance (Levin 1992; Heishman et al. 1994). No study has demonstrated gender-specific differences in such effects. Studies have shown the same enhancement of performance among women as among men or a combination of women and men, particularly during smoking deprivation (Heishman et al. 1994).

Much of the research examining gender-specific differences in the reinforcing effects of nicotine has been related to weight (see "Body Weight and Fat Distribution" earlier in this chapter, "Concerns About Weight Control" in Chapter 4, and "Weight Control" in Chapter 5). Tobacco use is inversely related to body weight, and women in particular report that they smoke to keep body weight down (USDHHS 1988; Gritz et al. 1989; Grunberg 1990; Camp et al. 1993) (see "Body Weight and Fat Distribution" earlier in this chapter). The difference in weight between smokers and nonsmokers is greater among women than among men (Klesges et al. 1989). After cessation of smoking, women are more likely to gain more weight than are men (e.g., Williamson et al. 1991), and among women but not among men, dose-related effects of

nicotine gum appear to limit weight gain after smoking cessation (Leischow et al. 1992). These data indicated that the weight-related reinforcing effects of nicotine and cigarette smoking are stronger among women than among men.

Physical Dependence on Nicotine

Physical dependence refers to the development of withdrawal symptoms after cessation of drug use. Withdrawal symptoms are associated with the development of tolerance, a decreased effect after repeated exposure to a drug, or the need for increased drug dose to obtain a specific effect. Some retrospective studies showed that symptoms of cigarette withdrawal are more severe among women than among men (Shiffman 1979), but results in other retrospective studies (Breslau et al. 1992) and prospective studies (Svikis et al. 1986; Hughes et al. 1991; Hughes 1992; Tate et al. 1993; Pomerleau et al. 1994) indicated that women and men have similar types and severity of withdrawal symptoms. Gender-specific differences observed in retrospective studies could be due to the finding that men tend to minimize cigarette withdrawal symptoms when asked to recall their experience (Pomerleau et al. 1994).

Nicotine addiction is also supported by stimuli that become associated with tobacco use through learning or conditioning. These cues include environmental and internal stimuli and sensory aspects of tobacco use. Stimuli that are repeatedly paired with abstinence from tobacco (e.g., being in locations where smoking is prohibited) can elicit withdrawal-like responses (Wikler 1965) that oppose or compensate for the effects of nicotine (Siegel 1983). Similarly, stimuli that are repeatedly paired with tobacco use (e.g., sight of ashtrays) can lead to states like those elicited by the drug itself (Stewart et al. 1984).

In particular, sensory aspects of smoking may also have a role in the maintenance of smoking. Cues such as the smell and taste of cigarette smoking, as well as irritation of the mouth, throat, and respiratory tree, may become conditioned reinforcers (Stolerman et al. 1973; Rose and Levin 1991). Blocking the sensory aspects of smoking attenuates the effects of inhaled nicotine on craving for cigarettes (Rose et al. 1985). Similarly, the administration of aerosols that mimic the sensory aspects of smoking (e.g., irritant effects on the respiratory tract) reduces craving (Rose and Hickman 1987; Behm et al. 1990, 1993; Rose and Behm 1994; Westman et al. 1995). The magnitude of reduction was similar to that produced by smoking of high-nicotine cigarettes (Rose et al. 1993). The aerosols also reduce smoking (Rose and Behm 1987; Rose et al. 1993) and enhance short-term smoking cessation rates (Levin et al. 1990; Behm et al. 1993; Westman et al. 1995).

Some investigations have shown that women are particularly sensitive to the sensory aspects of smoking (Hasenfratz et al. 1993; Baldinger et al. 1995) and may be more responsive to their effects than are men (Höfer et al. 1991b). Consequently, the presence of sensory cues associated with smoking in the absence of nicotine may cause greater discomfort among women smokers than among men smokers (Perkins et al. 1994d).

Results from studies of gender-specific differences in the efficacy of nicotine replacement therapy for tobacco withdrawal have varied. No such differences were found for the effects of 2-mg nicotine polacrilex gum (Schneider et al. 1984) or of the 21-mg transdermal nicotine system (Repsher 1994) on composite scores for symptoms of tobacco withdrawal. However, other studies of smoking cessation using nicotine replacement agents showed that such treatment tends to be less effective among women than among men (Perkins et al. 1996b). After cessation of use of nicotine polacrilex gum, withdrawal symptoms were observed to be more severe among women than among men—a difference seen for 2-mg doses of nicotine but not for 4-mg doses (Hatsukami et al. 1995). This finding suggested that women may have more severe withdrawal symptoms at lower doses of nicotine than do men. A similar finding was observed in another investigation with 2-mg polacrilex nicotine gum: women had no reduction in craving for cigarettes when they used active nicotine gum compared with placebo, but men did have a significant reduction (Killen et al. 1990).

Conclusions

1. Nicotine pharmacology and the behavioral processes that determine nicotine addiction appear generally similar among women and men; when standardized for the number of cigarettes smoked, the blood concentration of cotinine (the main metabolite of nicotine) is similar among women and men.
2. Women's regulation of nicotine intake may be less precise than men's. Factors other than nicotine (e.g., sensory cues) may play a greater role in determining smoking behavior among women.

Environmental Tobacco Smoke

During 1988–1991, 37 percent of adult non-tobacco users in the United States lived in a home with at least one smoker or reported exposure to ETS at work; the proportion reporting ETS exposure was somewhat lower among women (32.9 percent) than among men (43.5 percent) (Pirkle et al. 1996). Three major outcomes of ETS exposure are considered in this section—lung cancer, CHD, and reproductive effects. ETS exposure is also discussed briefly in "Breast Cancer" and "Cervical Cancer" earlier in this chapter. These are by no means the only conditions of importance to women's health potentially affected by exposure to ETS, but they are the outcomes that have been most studied to date.

Environmental Tobacco Smoke and Lung Cancer

Previous Reviews

In 1986, two major reviews of the data on exposure to ETS and its potential health effects, including lung cancer, were published (NRC 1986; USDHHS 1986b). In the NRC review (1986), the estimate of overall (summary) RR for lung cancer among women nonsmokers who lived with a spouse who smoked was 1.3 (95 percent CI, 1.2 to 1.5); the estimated RR among men, which was based on much smaller numbers of nonsmokers with lung cancer, was 1.6 (95 percent CI, 0.99 to 2.6). Among both genders combined, the estimated RR was 1.3 (95 percent CI, 1.2 to 1.5). Two additional analyses, which corrected RR estimates for two types of systematic errors, were provided in the NRC report. The first analysis incorporated plausible assumptions about misclassification of former smokers as "never smokers" and about the tendency for spouses to have similar smoking habits. The conclusions were that the observed overall RR of 1.3 could reflect an underlying true RR of no less than 1.2 and, more likely, 1.3, and that, under reasonable assumptions, this type of misclassification could not account for all the increased risk for lung cancer reported from these epidemiologic studies. The second analysis evaluated the effect of incorrectly classifying some nonsmokers as "unexposed" because of sole consideration of household exposure. The risk among a group of nonsmokers married to nonsmokers, but nevertheless exposed to ETS, was estimated to be at least 8 percent higher than the risk among nonsmokers who were never exposed to ETS. The overall adjusted RR estimate, corrected for both possible misclassification of smokers and background ETS exposure, was 1.4 (range, 1.2 to 1.6).

The 1986 Surgeon General's report (USDHHS 1986b) included a review of the same 13 epidemiologic studies (Garfinkel 1981; Hirayama 1981, 1984a; Chan and Fung 1982; Correa et al. 1983; Trichopoulos et al. 1983; Buffler et al. 1984; Gillis et al. 1984; Kabat and Wynder 1984; Koo et al. 1984; Garfinkel et al. 1985; Akiba et al. 1986; Lee et al. 1986; Pershagen et al. 1987) as well as an assessment of ETS chemistry, deposition, and absorption of specific constituents and determination of their carcinogenicity. This review focused on qualitative assessments of the studies and concluded that involuntary (passive) smoking is a cause of disease, including lung cancer, among healthy nonsmokers.

An international ETS working group met in 1985, and its findings were summarized in two monographs from IARC (1986, 1987). The 1986 IARC monograph stated that,

> The observations on nonsmokers that have been made so far are compatible with either an increased risk from "passive" smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of [lung] cancer (IARC 1986, p. 314).

In an assessment of ETS in the workplace and its relationship to lung cancer, the National Institute for Occupational Safety and Health (NIOSH 1991) reviewed the same 13 studies considered in the NRC report and the Surgeon General's report, plus 8 additional epidemiologic studies that were published in 1987–1990 (Brownson et al. 1987; Gao et al. 1987; Humble et al. 1987a; Lam et al. 1987; Geng et al. 1988; Shimizu et al. 1988; Hole et al. 1989; Janerich et al. 1990). NIOSH concluded that the results of these epidemiologic studies supported and reinforced the 1986 findings of the reports of NRC and the Surgeon

General, demonstrating an excess risk for lung cancer of about 30 percent among nonsmokers who live with a smoker compared with nonsmokers who live with a nonsmoker. The data on which NIOSH based the conclusion that ETS is potentially carcinogenic to occupationally exposed workers were not gathered in occupational settings but on the surrogate measure of "lived with a smoker."

In 1992, EPA produced a comprehensive review of the association between ETS and lung cancer among women nonsmokers (EPA 1992). EPA concluded that ETS is a human lung carcinogen. This conclusion was based on a "weight-of-the-evidence" analysis that included, but was not limited to, data from reports of 31 epidemiologic studies of lung cancer among women nonsmokers that were published in 1981–1991 (Garfinkel 1981; Trichopoulos et al. 1981, 1983; Chan and Fung 1982; Correa et al. 1983; Buffler et al. 1984; Hirayama 1984b; Kabat and Wynder 1984; Garfinkel et al. 1985; Lam 1985; Wu et al. 1985; Akiba et al. 1986; Lee et al. 1986; Brownson et al. 1987; Gao et al. 1987; Humble et al. 1987a; Koo et al. 1987; Lam et al. 1987; Pershagen et al. 1987; Butler 1988; Geng et al. 1988; Inoue and Hirayama 1988; Shimizu et al. 1988; Hole et al. 1989; Svensson et al. 1989; Janerich et al. 1990; Kalandidi et al. 1990; Sobue et al. 1990; Wu-Williams et al. 1990; Fontham et al. 1991; Liu et al. 1991).

In the EPA report, summary RRs were estimated by using meta-analysis, which included an assessment of the various study designs and an adjustment for possible misclassification of smokers. Exposure was defined as having lived with a spouse who smoked. Among women nonsmokers in the United States, the estimate of RR was 1.2 (90 percent CI, 1.04 to 1.4) for those who were ever exposed to ETS and 1.4 (90 percent CI, 1.1 to 1.7) at the highest exposure level. The summary RR estimate for the highest exposure level worldwide was 1.8 (90 percent CI, 1.6 to 2.1). The weight-of-the-evidence approach used by EPA in its determination that ETS is a human carcinogen included an assessment of biochemical and toxicologic data as well as data from epidemiologic studies.

The California Environmental Protection Agency (CEPA) published a report on the health effects of ETS (NCI 1999) that updated the EPA report. Eight additional epidemiologic studies were reviewed in addition to the 31 included in the EPA report (Brownson et al. 1992a; Stockwell et al. 1992; Liu et al. 1993; Fontham et al. 1994; Kabat et al. 1995; Schwartz et al. 1996; Cardenas et al. 1997; Ko et al. 1997). The report concluded that the studies subsequent to the EPA report provided additional evidence that ETS exposure is causally associated with lung cancer and that findings of recent studies and the EPA meta-analysis indicated about a 20-percent increased risk for lung cancer among nonsmokers.

Beside these comprehensive reviews, numerous meta-analyses have been published. Hackshaw and associates (1997) analyzed the 37 published studies on women and found a pooled RR of 1.2 (95 percent CI, 1.1 to 1.4). Tests of heterogeneity indicated that RR estimates for lung cancer and ETS exposure did not significantly differ between women and men, by geographic region, by year of publication, or between cohort and case-control studies. The pooled RR estimates were virtually identical each year from 1990 through 1997, indicating that the pooled RR was not materially influenced by the more recent larger studies.

In the year 2000, USDHHS released the ninth edition of the Report on Carcinogens, which identifies substances that are "known" or "reasonably anticipated" to cause cancer and to which a significant number of persons in the United States are exposed (USDHHS 2000). ETS was among the substances included on the list of known human carcinogens.

Epidemiologic Studies 1992–1998

Nine studies of the relationship between exposure to ETS and lung cancer (one cohort study and eight case-control studies) published since 1992 are summarized in Table 3.52.

Cohort Study

Cardenas and associates (1997) used data from the CPS-II cohort to evaluate the relationship between ETS and lung cancer deaths among 192,234 women and 96,542 men who had never smoked, with follow-up during 1982–1989. ETS exposure was defined as smoking status of the current spouse at enrollment in the study. Duration of exposure was defined as the number of years in the current marriage, intensity of exposure was defined as the number of cigarettes smoked per day by the spouse, and pack-years were estimated in this study as the product of the duration of marriage and the intensity of exposure to ETS. RRs were adjusted for age, race, years of education, blue-collar employment, occupational exposure to asbestos, weekly servings of vegetables and citrus fruit, total dietary fat, and self-reported history of chronic lung disease. The adjusted lung cancer death rate was 20 percent higher among women whose husband had ever smoked during their current marriage than among those married to a nonsmoker. At the highest level of cigarettes per day smoked by a spouse (≥ 40), the RR was 1.9 (95 percent CI, 1.0 to 3.6; p for trend

= 0.03). RRs were generally higher among women whose husband continued to smoke (1.2; 95 percent CI, 0.8 to 1.8), smoked cigars or pipes (1.5; 95 percent CI, 0.6 to 2.8), or exceeded 35 pack-years of smoking (1.5; 95 percent CI, 0.8 to 2.9). Although only one estimate of risk was statistically significant, the statistical power in this study was low. The authors concluded that their results were consistent with the EPA summary estimate that spousal smoking increases the risk for lung cancer by about 20 percent among women nonsmokers.

Case-Control Studies

Brownson and associates (1992a) reported findings from a population-based, case-control study of white women nonsmokers in Missouri aged 30 through 84 years. Age and previous lung disease were shown to confound the risk estimates and RRs were, therefore, adjusted for these two factors. No increased risk for lung cancer was associated with childhood ETS exposure in the study sample, but the validity of the data on childhood exposure is questionable because of the high proportion of proxy respondents. Qualitative indicators of exposure were associated with some increased risk: "moderate" exposure (RR, 1.7; 95 percent CI, 1.1 to 2.5) and "heavy" exposure (RR, 2.4; 95 percent CI, 1.3 to 4.7). The RR for lung cancer among women who were ever exposed to spousal ETS was 1.1 (95 percent CI, 0.8 to 1.3). Adulthood ETS exposure was associated with an increased risk at high levels of exposure (>40 pack-years): the RRs were 1.3 (95 percent CI, 1.0 to 1.7) for exposure from a spouse only and 1.3 (95 percent CI, 1.0 to 1.8) for exposure from all household members combined, including a spouse. The qualitative estimates of ETS exposure during adulthood indicated an increased risk associated with heavy exposure (RR, 1.8; 95 percent CI, 1.1 to 2.9).

Stockwell and associates (1992) conducted a population-based, case-control study in central Florida. ETS exposure was defined as any exposure to ETS from specific persons living in the household and was measured as smoke-years of exposure from household sources, and RRs were adjusted for age, race, and education. The RR for lung cancer among women who lived with a spouse who smoked was 1.6 (95 percent CI, 0.8 to 3.0) (Table 3.52). Other estimates of RR among women who were ever exposed to ETS from a specific source were similar: mother (RR, 1.6; 95 percent CI, 0.6 to 4.3), father (RR, 1.2; 95 percent CI, 0.6 to 2.3), and siblings and others (RR, 1.7; 95 percent CI, 0.8 to 3.9). Increasing risks were observed with increasing duration of ETS exposure, and statistically significant trends were found for adulthood household exposures (p = 0.025) and lifetime household exposures (p = 0.004).

Liu and associates (1993) conducted a hospital-based, case-control study in Quangzhou, China. The study included 38 women with lung cancer and 69 women in the control group who were lifetime nonsmokers. Among the nonsmokers, women who lived with a husband who smoked 20 or more cigarettes per day had a significantly higher risk for lung cancer than did women whose husband did not smoke (RR, 2.9; 95 percent CI, 1.2 to 7.3; p for trend = 0.03) (Table 3.52).

In a report of a five-year multicenter study of ETS and lung cancer among women who did not smoke, Fontham and colleagues (1994) extended the findings of an earlier three-year report (Fontham et al. 1991). At the home interview, a urine sample was obtained from consenting study participants—81 percent of the living patients with lung cancer (54 percent of the case group) and 83 percent of the control group. Test results from the urine sample were used to screen for misclassification of current smoking status. RRs were adjusted for age, race, study area, education, intake of fruits and vegetables and supplemental vitamins, dietary cholesterol, family history of lung cancer, and employment in potentially high-risk occupations for five years or more. The increased risk for lung cancer among women who lived with a spouse who smoked tobacco was about 30 percent (RR, 1.3; 95 percent CI, 1.04 to 1.6) (Table 3.52). An increasing risk for lung cancer was observed with increasing pack-years of smoking by a spouse (p for trend = 0.03). At the highest level of pack-years (≥ 80), the RR was 1.8 (95 percent CI, 0.99 to 3.3). Elevated RRs indicated an association between reported ETS exposure in the household (RR, 1.2; 95 percent CI, 0.96 to 1.6), in the workplace (RR, 1.4; 95 percent CI, 1.1 to 1.7), and in social settings (RR, 1.5; 95 percent CI, 1.2 to 1.9). A cumulative measure of ETS exposure in all three settings during adult life demonstrated increasing risk with increasing duration of exposure (p for trend = 0.0001) and an estimated RR of 1.7 (95 percent CI, 1.1 to 2.7) at the highest level of exposure (≥ 48 smoke-years). No significant association was found between exposure during childhood and lung cancer risk.

Wang and associates (1994a) conducted a matched-pair, case-control study of lung cancer in Harbin, China. Patients and controls were matched for age, residential area, and lifetime nonsmoking status. Information on indoor smoking was collected for each residence in which a participant lived for at least three years, and RR was assessed by age at the time of exposure to ETS. In this study, no increased risk for lung

Table 3.52. Epidemiologic studies of environmental tobacco smoke (ETS) and lung cancer published during 1992–1998

Factor	Brownson et al. (1992a)	Stockwell et al. (1992)	Liu et al. (1993)	Fontham et al. (1994)
Study design	Population-based, case-control study	Population-based, case-control study	Hospital-based, case-control study	Population-based, case-control study
Country	United States	United States	China	United States
Number of cases (women nonsmokers)	432	210	38	653
Type of interview	Telephone	In-person, in home 41% of cases 54% of controls Telephone 51% of cases 46% of controls Mail 8% of cases 0.3% of controls	In-person	In-person, in home
Respondent type	Cases: 35% self 65% proxy Controls: 100% self	Cases: 33% self 67% proxy Controls: 100% self	Cases: 100% self Controls: 100% self	Cases: 63% self 37% proxy Controls: 100% self
Pathologic confirmation	100%	100%	32%	100%
Percentage with independent slide review	76%	Not done	Not done	85%
Adjustment factors	Age, previous lung disease (dietary beta-carotene and fat also evaluated)	Age, race, education	Education, occupation, living area	Age, race, study area, education, family history of lung cancer, employment in high-risk occupation, dietary cholesterol, fruits, vegetables, supplemental vitamins (previous lung disease, dietary beta-carotene, vitamin C, vitamin E also evaluated)

*Lung cancer deaths.

cancer was observed for household exposures that occurred during adult life, but estimates of RR from childhood exposure to ETS were relatively high (>3.0).

Kabat and associates (1995) conducted a U.S. hospital-based, case-control study that included 69 women as case subjects and 187 women as control subjects. RRs were adjusted for age, education, and the type of hospital. Exposure to ETS in childhood was associated with a borderline increase in risk for lung cancer (RR, 1.6; 95 percent CI, 0.95 to 2.8) (Table 3.52). Risk was significantly elevated for the highest tertile of smoke-years for childhood exposure (RR, 2.2; 95 percent CI, 1.1 to 4.5), and the linear trend was statistically significant ($p = 0.02$). No increased risk

Wang et al. (1994a)	Kabat et al. (1995)	Cardenas et al. (1997)	Boffetta et al. (1998)	Jöckel et al. (1998)
Hospital-based, case-control study	Hospital-based, case-control study	Prospective cohort study	Mixed hospital and population-based, case-control study	Population-based, case-control study
China	United States	United States	7 European countries	Germany
55	69	150*	509	53
In person	In-person, in hospital	Questionnaire self-administered by spouse of nonsmoker		
Cases: 100% self Controls: 100% self	Cases: 100% self Controls: 100% self	Cohort: 100% self	Cases: 100% self Controls: 100% self	Cases: 100% self Controls: 100% self
100%	100%	Death certificate only	96.5%	100%
Not done	Not done	Not done	Not done	Not done
None	Age, education, type of hospital	Age, race, education, weekly vegetable and citrus fruit intake, dietary fat, self-reported history of chronic lung disease, occupational exposure to asbestos, blue-collar employment	Age, interaction between sex and study center	Age, sex, region

was observed for home exposure in adulthood (RR, 0.95; 95 percent CI, 0.5 to 1.7); the RR among women who reported having a husband who smoked was 1.1 (95 percent CI, 0.5 to 1.7).

Schwartz and associates (1996) conducted a population-based study of lung cancer among nonsmokers in metropolitan Detroit, Michigan. Control subjects were frequency-matched to cases by age group, sex, race, and county of residence. Participants were described as "non-cigarette smoking," and cigar and pipe smokers were later excluded from analyses. Of the participants, 72 percent of case subjects and 64 percent of control subjects were women, but no gender-specific risk estimates were provided. Estimates of RR for lung cancer for ETS exposure were reported for two sources, exposure at home (RR, 1.1;

Table 3.52. Continued

Factor	Brownson et al. (1992a)	Stockwell et al. (1992)	Liu et al. (1993)	Fontham et al. (1994)
Estimated relative risk (95% confidence interval) for lung cancer				
ETS exposure through spouse	Ever: 1.1 (0.8–1.3) >40 pack-years:[†‡] 1.3 (1.0–1.7)	Ever: 1.6 (0.8–3.0)	≥ 20 cigarettes / day:[†] 2.9 (1.2–7.3) p for trend = 0.03	Ever: 1.3 (1.04–1.6) ≥ 80 pack-years:[†] 1.8 (0.99–3.3) p for trend = 0.03
Other measures of ETS exposure	Adult household exposure (>40 pack-years vs. no exposure): 1.3 (1.0–1.8) Childhood exposure to parental smoking: 0.7 (0.5–0.9) Adult workplace exposure (highest quartile): 1.2 (0.9–1.7)	Adult household exposure (≥ 40 smoke-years[§] vs. no exposure): 2.4 (1.1–5.3) Lifetime household exposure (≥ 40 smoke-years): 2.3 (1.1–4.6) Childhood / adolescent household exposure (≥ 22 smoke-years): 2.4 (1.1–5.4) Adult workplace exposure: no increased risk (data not shown) Adult social exposure: no increased risk (data not shown)		Childhood household exposure: 0.9 (0.7–1.1) Adult household exposure: Ever, 1.2 (0.96–1.6) High,[Δ] 1.2 (0.9–1.7) Adult workplace exposure: Ever, 1.4 (1.1–1.7) High, 1.9 (1.2–2.8) Adult societal exposure: Ever, 1.5 (1.2–1.9) High, 1.5 (0.9–2.5)
Power to detect relative risk = 1.2 (α = 0.05) for ETS exposure through spouse (%)	24	13	<5	34

[†]Highest level of ETS exposure examined.
[‡]Pack-years = number of years of smoking multiplied by the number of packs of cigarettes smoked.
[§]Sum of reported years of exposure to ETS from variety of sources; does not represent years per se, because these exposures may occur concurrently.
[Δ]>30 years.

95 percent CI, 0.8 to 1.6) and exposure at work (RR, 1.5; 95 percent CI, 1.0 to 2.2).

The first large multicenter study of ETS and lung cancer from Europe was published in 1998 (Boffetta et al. 1998). This study did not employ a single protocol but had a core of common questions used by all centers. The selection of controls varied by center: five centers were hospital based, one center was hospital and community based, and six centers were community based. Control subjects were individually matched to case subjects by gender and age in some centers, and frequency matching was performed in

Wang et al. (1994a)	Kabat et al. (1995)	Cardenas et al. (1997)	Boffetta et al. (1998)	Jöckel et al. (1998)
	Ever: 1.1 (0.6–1.9) ≥ 11 cigarettes / day:[†] 1.1 (0.5–2.3)	Ever: 1.2 (0.8–1.6) ≥ 40 cigarettes / day:[†] 1.9 (1.0–3.6) p for trend = 0.03	Ever: 1.1 (0.9–1.4) High (years x hours / day): 1.7 (1.1–2.8)	Ever : 1.1 (0.5–2.3) High: 1.9 (0.5–7.7)
Residential exposure, risk by age at exposure: 0–6 years, 3.6 (1.2–13.3) 7–14 years, 3.4 (1.1–12.7) 15–22 years, 2.4 (0.9–7.3) 23–30 years, 0.9 (0.4–2.3) 31–69 years, 0.9 (0.3–2.5)	Childhood household exposure: Any, 1.6 (0.95–2.8) High, 2.2 (1.1–4.5) Adult household exposure: Any, 0.95 (0.5–1.7) High, 1.1 (0.6–2.3) Adult workplace exposure: Any, 1.2 (0.6–2.1) High, 1.4 (0.6–2.8)		Childhood household exposure: Ever, 0.8 (0.6–0.96) High, 1.1 (0.7–1.9) Adult workplace exposure: Ever, 1.2 (0.9–1.5) High (years), 1.2 (0.7–2.3) High (years × hours / day × level of smokiness), 1.9 (1.1–3.2)	Childhood household exposure: High, 2.0 (0.6–6.8) Adulthood other sources: High, 3.1 (1.1–8.6) Total cumulative exposure: High, 3.2 (1.4–7.3)
<5	5	15	<30	<5

the others. Nonsmoking status was defined as never having smoked more than 400 cigarettes over one's lifetime. The overall RR associated with ever having been exposed to ETS in childhood was 0.8 (95 percent CI, 0.6 to 0.96) (Table 3.52). Among women who were ever married, a RR of 1.2 (95 percent CI, 0.9 to 1.6) was found for any exposure to spousal ETS. No significant trend was associated with duration of ETS exposure from husbands, in years, but the cumulative measure of hours per day times years of exposure demonstrated a significant positive trend (p = 0.03). The RR at the highest level of cumulative dose related to spousal ETS was 1.7 (95 percent CI, 1.1 to 2.8).

The authors noted that exposure to ETS in a large number of subjects had ended several years before the study and hypothesized that the somewhat lower estimates of risk in this study compared with other European studies may, in part, reflect risk reduction after cessation of exposure.

Findings from one of the participating European centers, in northwestern Germany, were reported separately by Jöckel and colleagues (1998). The

nonsmokers in this study included occasional smokers, but data for the subgroup of persons who had never smoked were also examined separately. However, results were not reported by gender. Total ETS exposure was estimated by a variable that included cumulative duration of exposure during childhood and from spouse and other sources during adult life. The RRs were 2.1 (95 percent CI, 1.02 to 4.3) among nonsmokers and 3.2 (95 percent CI, 1.4 to 7.3) among persons who had never smoked, for the highest total ETS exposure from all sources; 1.5 (95 percent CI, 0.4 to 5.9) and 1.9 (95 percent CI, 0.5 to 7.7) for high level of exposure to spousal ETS; 1.3 (95 percent CI, 0.5 to 3.8) and 2.0 (95 percent CI, 0.6 to 6.8) for high childhood exposure; and 2.3 (95 percent CI, 0.9 to 5.9) and 3.1 (95 percent CI, 1.1 to 8.6) for high exposure to other ETS sources during adulthood (workplace, public transportation, and other public places). Because of small numbers, this study had limited statistical power.

Another epidemiologic study, by Trichopoulos and coworkers (1992), focused on the association of ETS exposure and pathologic indicators of lung cancer risk. In this autopsy-based study, lung specimens taken within four hours of death from 400 persons aged 35 years or older were evaluated. Specimens were examined and scored for basal cell hyperplasia, squamous cell metaplasia, cell atypia, and mucous cell metaplasia; an index of epithelial lesions that were possibly precancerous was generated. Included in the study were 17 women nonsmokers whose husband smoked at some time and 13 women nonsmokers whose husband had never smoked. Women nonsmokers exposed to ETS from spousal smoking had a significantly higher mean index of possibly precancerous epithelial lesions than did women who lived with a spouse who did not smoke ($p = 0.02$). The results of this study provided additional support for a causative association between ETS and pulmonary carcinogenesis.

Thus, the results of recent epidemiologic studies of ETS support the findings of the EPA's 1992 detailed assessment, which concluded that ETS is causally associated with lung cancer among persons who have never smoked.

Workplace Exposure to Environmental Tobacco Smoke

Assessments of lung cancer risk associated with ETS exposure among women smokers have primarily focused on exposure from the spouse because this indicator can be consistently defined (NRC 1986; USDHHS 1986b; NIOSH 1991; EPA 1992). Table 3.53 lists studies that specifically assessed workplace exposure; several of these studies are also included among the studies of ETS exposure conducted since 1992 shown in Table 3.52. Although the results of nine U.S. studies have been reported, the data in one study related only to current work exposure. Of the remaining eight studies, five showed RRs of 1.2 to 1.9, primarily at high exposure levels (Wu et al. 1985; Butler 1988; Brownson et al. 1992a; Fontham et al. 1994; Kabat et al. 1995), although results were statistically significant only in the largest study (Fontham et al. 1994). Two studies showed RRs less than 1.0 (Garfinkel et al. 1985; Janerich et al. 1990), and one study did not provide risk estimates but reported no association (Stockwell et al. 1992). The largest U.S. study (Fontham et al. 1994) showed an increasing risk for lung cancer with increasing years of exposure in the workplace. RRs were 1.3 (95 percent CI, 1.01 to 1.7) for 1 through 15 years, 1.4 (95 percent CI, 1.04 to 1.9) for 16 through 30 years, and 1.9 (95 percent CI, 1.2 to 2.8) for more than 30 years (p for trend = 0.001). A later analysis of these data, reported by Reynolds and associates (1996), was restricted to women who were ever employed outside the home for six months or more, and values were adjusted for sources of ETS exposure other than the workplace during adult life. The resulting RRs were slightly higher than those reported in the study by Fontham and colleagues (1994), and the trend remained statistically significant.

Workplace exposure was also examined in the European multicenter study of ETS and lung cancer (Boffetta et al. 1998). Among women who were ever exposed to ETS, RR was 1.2 (95 percent CI, 0.9 to 1.5). Although no significant increase in risk was correlated with duration of exposure in years, trend in risk increased significantly (p for trend = 0.03) for the measure of weighted cumulative exposure (hours per day x years x level of smokiness of workplace). At the highest level of cumulative workplace exposure, RR was 1.9 (95 percent CI, 1.1 to 3.2).

Conclusion

1. Exposure to ETS is a cause of lung cancer among women who have never smoked.

Environmental Tobacco Smoke and Coronary Heart Disease

Previous Reviews

Approximately 20 reports of epidemiologic studies that investigated the association between ETS and risk for CHD among nonsmokers have been

Table 3.53. Relative risks for lung cancer associated with workplace exposure to environmental tobacco smoke among women who never smoked

Study	Country	Workplace exposure indicator	Relative risk (95% confidence interval)
Kabat and Wynder 1984	United States	Current regular exposure	0.7 (0.3–1.5)
Koo et al. 1984	Hong Kong	Exposure at work or work and home*	1.4 (0.5–3.7)
Garfinkel et al. 1985	United States	Exposure at work for last 25 years	0.9 (0.7–1.2)
Wu et al. 1985	United States	Exposure at work	1.3 (0.5–3.3)
Lee et al. 1986	England	Exposure at work	0.6 (0.2–2.3)
Butler 1988	United States	Exposure at work for ≥ 11 years	1.5 (0.2–14.1)
Shimizu et al. 1988	Japan	Exposure at work	1.2 (0.7–2.0)
Janerich et al. 1990	United States	Exposure at work, 150 person-years	0.9 (0.8–1.04)†
Kalandidi et al. 1990	Greece	Highest level of exposure	1.1 (0.2–1.9)
Wu-Williams et al. 1990	China	Exposure at work	1.1 (0.9–1.6)
Brownson et al. 1992a	United States	Any exposure Highest level of exposure	No association 1.2 (0.9–1.7)
Stockwell et al. 1992	United States	Not specified	No association
Fontham et al. 1994	United States	Any exposure Highest level of exposure	1.4 (1.1–1.7) 1.9 (1.2–2.8)
Kabat et al. 1995	United States	Any exposure Highest level of exposure	1.2 (0.6–2.1) 1.4 (0.6–2.8)
Boffetta et al. 1998	7 European countries	Any exposure Highest level of exposure	1.2 (0.9–1.5) 1.9 (1.1–3.2)
Jöckel et al. 1998	Germany	Highest level of exposure	2.7 (0.7–9.7)†

*Total exposure was as follows: 2,121 hours over 2.0 years for cases; 1,681 hours over 1.2 years for controls.
†Includes women and men study participants. No separate data reported for women.

published. Several reviews (Table 3.54), a position paper from the American Heart Association (Taylor et al. 1992), and commentaries on methodologic issues of concern (Glantz and Parmley 1996; Kawachi and Colditz 1996) were also published on this topic. The reviews included qualitative evaluation of the studies, meta-analyses deriving a pooled estimate of the RR for CHD in relation to ETS exposure, and risk assessments estimating the number of CHD deaths among nonsmokers that were attributable to ETS exposure. These reviews concluded that ETS exposure significantly increases the risk for CHD among nonsmokers. The pooled estimates for CHD mortality and morbidity reported in the different reviews were similar.

Cohort Studies

Cohort studies that examined the relationship between ETS and the risk for CHD among nonsmokers, including deaths and nonfatal events, are listed in Table 3.55. Of the eight studies that provided data for women, seven showed higher risk for CHD

Table 3.54. Associations between risk for coronary heart disease (CHD) mortality or morbidity and exposure to environmental tobacco smoke among persons who never smoked, reviews

Review	References*	Qualitative review	Population	Pooled relative risk (95% confidence interval)	Estimated number of deaths from CHD/year among women and men combined
National Research Council 1986	1–4	Yes	NR[†]	NR	NR
U.S. Department of Health and Human Services 1986b	1–4	Yes	NR	NR	NR
Wells 1988, 1989	1–6	No	Women Men	1.2 (1.1–1.4)[‡] 1.3 (1.1–1.6)[‡]	31,900
Wu-Williams and Samet 1990	1–6	Yes	NR	NR	NR
Glantz and Parmley 1991	1–10	Yes	Women Men Women and men	1.3 (1.2–1.4)[‡] 1.3 (1.1–1.6)[‡] 1.3 (1.2–1.4)[‡]	37,000
Steenland 1992	1, 3–9, 11	Yes	NR	NR	28,026
Wells 1994	1, 3–5, 7–14, 15	Yes	Women Women Men Men Women and men Women and men	1.2 (1.1–1.4)[§] 1.5 (1.2–2.0)[Δ] 1.3 (1.03–1.5)[§] 1.3 (0.9–1.8)[Δ] 1.2 (1.1–1.4)[§] 1.4 (1.1–1.8)[Δ]	61,912
Law et al. 1997b	1, 3–5, 7–9, 11–13, 15–20	Yes	Women and men	1.3 (1.2–1.3)[‡]	
Wells 1998	1, 3–5, 7–20	Yes	Women Women Men Men Women and men Women and men	2.8 (0.95–8.3)[§] 1.9 (1.3–3.0)[Δ] 1.1 (0.2–5.2)[§] 2.7 (0.6–12.1)[Δ] 1.2 (1.1–1.3)[§] 1.5 (1.3–1.8)[Δ]	
He et al. 1999	1, 3–5, 7–19	Yes	Women Men	1.2 (1.2–1.3)[‡] 1.2 (1.1–1.4)[‡]	NR

*References included Hirayama 1984b (1), Gillis et al. 1984 (2), Garland et al. 1985 (3), Lee et al. 1986 (4), Svendsen et al. 1987 (5), Helsing et al. 1988 (6), He et al. 1989 (7), Hole et al. 1989 (8), Humble et al. 1990 (9), Butler 1988 (10), Dobson et al. 1991b (11), He et al. 1994 (12), La Vecchia et al. 1993a (13), Jackson 1989 (14), Sandler et al. 1989 (15), Muscat and Wynder 1995a (16), Steenland et al. 1996 (17), Kawachi et al. 1997a (18), Ciruzzi et al. 1998 (19), Tunstall-Pedoe et al. 1995 (20). References 2 and 8 described the same study population; references 6 and 15 described the same study population.

[†]NR = Data not calculated or not reported.

[‡]CHD mortality and morbidity.

[§]CHD mortality.

[Δ]CHD morbidity.

among women whose husband was a smoker than among women whose husband was a nonsmoker (Hirayama 1984a; Garland et al. 1985; Butler 1988; Helsing et al. 1988; Humble et al. 1990; Steenland et al. 1996; Kawachi et al. 1997a) (Table 3.55 and Figure 3.10). Three of five studies that included data for men also showed higher risk for CHD associated with wives' smoking (Svendsen et al. 1987; Helsing et al. 1988; Steenland et al. 1996) (Table 3.55 and Figure 3.10). One cohort analysis that used CPS-I and CPS-II data showed no association between the risk for CHD mortality and spousal smoking among either women or men (LeVois and Layard 1995). However, this conclusion was based on any ETS exposure (i.e., former or current) from the spouse, and the effect of the spouse's current smoking on the risk for CHD was not reported separately. A more careful and complete analysis of the CPS-II data was conducted by Steenland and coworkers (1996). Their analysis showed that exposure to the spouse's current smoking was associated with an increased risk for CHD among both women and men. The U.S. Nurses' Health Study (Kawachi et al. 1997a) also demonstrated that ETS exposure at home and at work separately or in combination was associated with an increased risk for both nonfatal MI and fatal CHD.

Case-Control Studies

Almost all of the 10 case-control studies that examined the association between exposure to ETS and CHD risk were small, hospital-based studies with direct interviews about relevant sources of ETS exposure among both case subjects and control subjects (Table 3.56). Only 1 study (Layard 1995) relied exclusively on mailed responses provided by next of kin for persons who had died of CHD or unspecified causes not related to smoking. In 7 studies, risk for CHD was elevated among persons with a spouse who smoked (He 1989; Jackson 1989; La Vecchia et al. 1993a; He et al. 1994; Muscat and Wynder 1995a; Ciruzzi et al. 1998) or among persons who were exposed to unspecified sources of ETS (Tunstall-Pedoe et al. 1995). In 2 other studies, associations were reported either among women (Dobson et al. 1991b) or among men (Lee et al. 1986) but not among both genders (Figure 3.11). In 1 study (Layard 1995), no association was found between spousal smoking and risk for CHD. However, the quality of information on ETS exposure in this study was questionable. It is not known whether spousal ETS exposure was current or former exposure or whether it was from a current or previous marriage. All respondents for both case and control groups were next of kin, and 18 percent of respondents were not even first-degree relatives. Approximately one-half of all available CHD deaths in this study were also excluded from the analysis because of missing information on marital status, smoking behavior of the spouse, or both factors.

Dose-Response Relationship

More than one-half of the studies shown in Tables 3.55 and 3.56 investigated whether a dose-response relationship exists between exposure to ETS from spousal smoking and risk for CHD among nonsmokers. Some studies determined risk among nonsmokers whose spouse was a former or current smoker and among nonsmokers whose spouse had never smoked (Garland et al. 1985; Butler 1988; La Vecchia et al. 1993a; Steenland et al. 1996). Three of these studies reported that the risk was higher among nonsmokers married to a current smoker than among nonsmokers married to a former smoker (Butler 1988; La Vecchia et al. 1993a; Steenland et al. 1996). Several studies also investigated the intensity of ETS exposure by examining the number of cigarettes smoked by the spouse of nonsmokers (Hirayama 1984a, 1990; He 1989; La Vecchia et al. 1993a; Layard 1995; LeVois and Layard 1995; Ciruzzi et al. 1998), the number of years of smoking (Butler 1988; Muscat and Wynder 1995a; Kawachi et al. 1997a), the number of pack-years of smoking (Steenland et al. 1996), a cumulative index of ETS exposure from the spouse and coworkers (He et al. 1994; Kawachi et al. 1997a), a score representing household exposure (Helsing et al. 1988), and a qualitative assessment of level of exposure (Tunstall-Pedoe et al. 1995). More intense ETS exposure was associated with a higher risk for CHD in some of these studies, but the differences in risk between levels of ETS exposure were not large (Hirayama 1984b; Butler 1988; Helsing et al. 1988; He 1989; La Vecchia et al. 1993a; He et al. 1994; Tunstall-Pedoe et al. 1995; Steenland et al. 1996; Kawachi et al. 1997a).

Sources of Exposure Other than Spousal Smoking

Several case-control and cohort studies collected information on exposure to ETS from sources other than the spouse (Lee et al. 1986; Svendsen et al. 1987; Butler 1988; Dobson et al. 1991b; He et al. 1994; Muscat and Wynder 1995a; Steenland et al. 1996; Kawachi et al. 1997a; Ciruzzi et al. 1998). One study specifically assessed ETS exposure from children of index subjects and reported an increase of 80 percent in

Table 3.55. Associations between adult exposure to environmental tobacco smoke (ETS) from spouses or household members or in the workplace and relative risks for mortality or morbidity from coronary heart disease (CHD), among persons who never smoked, cohort studies

Study	Population	Year study began/average length of follow-up	Number of CHD events	Relative risk (95% confidence interval)	Adjustment factors
Hirayama 1984b	91,540 married women Japan	1966 16 years	494 deaths	1.3 (1.1–1.6)*	Age, spouse's occupation
Garland et al. 1985	695 married women San Diego, California	1972 10 years	10 deaths	2.7†	Age, systolic blood pressure, plasma cholesterol level, obesity, years of marriage
Svendsen et al. 1987	1,245 married men 18 U.S. cities	1973 7 years	13 deaths 69 fatal and nonfatal events	2.2 (0.7–6.9)‡ 1.6 (1.0–2.7)‡	Age, blood pressure, cholesterol level, weight, alcohol use, education
Butler 1988	9,785 women (from spouse pairs) Loma Linda, California	1976 6 years	87 deaths	1.4 (0.5–3.8)§	Body mass index, history of hypertension and diabetes, exercise
	3,488 women, 1,489 men Adventist Health Smog Study Loma Linda, California	1976 6 years	Women: 70 deaths Men: 76 deaths	1.5 (0.9–2.5)Δ 0.6 (0.3–1.2)Δ	Age
Helsing et al. 1988	12,348 women, 3,454 men Western Maryland	1963	Women: 988 deaths Men: 370 deaths	1.2 (1.1–1.4)¶ 1.3 (1.1–1.6)¶	Education, marital status, age, housing quality
Hole et al. 1989	2,455 women and men Scotland	1972 11.5 years	84 deaths	2.0 (1.2–3.4)**	Age, gender, social class, diastolic blood pressure, serum cholesterol level, body mass index
Humble et al. 1990	513 married women Evans County, Georgia	1960 20 years	76 deaths	1.6 (1.0–2.6)‡	Age, blood pressure, cholesterol level, body mass index

*Spouse smoked >20 cigarettes / day vs. spouse never smoked.
†Spouse was current or former smoker vs. spouse did not smoke; the confidence interval was not provided, but the p value was reported to be ≤ 0.10.
‡Spouse smoked vs. spouse did not smoke.
§Spouse was current smoker vs. spouse never smoked.
ΔLived with a smoker for >11 years vs. no ETS exposure at home.
¶Score for household ETS >1 vs. 0.
**Any passive smoking vs. none.

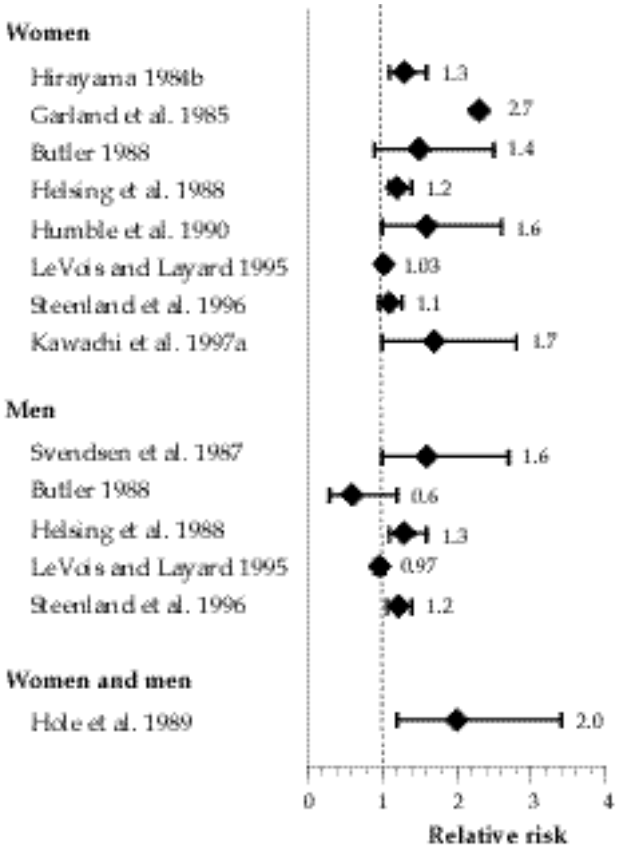
Table 3.55. Continued

Study	Population	Year study began/average length of follow-up	Number of CHD events	Relative risk (95% confidence interval)	Adjustment factors
LeVois and Layard 1995	247,412 women, 88,458 men CPS-I[††]	1960 13 years	Women and men: 14,901 deaths	1.00 (0.97–1.04)[‡]	Age, race
			Women: 7,133 deaths	1.03 (0.98–1.1)[‡]	
			Men: 7,768 deaths	0.97 (0.9–1.1)[‡]	
	226,067 women, 108,772 men CPS-II[‡‡]	1983 6 years	Women: 1,099 deaths	1.0 (0.98–1.1)[‡]	
			Men: 1,966 deaths	0.97 (0.9–1.1)[‡]	
Steenland et al. 1996	208,372 women, 101,227 men CPS-II	1982 7 years	Women: 1,325 deaths	1.1 (0.96–1.3)[§]	Age; history of heart disease, hypertension, arthritis; body mass index; alcohol use; use of aspirin and diuretics; employment status; exercise; estrogen use in women
			Men: 2,494 deaths	1.2 (1.1–1.4)[§]	
Kawachi et al. 1997a	32,046 women Nurses' Health Study	1982 10 years	152 total events	1.7 (1.03–2.8)[§§]	Alcohol use; body mass index; history of hypertension, diabetes, hypercholesterolemia, infarctions; menopausal status; use of hormones; physical activity; intake of vitamin E and fat; aspirin use; family history
			127 nonfatal myocardial infarctions	1.7 (0.99–3.0)[§§]	
			25 deaths	1.9 (0.6–8.2)[§§]	

[‡]Spouse smoked vs. spouse did not smoke.
[§]Spouse was current smoker vs. spouse did not smoke.
[††]CPS-I = Cancer Prevention Study I; American Cancer Society cohort.
[‡‡]CPS-II = Cancer Prevention Study II; American Cancer Society cohort.
[§§]Any ETS exposure at home or at work vs. none.

association with such exposure (Ciruzzi et al. 1998). The strongest evidence of ETS exposure in the workplace associated with CHD was observed in a case-control study from China (He et al. 1994) and a cohort study of nurses in the United States—the U.S. Nurses' Health Study (Kawachi et al. 1997a). He and colleagues (1994) reported that the risk for CHD was higher among women who had more hours of ETS exposure per day in the workplace, were exposed to a greater number of smokers, were exposed for more years, or had a higher cumulative exposure (number of cigarettes per day x duration). However, a smooth dose-response trend for years of exposure at work was not observed. In the U.S. Nurses' Health Study (Kawachi et al. 1997a), the multivariate RRs for total CHD (fatal and nonfatal events combined) among women who had never smoked and who were exposed to ETS only at work were 1.5 (95 percent CI, 0.7 to 3.1) for occasional exposure and 1.9 (95 percent CI, 0.9 to 4.2) for regular exposure. Weaker effects associated with ETS exposure at work were reported in other U.S. studies (Svendsen et al. 1987; Butler 1988; Steenland et al. 1996).

Figure 3.10. Exposure to environmental tobacco smoke from spouses' smoking and relative risks for mortality or morbidity from coronary heart disease (CHD), cohort studies



*The confidence interval was not provided, but the p value was reported to be ≤ 0.10.

Mortality, Morbidity, and Symptoms

ETS exposure is associated with risk for CHD mortality (fatal events), morbidity (nonfatal events), and symptoms. Most of the data on the association with mortality were from cohort studies, but most of the data on the association with morbidity were from case-control investigations. Nonetheless, the magnitude of association is similar in both sets of results. The risk for CHD morbidity and mortality from ETS exposure could be directly compared within two studies (Svendsen et al. 1987; Hole et al. 1989). These comparisons suggested that the effect of ETS may be stronger for CHD mortality than for CHD morbidity. In one study (Hole et al. 1989), the RR for CHD mortality was 2.0 (95 percent CI, 1.2 to 3.4) (Table 3.55), but for angina or major abnormalities shown by electrocardiography, the RRs were 1.1 (95 percent CI, 0.7 to 1.7) and 1.3 (95 percent CI, 0.5 to 3.4), respectively. In another study (Svendsen et al. 1987), the RR for CHD mortality was 2.2 (95 percent CI, 0.7 to 6.9), but the RR for mortality and morbidity combined was 1.6 (95 percent CI, 1.0 to 2.7) (Table 3.55).

In summary, data from cohort and case-control studies for diverse populations of women and men support a causal association between ETS exposure and CHD mortality and morbidity among nonsmokers. Although few of the risk estimates in individual studies were statistically significant, pooled estimates from meta-analyses showed a significant, 30-percent increase in risk for CHD in relation to ETS exposure. More than one-half of the studies were cohort studies, and the information on smoking status and exposure to ETS was obtained at study entry, thus minimizing recall and misclassification bias. Estimates of risk were determined after adjustment for demographic factors and often for other factors related to CHD that may confound the association.

Effects on Markers of Cardiovascular Function

Studies of mechanisms through which exposure to ETS increases the risk for CHD among nonsmokers have been reviewed (Glantz and Parmley 1991, 1995; National Cancer Institute 1999). Evidence suggested that exposure to ETS has acute effects on cardiovascular function among healthy nonsmokers and among those at risk for CHD. These deleterious effects include thickening of the carotid artery wall, dysfunction of endothelium, compromised exercise performance, change in lipoprotein distribution, increased plasma fibrinogen, and increased platelet aggregation—conditions that may account for both short-term and long-term effects of ETS on the heart.

Conclusion

1. Epidemiologic and other data support a causal relationship between ETS exposure from the spouse and coronary heart disease mortality among women nonsmokers.

Environmental Tobacco Smoke and Reproductive Outcomes

Active smoking has been causally associated with various adverse reproductive outcomes, including LBW and early age at menopause (see "Reproductive Outcomes" earlier in this chapter). This

section summarizes studies published between 1966 and early 1999 that examined the relationship between exposure to ETS and developmental and reproductive outcomes. Several previous reviews have been published, the most comprehensive of which is the one by CEPA and the California Department of Health Services (CEPA 1997; Hood 1990; Seidman and Mashiach 1991; Ahlborg 1994). Two meta-analyses have also been conducted (Peacock et al. 1998; Windham et al. 1999a).

Perinatal Effects

Three categories of adverse pregnancy outcomes are reviewed here in relation to ETS exposure during pregnancy: fetal growth, including LBW and IUGR; fetal loss, including spontaneous abortion and perinatal mortality; and congenital malformations. Emphasis is on fetal growth, the outcome for which the most epidemiologic data have been collected.

Fetal Growth

More than 25 epidemiologic studies of the relationship between fetal growth and ETS exposure have been published. Some studies included fetal length (Karakostov 1985; Schwartz-Bickenbach et al. 1987; Lazzaroni et al. 1990; Roquer et al. 1995; Luciano et al. 1998), which was slightly lower with ETS exposure (0.3 to 1.1 cm). In three of these studies, however, results were not adjusted for covariates. The findings of these studies on fetal length are not considered further here.

When fetal growth is examined, several covariables should be considered. These covariables include maternal age, race, parity or previous reproductive history, and socioeconomic status or access to prenatal care. Few studies have information on maternal stature or weight gain, but these data are also important determinants of fetal weight, as are certain maternal illnesses, complications of pregnancy, and the gender of the infant. However, only if these factors were also related to ETS exposure would they be confounders. Gestational age at delivery, the strongest predictor of birth weight, was taken into account in some but not all studies.

Mean Birth Weight

Studies that examined mean birth weight and reported a measure of variability generally also reported lower birth weights in association with ETS exposure, although some of the differences in weight were small (Figure 3.12). Four studies (Haddow et al. 1988; Eskenazi et al. 1995b; Rebagliato et al. 1995; Peacock et al. 1998) measured cotinine, a biomarker of ETS exposure, and adjusted differences in mean birth weight for covariates (Table 3.57 and Figure 3.12, bottom). Haddow and colleagues (1988) found an average weight deficit of 104 g among the offspring of women who had a cotinine level of 1 to 10 ng/mL compared with women who had a level of less than 0.5 ng/mL.

Eskenazi and coworkers (1995b) reported an adjusted weight decrement of 45 g among infants of mothers who had a cotinine level of 2 to 10 ng/mL compared with mothers who had a level of less than 2 ng/mL (defined as unexposed). However, the proportion of women categorized as exposed to ETS (5 percent) was smaller than that in other studies, and 50 percent of the women whose cotinine level indicated nonexposure reported having a husband who smoked. The detection limit of the cotinine assay was high (2 ng/mL) and samples were stored for 25 years, which may indicate that persons in the unexposed group may be misclassified.

In the study by Rebagliato and coworkers (1995), mean infant birth weight was decreased 87.3 g at the highest quintile of maternal cotinine level (>1.7 ng/mL) among nonsmokers, but the dose-response trend was inconsistent in a multiple regression model. When the categories were combined, the estimated crude decrement in birth weight at a cotinine level higher than 0.5 ng/mL was 34.5 g. Peacock and colleagues (1998) also examined mean birth weight in relation to quintiles of serum cotinine level less than 15 ng/mL among white, nonsmoking pregnant women. A statistically significant trend toward lower mean birth weight was noted across increasing cotinine level; however, the decrement of 73 g in the highest quintile group (≥ 0.796 ng/mL) compared with the lowest quintile group (≤ 0.18 ng/mL) was not statistically significant. After adjustment for gestational age and other covariates, the birth weight ratio (observed to expected based on an external standard) indicated a nonsignificant weight decrement of only 0.2 percent for ETS exposure compared with 5 percent for active smoking. Thus, the results from the more recent studies were in the direction of findings in the study of Haddow and colleagues (1988) but showed weaker effects. Adjustment for gestational age (e.g., Eskenazi et al. 1995b; Peacock et al. 1998) may represent overcontrolling because gestational age is a determinant of birth weight, but the adjustment was performed in an attempt to separate effects of gestational age from effects of growth retardation.

Table 3.56. Relative risks for coronary heart disease (CHD) associated with adult exposure to environmental tobacco smoke (ETS) among persons who never smoked or nonsmokers, case-control studies

Study	Population*	Source: Cases	Source: Controls	Relative risk† (95% confidence interval)	Adjustment factors
Lee et al. 1986	Women 77 cases 318 controls Men 41 cases 133 controls United Kingdom	Hospital	Hospital	Women: 0.9 (0.6–1.7) 0.4 (0.1–1.4)‡ Men: 1.2 (0.6–2.8) 0.8 (0.2–2.0)‡	Not available
He 1989	Women§ 34 cases 68 controls China	Hospital	Hospital and population	Women: 1.5 (1.3–1.8)	Alcohol use; exercise; personal and family history of CHD, hypertension, hyperlipidemia
Jackson 1989	Women△ 22 cases 174 controls Men△ 44 cases 84 controls New Zealand	Hospital Myocardial infarction Death from CHD	Hospital	Women: 2.7 (0.6–12.3)¶ Men: 1.0 (0.3–3.0)¶ Women: 5.8 (1.0–35.2)¶ Men: 1.1 (0.2–5.3)¶	Age, social status, history of CHD
Dobson et al. 1991b	Women△ 160 cases 532 controls Men△ 183 cases 293 controls Australia	Hospital deaths from myocardial infarction and CHD	Community-based survey of risk	Women: 2.5 (1.5–4.1)¶ Men: 1.0 (0.5–1.8)¶	Age, history of myocardial infarction
La Vecchia et al. 1993a	Women 43 cases 56 controls Men 64 cases 161 controls Italy	Hospital	Hospital	Women and men: 1.2 (0.6–2.5)**	Gender, age, coffee intake, body mass index, cholesterol level, diabetes, hypertension, family history of myocardial infarction

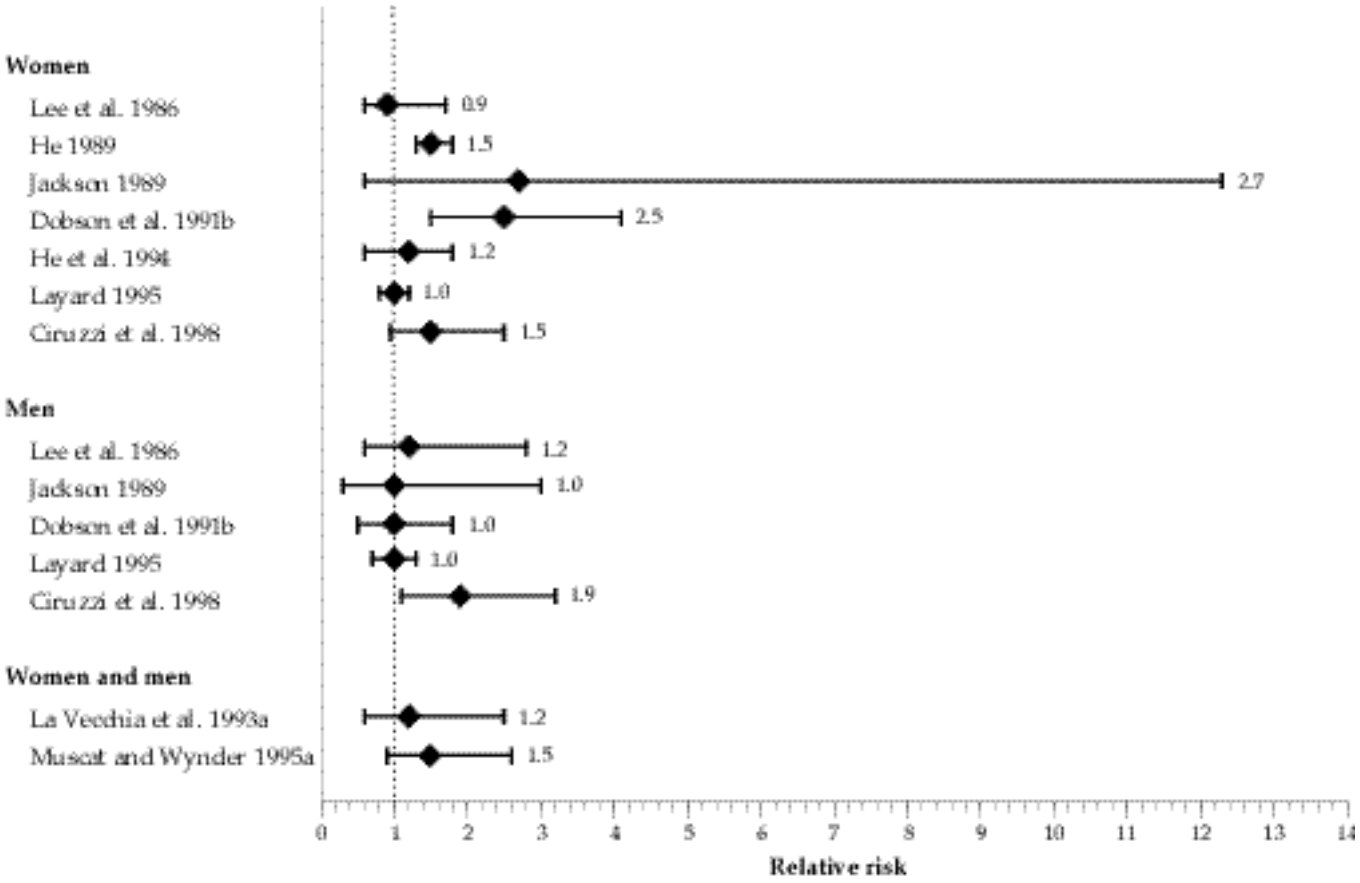
*Unless otherwise specified, study population never smoked.
†Unless otherwise specified, relative risk from any exposure to ETS from spouse vs. no exposure.
‡ETS score 5–12 vs. 0–1, including ETS exposure at home, work, travel, and leisure.
§Nonsmokers.
△Nonsmokers, but unclear whether population never smoked.
¶For any exposure to ETS at home vs. no exposure.
**Spouse was current smoker vs. spouse did not smoke.

Table 3.56. Continued

Study	Population*	Source: Cases	Source: Controls	Relative risk† (95% confidence interval)	Adjustment factors
He et al. 1994	Women 59 cases 126 controls China	Hospital	Hospital Population	Women: 1.2 (0.6–1.8) 1.9 (0.9–4.0)††	Age, type A personality, total and high-density lipoprotein cholesterol levels, history of hypertension
Layard 1995	Women 914 cases 969 controls Men 475 cases 998 controls National Mortality Follow-back Survey United States	Deaths from ischemic heart disease identified in survey	Deaths from unspecified causes not related to smoking	Women: 1.0 (0.8–1.2) Men: 1.0 (0.7–1.3)	Age, race
Muscat and Wynder 1995a	Women 46 cases 50 controls Men 68 cases 108 controls 4 U.S. cities	Hospital	Hospital	Women and men: 1.5 (0.9–2.6)‡‡ Women: 1.3 (0.7–2.4)‡‡ Men: 1.7 (0.7–3.7)‡‡	Age, education, hypertension
Tunstall-Pedoe et al. 1995	Women and men 70 cases 2,278 controls Scotland	General practitioner list; self-report of a diagnosed CHD	General practitioner list; self-report of a diagnosed CHD	Women and men: 2.4 (1.1–4.8)§§	Age, housing, tenure, cholesterol level, diastolic blood pressure
Ciruzzi et al. 1998	Women 180 cases 218 controls Men 156 cases 228 controls 10 South American countries	Hospital	Hospital	Women: 1.5 (0.95–2.5)ΔΔ Men: 1.9 (1.1–3.2)	Age, cholesterol level, diabetes, hypertension, body mass index, education, socioeconomic status, exercise, family history of myocardial infarction

*Unless otherwise specified, study population never smoked.
†Unless otherwise specified, relative risk from any exposure to ETS from spouse vs. no exposure.
††For any ETS exposure at work vs. no exposure.
‡‡For any ETS exposure including spouse, work, transportation, and other vs. no exposure.
§§Any exposure to ETS from someone else in last 3 days.
ΔΔOne or more relatives smoking.

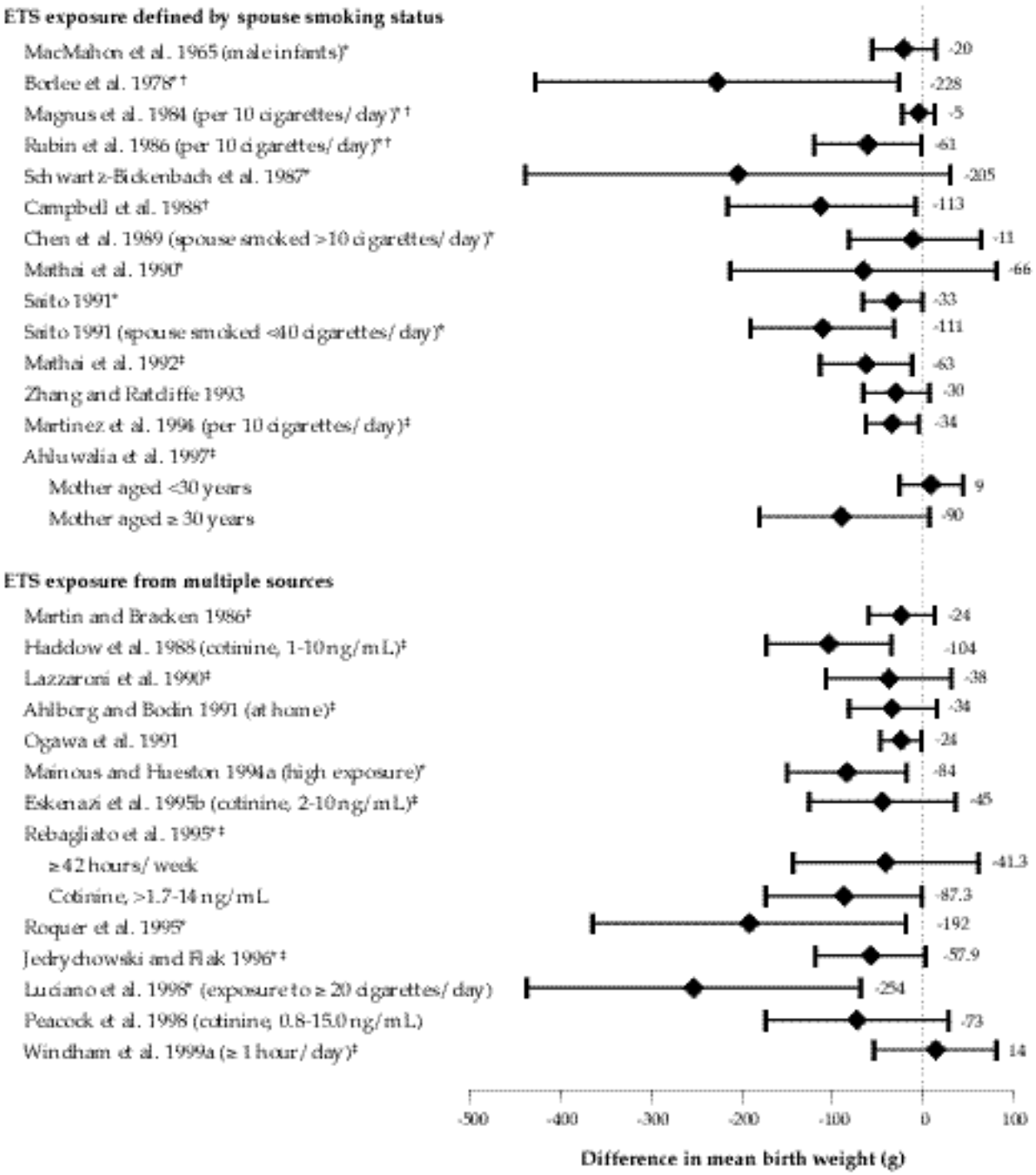
Figure 3.11. Exposure to environmental tobacco smoke from spouses' smoking and risk of coronary heart disease (CHD), case-control studies



Studies that attempted to ascertain total ETS exposure from multiple sources by self-report provided further evidence of an effect of ETS exposure (Figure 3.12, bottom). After adjustment for potential confounders, most of the studies (Figure 3.12, bottom) showed small-to-moderate decrements in mean birth weight (10 to 90 g) associated with ETS exposure. Ogawa and associates (1991) provided an adjusted estimate of a 10.8-g decrement, but because no CI was provided, it is not included in Figure 3.12. The studies were not, however, comparable in their definition of exposure, and the reference groups may have included some women whose exposure was low (particularly Ahlborg and Bodin 1991; Ogawa et al. 1991). Some studies examined term births only (Martin and Bracken 1986; Lazzaroni et al. 1990; Ogawa et al. 1991; Luciano et al. 1998); weight differences for term births tended to be less variable than those for all births. Findings of the prospective studies (Martin and Bracken 1986; Ahlborg and Bodin 1991; Rebagliato et al. 1995) were not consistently different from those of other studies. Two European studies found large weight decrements in relation to high exposure, that is, among infants of mothers exposed to the equivalent of one pack of cigarettes per day at home or work, but results were not adjusted for potential confounding factors (Roquer et al. 1995; Luciano et al. 1998).

Several of these studies provided information on level of exposure to ETS. Mainous and Hueston (1994a) found a weight decrement among infants of mothers in the highest category of exposure only (e.g., mothers who were always in contact with persons who smoked), whereas Rebagliato and colleagues (1995) found a decrement for all quintiles of total hours of exposure but no consistent gradient with increasing exposure. Lazzaroni and coworkers (1990) reported evidence of greater weight decrements with greater exposure, and the mean birth weight among infants of women who were exposed five or more

Figure 3.12. Differences in mean birth weight (and 95% confidence interval) among infants of mothers exposed to environmental tobacco smoke (ETS) compared with infants of mothers not exposed to ETS



*Differences and confidence intervals calculated by using data from published report of study.
†Study includes maternal smokers; results adjusted for maternal smoking.
‡Adjusted for various confounders, depending on study.

Table 3.57. Differences in birth weight between infants of nonsmoking mothers exposed to environmental tobacco smoke (ETS) and infants of mothers not exposed to ETS, based on measurement of biomarkers

Study (location)	Number of samples	Cotinine level defining exposure (% of mothers exposed)	Difference in mean birth weight between exposed and unexposed (95% confidence interval)	Results for low birth weight
Haddow et al. 1988 (Maine)	1,231 serum samples obtained in second trimester	1–10 ng / mL(3.4%)	-104 g (-173 to 35 g)	29% increase in rate*
Eskenazi et al. 1995b (California)	2,243 serum samples obtained in second trimester	2–10 ng / mL (5%)	-45 g (-125.6 to 36.0 g)	Relative risk = 1.4 (95% confidence interval, 0.6–3.0)
Rebagliato et al. 1995 (Spain)	690 saliva samples obtained in third trimester	>1.7–14 ng / mL (19%)	-87.3 g (-173.5 to -1.1 g)	Not given
Peacock et al. 1998 (United Kingdom)	Serum samples from 827 nonsmokers Mean of two or three serum cotinine levels	Quintiles Lowest: 0–0.18 ng / mL Highest: 0.796–15 ng / mL	-73 g (-174 to 28 g) Unadjusted mean difference between infants of women in highest and lowest quintiles; significant dose trend	Not given

*No statistical test.

hours per day was similar to that among infants of women who were light smokers.

A few studies examined sources of exposure separately. In Sweden, Ahlborg and Bodin (1991) found a slight decrement in infant weight in relation to maternal exposure to ETS at home (-34 g; 95 percent CI, -82 to 15 g) and a slight increment in relation to exposure at work (20 g; 95 percent CI, -37 to 77 g), but neither estimate was statistically significant. In Spain, Rebagliato and associates (1995) found birth weight decrements at all levels of maternal exposure to ETS at work and other public places but a slight increment with exposure at home; statistical significance varied by type and level of exposure. Workplace exposure may differ from that at home because of the number of smokers contributing to ETS and the influence of environmental conditions (e.g., rates of air exchange, temperature, and room size).

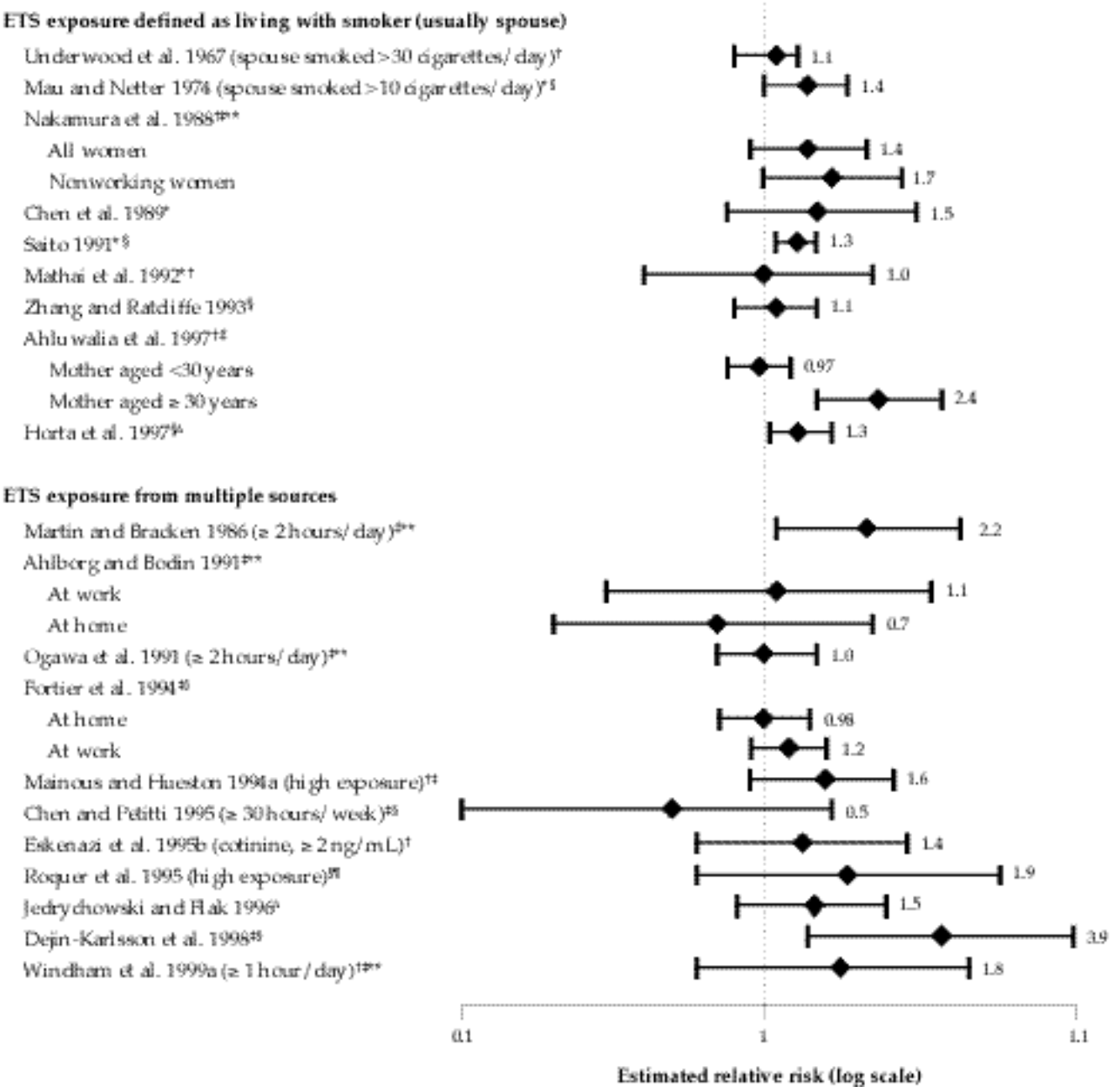
Thus, minor inconsistencies related to dose and source of exposure emerge from studies of multiple sources of exposure. On average, however, the infants of women exposed to ETS during pregnancy appear to have a weight decrement in the range of 40 to 50 g. Furthermore, the decrease in birth weight may be greatest among infants of women with the highest exposure to ETS.

The weight differences among infants that were reported from studies based only on maternal exposure to ETS from spousal or household smokers vary greatly—from a decrement of 5 g to a decrement of more than 200 g. (See Figure 3.12, top, for studies that provided CIs or data to calculate them.) The studies were difficult to compare because of their many differences, including when they were conducted over a 25-year span, the location and nationality of study populations, the sample size and selection, the extent to which confounders were controlled, and the analytic methods used. Some of these earlier studies included maternal smokers but adjusted for that variable (Magnus et al. 1984; Rubin et al. 1986; Campbell et al. 1988).

Low Birth Weight and Intrauterine Growth Retardation

Most studies that have reported RRs for LBW or IUGR in relation to ETS exposure found a slightly elevated risk for these conditions among infants of mothers exposed to ETS (Table 3.57 and Figure 3.13). The area of overlap for all the CIs is consistent with up to a 1.4- or 1.5-fold higher risk for small fetal size, but is also consistent with no association. One study that used cotinine to assess ETS exposure (Eskenazi et

Figure 3.13. Relative risks (95% confidence interval) for low birth weight (LBW) or intrauterine growth retardation (IUGR) among infants of mothers exposed to environmental tobacco smoke (ETS) compared with infants of mothers not exposed to ETS



*Relative risks and confidence intervals calculated by using data from published report of study.
†Examined LBW, usually defined as <2,500 g, but Mathai et al. (1992) defined it as <2,000 g.
‡Adjusted for various confounders, depending on study.
§Examined IUGR, usually defined as <10th percentile of weight for gestational age, but Saito et al. (1991) defined it as <1.5 standard deviations of the mean for gestational age, and Dejin-Karlsson (1998) defined it as <2 standard deviations below the mean.
ΔStudy includes maternal smokers; results adjusted for maternal smoking.
¶High exposure at work or home, based on 1 smoker of >1 pack / day or ≥ 2 smokers of 10 cigarettes / day.
**Based on low birth weight at term.

al. 1995b) found a slight and nonsignificant elevation in risk for LBW. The comparison group may have included women who were exposed to ETS, as discussed earlier in this section, which would dilute the estimated effect. Another study that used cotinine measurement reported a 29-percent increase in risk, but did not adjust for potential confounders nor provide a CI for its finding on LBW (Haddow et al. 1988) (Table 3.57). A recent small, case-control study of IUGR found an association with detectable nicotine level in infant hair samples (RR, 2.6; 95 percent CI, 0.9 to 8.1) and with detectable maternal hair nicotine level among nonsmokers (Nafstad et al. 1998). The reported results were not adjusted for confounders, although the authors stated that several potential confounders had no effect.

Except for a small case-control study (Chen and Petitti 1995), the studies of LBW or IUGR that assessed maternal exposure to ETS from multiple sources (Figure 3.13, bottom) also reported slightly or highly elevated risks for LBW or IUGR. Findings from only two of the studies achieved statistical significance (Martin and Bracken 1986; Dejin-Karlsson et al. 1998). The studies that separately examined ETS exposure at work and home generally reported slightly higher risk from exposure at work than at home (Ahlborg and Bodin 1991; Fortier et al. 1994; Chen and Petitti 1995), but the CIs overlapped considerably. The first two of these studies also found evidence of a slight dose-response trend with increasing level of ETS exposure in the workplace. Astudy of LBW found a moderate increase in risk with the highest maternal exposure to ETS (RR, 1.6) and some evidence of a dose-response trend (Mainous and Hueston 1994a).

The studies of exposure to paternal or household ETS (Figure 3.13, top) showed RR estimates that were only slightly lower than those in the studies of ETS exposure from multiple sources described earlier. The best and the most recent of these studies, which were conducted since the late 1980s, were consistent in showing a slight increase in the risk for LBW or IUGR (RRs, 1.1 to 1.7). Two of these studies showed no indication of a greater effect at higher exposure levels (Chen et al. 1989; Zhang and Ratcliffe 1993), but two others suggested a greater effect (Nakamura et al. 1988; Saito 1991). The large U.S. study of low-income women, which was stratified by maternal age, found increased risks for LBW (RR, 2.4; 95 percent CI, 1.5 to 3.9) and preterm birth (RR, 1.9; 95 percent CI, 1.2 to 2.9) only among infants of women aged 30 years or older (Ahluwalia et al. 1997).

The biological plausibility of the findings from epidemiologic studies is supported by the well-established relationships between active smoking and IUGR among humans and between constituents of tobacco smoke (e.g., nicotine, CO, toluene, or cadmium) and fetal growth retardation among animals (Longo 1977; Baranski 1985; Ungváry and Tátrai 1985; Seidenberg et al. 1986; Donald et al. 1991). A primary mechanism of the effects of nicotine and CO is thought to be fetal hypoxia, because CO binds to hemoglobin and nicotine has vasoconstrictive properties.

Thus, in numerous epidemiologic studies, maternal exposure to ETS is associated with a slight decrement in birth weight and increases in LBW and IUGR. A meta-analysis of studies conducted before mid-1995 reported a weighted-average decrement in mean birth weight of -28 g (95 percent CI, -41 to -16 g) among the offspring of women nonsmokers exposed to ETS and a summary RR of 1.2 (95 percent CI, 1.1 to 1.3) for IUGR or LBW at term among these offspring (Windham et al. 1999a). Greater decrements were found in the three studies that measured cotinine. A subsequent analysis (Peacock et al. 1998) reported a pooled weight decrement of -31 g (95 percent CI, -44 to -19), which was very similar to that reported by Windham and associates (1999a). A small effect (e.g., 25 to 50 g) may not be clinically significant for an otherwise healthy infant, but such a decrement may put infants who are already compromised by other health conditions or risk factors at even higher risk. An increased risk of even 20 percent for LBW or IUGR with maternal exposure to ETS would affect many infants nationwide, because household ETS exposure is common.

Residual confounding or misclassification may be difficult to rule out in studies reporting weakly elevated RRs. Nevertheless, the studies reviewed here have consistently found an association, and some have found evidence of dose-response effects. Studies with better data on ETS exposure, including biochemical measures of exposure, are needed, but maternal exposure to ETS appears to be causally associated with detrimental effects on fetal growth.

Fetal Loss and Neonatal Mortality

Few studies have addressed whether maternal exposure to ETS affects the risk for stillbirth. Some studies examined the effect of ETS exposure on spontaneous abortion or miscarriage, which affects 10 to 15 percent of recognized pregnancies (Kline and Stein 1984) and is now commonly defined as fetal loss in the first 20 weeks of gestation.

Results of several early studies that examined neonatal mortality (Comstock and Lundin 1967) and perinatal mortality rates (Mau and Netter 1974) or spontaneous abortion (Koo et al. 1988; Lindbohm et al. 1991) by paternal smoking status suggested an increased risk of up to 50 percent from ETS exposure, but interpretation of these studies is hampered by lack of control for confounding factors, lack of restriction of analysis to nonsmokers, or insufficient presentation of data.

Two studies of fetal loss and maternal exposure to ETS (Ahlborg and Bodin 1991; Windham et al. 1992) that assessed self-reported exposure at home, at work, or both reported about a 50-percent increase in risk. In the Swedish study (Ahlborg and Bodin 1991), an increase associated with exposure at work was observed only for early losses (≤ 12 weeks) (Table 3.58). In the California study (Windham et al. 1992), risk was increased among women who reported any exposure of an hour or more per day; work exposure could not be assessed separately, although the study examined paternal smoking separately and found RRs across categories of amount smoked by the father that were all close to unity. The California study found a greater association with spontaneous abortion in the second trimester than in the first trimester. Some of the estimates of association between ETS exposure and spontaneous abortion reported in these two studies are as high as those found for active smoking (see "Reproductive Outcomes" earlier in this chapter), which seems biologically implausible.

In contrast, a large prospective study in California based on more detailed questions about hours of exposure at home and work did not confirm previous findings (Windham et al. 1999c) (Table 3.58). The adjusted RR for spontaneous abortion was slightly greater than 1.0 for home exposure and slightly less than 1.0 for work exposure, and no trend was found with increasing hours of exposure.

In clinical studies and animal studies, very high levels of several components of tobacco smoke, including CO (Singh and Scott 1984; Koren et al. 1991), toluene (Ungváry and Tátrai 1985; Ng et al. 1992), and cadmium (Baranski et al. 1982; Wardell et al. 1982; Kaur 1989) were associated with fetal death. Some but not all studies in humans have suggested that active smoking contributes to neonatal mortality and late spontaneous abortion (Kline et al. 1977; Kleinman et al. 1988) (see "Reproductive Outcomes" earlier in this chapter).

There are few studies of ETS exposure during pregnancy in relation to spontaneous abortion and perinatal mortality and few studies of the effect of prenatal, as distinct from postnatal, ETS exposure on risk for SIDS. Results of these studies have been inconsistent, and further work in these areas would be useful.

Table 3.58. Relative risks for spontaneous abortion among nonsmokers exposed to environmental tobacco smoke (ETS) compared with nonsmokers not exposed to ETS

Study (location)	Study design	Population	Measure of exposure to ETS	Relative risk (95% confidence interval)
Ahlborg and Bodin 1991 (Sweden)	Prospective study Self-administered questionnaire	2,936 nonsmokers	Living with smoker Spending most time at work around smokers	1.0 (0.7–1.5) for exposure at home* 1.5 (1.0–2.4) for exposure at workplace* 1.1 (0.8–1.5) for any exposure*
Windham et al. 1992 (California)	Case-control study Telephone interview	626 cases 1,300 controls	Spending ≥ 1 hour / day at home or work around smokers Number of cigarettes smoked by father	1.6 (1.2–2.1) for any exposure ≥ 1 hour / day† 1.0 (0.8–1.3) for any paternal smoking† No dose-response effect
Windham et al. 1999c (California)	Prospective study Telephone interview	5,144 pregnancies 4,209 nonsmokers	Hours / day at home and / or work Amount smoked by spouse or partner	1.0 (0.8–1.3)† for any ETS; no dose-response effect

*Adjusted relative risk for spontaneous abortions and stillbirths combined.
†Adjusted relative risk for spontaneous abortion at ≤ 20 weeks' gestation.
‡Adjusted for age, prior spontaneous abortion, alcohol and caffeine consumption, and gestational age at interview.

Congenital Malformations

Congenital malformations include a wide variety of diagnoses, such as neural tube defects (e.g., anencephaly and spina bifida), orofacial clefts, and defects of the genitourinary and cardiovascular systems. Because of potential differences in causality, lumping all defects may obscure specific associations. The few studies that provided data on effects of prenatal exposure to ETS on congenital malformations (Table 3.59) were not all designed to examine this issue, so several based exposure assessment solely on paternal smoking status. In these types of studies, a direct effect of active smoking on the genetic material in the sperm cannot be ruled out as a mechanism for any association observed.

The findings of these studies suggested that paternal smoking results in a slight risk for severe congenital malformations (RR, 1.2 to 1.4), for all malformations combined, or for major malformations (Table 3.59). Several studies found a greater risk for specific defects, but these defects differed across studies, suggesting that some of these associations may have occurred by chance. The findings were most consistent for cleft lip, cleft palate, or both. Two studies reported indications of a dose-response trend for at least some diagnoses (Savitz et al. 1991; Zhang et al. 1992), but these results were based on small numbers of cases and were not adjusted for confounders.

A case-control study of orofacial clefts examined maternal and paternal smoking and various sources of ETS exposure (Shaw et al. 1996). Paternal smoking in the months surrounding conception was not an independent risk factor, but women nonsmokers exposed to ETS at home at least once a week and with exposure that occurred at close range (within 6 feet) were at increased risk for having offspring with orofacial cleft malformations, particularly isolated cleft lip or cleft palate (RR, 2.0; 95 percent CI, 1.2 to 3.4). The investigators reported slightly increased but nonsignificant risks from workplace exposure to ETS, but neither RRs nor raw data were presented for that association. Among infants born to women nonsmokers, risks associated with ETS exposure were higher for infants with the less common genotype of an allele (*A2*) for transforming growth factor alpha, a secretory protein.

Another study (Wasserman et al. 1996) examined ETS exposure of maternal nonsmokers during early pregnancy in relation to three types of birth defects (Table 3.59). Maternal exposure to ETS, particularly at work, was associated with conotruncal heart defects and limb-reduction defects, with particularly high risk for a subset of heart defects—tetralogy of Fallot (for ETS at work, RR, 2.9; 95 percent CI, 1.3 to 6.6). Paternal smoking of one or more packs of cigarettes per day was also associated with increases of 60 to 110 percent in these two categories of major congenital defects, but maternal smokers were included in the analysis. When the mother was a nonsmoker, any paternal smoking, regardless of the amount, was not associated with the heart defects but was slightly associated with the limb-reduction defects (RR, 1.4; 95 percent CI, 0.9 to 2.2). The RRs presented were not adjusted for other variables, but the authors noted that little change occurred in any estimates when results were adjusted for race, gravidity, alcohol use, or vitamin use.

Thus, several studies showed associations between paternal smoking and congenital malformations among offspring, but whether these are due to maternal exposure to paternal smoking or to direct effects of paternal smoking or other factors is unclear.

Because results on the effects of active smoking on perinatal development have been inconsistent (see "Reproductive Outcomes" earlier in this chapter), it would be premature to draw conclusions about the risks associated with ETS exposure. Detecting a weak teratogen with rare outcomes such as birth defects is difficult. A few studies suggested associations, but further studies with adequate power to examine specific defects and with more comprehensive assessments of exposure would be necessary to determine the relationship of ETS exposure with the occurrence of birth defects.

Fertility and Fecundity

The epidemiologic data on whether ETS exposure may be associated with reduced fertility have been limited and inconsistent. If delayed conception is found when exposure is defined as spousal smoking, the results may be due to effects of ETS exposure per se or to direct effects of paternal smoking on male reproductive parameters (e.g., semen quality). One study in Denmark (Olsen 1991) found a slight but significant increase in risk for delay of 6 to 12 months in conception, but a more rigorous U.S. study did not find an increased risk (Baird and Wilcox 1985). A recent study from Denmark (Jensen et al. 1998) also found reduced fecundity with male partner's smoking. Two additional studies, one in Scandinavia and one in the Netherlands (Suonio et al. 1990; Florack et al. 1994), examined the relationship between delay to conception and partner smoking. The Scandanavian study reported an effect similar to that of the Danish

Table 3.59. Relative risks for congenital malformations among infants with prenatal exposure to environmental tobacco smoke (ETS)

Study (location)	Study design	Population	Relative risk (95% confidence interval)
Seidman et al. 1990[†‡] (Israel)	Cross-sectional study Postpartum interview	14,477 infants of nonsmokers	1.5 (0.7–2.8) for major birth defects* 1.1 (0.9–1.5) for minor birth defects*
Savitz et al. 1991[†‡§] (California)	Prospective cohort of health maintenance organization members	14,685 infants of nonsmokers and smokers	2.4 (0.6–9.3) for hydrocephalus 2.0 (0.9–4.3) for ventricular septal defect 2.0 (0.6–6.4) for urethral stenosis 1.7 (0.5–6.0) for cleft lip and/or palate 0.6 (0.2–2.5) for neural tube defects (All results adjusted for smoking)
Zhang et al. 1992[†‡] (China)	Case-control study Interview in hospital	Infants of nonsmokers 1,012 cases 1,012 controls	1.2 (1.0–1.5) for all birth defects 1.6 for cleft palate[Δ] <1.5 for hydrocephalus[Δ] <1.0 for ventricular septal defect[Δ] 2.0 (1.1–3.7) for neural tube defects
Shaw et al. 1996[¶**] (California)	Case-control study of orofacial clefts	Infants of nonsmokers 487 cases 554 controls	2.0 (1.2–3.4) for isolated cleft lip and/or palate, for home exposure to ETS[††] 9.8 (1.1–218.0) for isolated cleft lip and/or palate with A2 allele for transforming growth factor alpha, for any ETS exposure
Wasserman et al. 1996[‡‡] (California)	Case-control study of three types of birth defects	207 infants with conotruncal heart defects 264 infants with neural tube defects 178 infants with limb-reduction defects 481 control infants	1.3 (0.8–2.1) for conotruncal defects, for ETS at home 1.7 (0.9–3.0) for conotruncal defects, for ETS at work 1.2 (0.8–1.9) for neural tube defects, for ETS at home or work 1.3 (0.8–2.1) for limb-reduction defects, for ETS at home 1.4 (0.7–2.5) for limb-reduction defects, for ETS at work

*Adjustment did not change relative risk.
[†]Confidence intervals were calculated by using data from the published report of the study.
[‡]For Seidman et al. 1990, ETS exposure was defined as paternal smoking of >30 cigarettes/day. For Savitz et al. 1991 and Zhang et al. 1992, ETS exposure was defined as any paternal smoking.
[§]Included maternal smokers. Results are adjusted for maternal smoking.
[Δ]Not significant ($p > 0.05$).
[¶]Besides paternal smoking, other sources of ETS exposure were examined, including exposure of mothers at home and at work.
**ETS exposure at home was defined as at least weekly tobacco smoking in the home within 6 feet of the mother, during the period from 1 month before to 3 months after conception.
[††]Risk of orofacial clefts was slightly but not significantly elevated with paternal smoking around the time of conception and with ETS exposure at work.
[‡‡]ETS exposure was defined as others smoking at home, work, and/or other places and was assessed in maternal nonsmokers. Paternal smoking was evaluated separately.

study (Jensen et al. 1998), but the Dutch study did not show evidence of an adverse effect. A large population-based study of pregnant women in England found that, after adjustment for multiple factors, the RR for conception delay of more than 6 months among nonsmokers exposed to ETS was 1.17 (95 percent CI, 1.02 to 1.37); the RR for conception delay of more than 12 months was 1.14 (95 percent CI, 0.92 to 1.42) (Hull et al. 2000).

Four studies investigated childhood exposure to ETS and fecundity (Weinberg et al. 1989; Wilcox et al. 1989; Schwingl 1992; Jensen et al. 1998). The same investigators conducted two of the studies in different populations (Weinberg et al. 1989; Wilcox et al. 1989). They reported that such exposure tended to increase the adjusted fecundity ratio, that is, the relative probability of conceiving in a given cycle among exposed women compared with unexposed women. The two other studies found little association between fecundity and exposure to ETS as a child. Problems with these studies include the potential unreliability of self-reported recall of exposure and the lack of ascertainment of possible confounders associated with childhood exposure to ETS.

Conclusions

1. Infants born to women who are exposed to ETS during pregnancy may have a small decrement in birth weight and a slightly increased risk for intrauterine growth retardation compared with infants born to women who are not exposed; both effects are quite variable across studies.
2. Studies of ETS exposure and the risks for delay in conception, spontaneous abortion, and perinatal mortality are few, and the results are inconsistent.

Conclusions

Total Mortality

1. Cigarette smoking plays a major role in the mortality of U.S. women.
2. The excess risk for death from all causes among current smokers compared with persons who have never smoked increases with both the number of years of smoking and the number of cigarettes smoked per day.
3. Among women who smoke, the percentage of deaths attributable to smoking has increased over the past several decades, largely because of increases in the quantity of cigarettes smoked and the duration of smoking.
4. Cohort studies with follow-up data analyzed in the 1980s show that the annual risk for death from all causes is 80 to 90 percent greater among women who smoke cigarettes than among women who have never smoked. A woman's annual risk for death more than doubles among continuing smokers compared with persons who have never smoked in every age group from 45 through 74 years.
5. In 1997, approximately 165,000 U.S. women died prematurely from a smoking-related disease. Since 1980, approximately three million U.S. women have died prematurely from a smoking-related disease.
6. U.S. females lost an estimated 2.1 million years of life each year during the 1990s as a result of smoking-related deaths due to neoplastic, cardiovascular, respiratory, and pediatric diseases as well as from burns caused by cigarettes. For every smoking attributable death, an average of 14 years of life was lost.
7. Women who stop smoking greatly reduce their risk for dying prematurely. The relative benefits of smoking cessation are greater when women stop smoking at younger ages, but smoking cessation is beneficial at all ages.

Lung Cancer

8. Cigarette smoking is the major cause of lung cancer among women. About 90 percent of all lung cancer deaths among U.S. women smokers are attributable to smoking.
9. The risk for lung cancer increases with quantity, duration, and intensity of smoking. The risk for dying of lung cancer is 20 times higher among

women who smoke two or more packs of cigarettes per day than among women who do not smoke.

10. Lung cancer mortality rates among U.S. women have increased about 600 percent since 1950. In 1987, lung cancer surpassed breast cancer to become the leading cause of cancer death among U.S. women. Overall age-adjusted incidence rates for lung cancer among women appear to have peaked in the mid-1990s.
11. In the past, men who smoked appeared to have a higher relative risk for lung cancer than did women who smoked, but recent data suggest that such differences have narrowed considerably. Earlier findings largely reflect past gender-specific differences in duration and amount of cigarette smoking.
12. Former smokers have a lower risk for lung cancer than do current smokers, and risk declines with the number of years of smoking cessation.

International Trends in Female Lung Cancer

13. International lung cancer death rates among women vary dramatically. This variation reflects historical differences in the adoption of cigarette smoking by women in different countries. In 1990, lung cancer accounted for about 10 percent of all cancer deaths among women worldwide and more than 20 percent of cancer deaths among women in some developed countries.

Female Cancers

14. The totality of the evidence does not support an association between smoking and risk for breast cancer.
15. Several studies suggest that exposure to environmental tobacco smoke is associated with an increased risk for breast cancer, but this association remains uncertain.
16. Current smoking is associated with a reduced risk for endometrial cancer, but the effect is probably limited to postmenopausal disease. The risk for this cancer among former smokers generally appears more similar to that of women who have never smoked.
17. Smoking does not appear to be associated with risk for ovarian cancer.
18. Smoking has been consistently associated with an increased risk for cervical cancer. The extent to which this association is independent of human papillomavirus infection is uncertain.
19. Smoking may be associated with an increased risk for vulvar cancer, but the extent to which the association is independent of human papillomavirus infection is uncertain.

Other Cancers

20. Smoking is a major cause of cancers of the oropharynx and bladder among women. Evidence is also strong that women who smoke have increased risks for cancers of the pancreas and kidney. For cancers of the larynx and esophagus, evidence among women is more limited but consistent with large increases in risk.
21. Women who smoke may have increased risks for liver cancer and colorectal cancer.
22. Data on smoking and cancer of the stomach among women are inconsistent.
23. Smoking may be associated with an increased risk for acute myeloid leukemia among women but does not appear to be associated with other lymphoproliferative or hematologic cancers.
24. Women who smoke may have a decreased risk for thyroid cancer.
25. Women who use smokeless tobacco have an increased risk for oral cancer.

Cardiovascular Disease

26. Smoking is a major cause of coronary heart disease among women. For women younger than 50 years, the majority of coronary heart disease is attributable to smoking. Risk increases with the number of cigarettes smoked and the duration of smoking.
27. The risk for coronary heart disease among women is substantially reduced within 1 or 2 years of smoking cessation. This immediate benefit is followed by a continuing but more gradual reduction in risk to that among nonsmokers by 10 to 15 or more years after cessation.
28. Women who use oral contraceptives have a particularly elevated risk of coronary heart disease if they smoke. Currently evidence is conflicting as to whether the effect of hormone replacement therapy on coronary heart disease risk differs between smokers and nonsmokers.
29. Women who smoke have an increased risk for ischemic stroke and subarachnoid hemorrhage. Evidence is inconsistent concerning the association between smoking and primary intracerebral hemorrhage.
30. In most studies that include women, the increased risk for stroke associated with smoking

is reversible after smoking cessation; after 5 to 15 years of abstinence, the risk approaches that of women who have never smoked.

31. Conflicting evidence exists regarding the level of the risk for stroke among women who both smoke and use either the oral contraceptives commonly prescribed in the United States today or hormone replacement therapy.
32. Smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women. Smoking cessation appears to slow the rate of progression of carotid atherosclerosis.
33. Women who are current smokers have an increased risk for peripheral vascular atherosclerosis. Smoking cessation is associated with improvements in symptoms, prognosis, and survival.
34. Women who smoke have an increased risk for death from ruptured abdominal aortic aneurysm.

Chronic Obstructive Pulmonary Disease (COPD) and Lung Function

35. Cigarette smoking is a primary cause of COPD among women, and the risk increases with the amount and duration of smoking. Approximately 90 percent of mortality from COPD among women in the United States can be attributed to cigarette smoking.
36. In utero exposure to maternal smoking is associated with reduced lung function among infants, and exposure to environmental tobacco smoke during childhood and adolescence may be associated with impaired lung function among girls.
37. Adolescent girls who smoke have reduced rates of lung growth, and adult women who smoke experience a premature decline of lung function.
38. The rate of decline in lung function is slower among women who stop smoking than among women who continue to smoke.
39. Mortality rates for COPD have increased among women over the past 20 to 30 years.
40. Although data for women are limited, former smokers appear to have a lower risk for dying from COPD than do current smokers.

Sex Hormones, Thyroid Disease, and Diabetes Mellitus

41. Women who smoke have an increased risk for estrogen-deficiency disorders and a decreased risk for estrogen-dependent disorders, but circulating levels of the major endogenous estrogens are not altered among women smokers.
42. Although consistent effects of smoking on thyroid hormone levels have not been noted, cigarette smokers may have an increased risk for Graves' ophthalmopathy, a thyroid-related disease.
43. Smoking appears to affect glucose regulation and related metabolic processes, but conflicting data exist on the relationship of smoking and the development of type 2 diabetes mellitus and gestational diabetes among women.

Menstrual Function, Menopause, and Benign Gynecologic Conditions

44. Some studies suggest that cigarette smoking may alter menstrual function by increasing the risks for dysmenorrhea (painful menstruation), secondary amenorrhea (lack of menses among women who ever had menstrual periods), and menstrual irregularity.
45. Women smokers have a younger age at natural menopause than do nonsmokers and may experience more menopausal symptoms.
46. Women who smoke may have decreased risk for uterine fibroids.

Reproductive Outcomes

47. Women who smoke have increased risks for conception delay and for both primary and secondary infertility.
48. Women who smoke may have a modest increase in risks for ectopic pregnancy and spontaneous abortion.
49. Smoking during pregnancy is associated with increased risks for preterm premature rupture of membranes, abruptio placentae, and placenta previa, and with a modest increase in risk for preterm delivery.
50. Women who smoke during pregnancy have a decreased risk for preeclampsia.
51. The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy.
52. Infants born to women who smoke during pregnancy have a lower average birth weight and are more likely to be small for gestational age than are infants born to women who do not smoke.

53. Smoking does not appear to affect the overall risk for congenital malformations.
54. Women smokers are less likely to breastfeed their infants than are women nonsmokers.
55. Women who quit smoking before or during pregnancy reduce the risk for adverse reproductive outcomes, including conception delay, infertility, preterm premature rupture of membranes, preterm delivery, and low birth weight.

Body Weight and Fat Distribution

56. Initiation of cigarette smoking does not appear to be associated with weight loss, but smoking does appear to attenuate weight gain over time.
57. The average weight of women who are current smokers is modestly lower than that of women who have never smoked or who are long-term former smokers.
58. Smoking cessation among women typically is associated with a weight gain of about 6 to 12 pounds in the year after they quit smoking.
59. Women smokers have a more masculine pattern of body fat distribution (i.e., a higher waist-to-hip ratio) than do women who have never smoked.

Bone Density and Fracture Risk

60. Postmenopausal women who currently smoke have lower bone density than do women who do not smoke.
61. Women who currently smoke have an increased risk for hip fracture compared with women who do not smoke.
62. The relationship among women between smoking and the risk for bone fracture at sites other than the hip is not clear.

Gastrointestinal Diseases

63. Some studies suggest that women who smoke have an increased risk for gallbladder disease (gallstones and cholecystitis), but the evidence is inconsistent.
64. Women who smoke have an increased risk for peptic ulcers.
65. Women who currently smoke have a decreased risk for ulcerative colitis, but former smokers have an increased risk—possibly because smoking suppresses symptoms of the disease.
66. Women who smoke appear to have an increased risk for Crohn's disease, and smokers with Crohn's disease have a worse prognosis than do nonsmokers.

Arthritis

67. Some but not all studies suggest that women who smoke may have a modestly elevated risk for rheumatoid arthritis.
68. Women who smoke have a modestly reduced risk for osteoarthritis of the knee; data regarding osteoarthritis of the hip are inconsistent.
69. The data on the risk for systemic lupus erythematosus among women who smoke are inconsistent.

Eye Disease

70. Women who smoke have an increased risk for cataract.
71. Women who smoke may have an increased risk for age-related macular degeneration.
72. Studies show no consistent association between smoking and open-angle glaucoma.

Human Immunodeficiency Virus (HIV) Disease

73. Limited data suggest that women smokers may be at higher risk for HIV-1 infection than are nonsmokers.

Facial Wrinkling

74. Limited but consistent data suggest that women smokers have more facial wrinkling than do nonsmokers.

Depression and Other Psychiatric Disorders

75. Smokers are more likely to be depressed than are nonsmokers, a finding that may reflect an effect of smoking on the risk for depression, the use of smoking for self-medication, or the influence of common genetic or other factors on both smoking and depression. The association of smoking and depression is particularly important among women because they are more likely to be diagnosed with depression than are men.
76. The prevalence of smoking generally has been found to be higher among patients with anxiety disorders, bulimia, attention deficit disorder, and alcoholism than among individuals without these conditions; the mechanisms underlying these associations are not yet understood.
77. The prevalence of smoking is very high among patients with schizophrenia, but the mechanisms underlying this association are not yet

understood.

78. Smoking may be used by some persons who would otherwise manifest psychiatric symptoms to manage those symptoms; for such persons, cessation of smoking may lead to the emergence of depression or other dysphoric mood states.

Neurologic Diseases

79. Women who smoke have a decreased risk for Parkinson's disease.
80. Data regarding the association between smoking and Alzheimer's disease are inconsistent.

Nicotine Pharmacology and Addiction

81. Nicotine pharmacology and the behavioral processes that determine nicotine addiction appear generally similar among women and men; when standardized for the number of cigarettes smoked, the blood concentration of cotinine (the main metabolite of nicotine) is similar among women and men.
82. Women's regulation of nicotine intake may be less precise than men's. Factors other than nicotine (e.g., sensory cues) may play a greater role in determining smoking behavior among women.

Environmental Tobacco Smoke (ETS) and Lung Cancer

83. Exposure to ETS is a cause of lung cancer among women who have never smoked.

ETS and Coronary Heart Disease

84. Epidemiologic and other data support a causal relationship between ETS exposure from the spouse and coronary heart disease mortality among women nonsmokers.

ETS and Reproductive Outcomes

85. Infants born to women who are exposed to ETS during pregnancy may have a small decrement in birth weight and a slightly increased risk for intrauterine growth retardation compared with infants born to women who are not exposed; both effects are quite variable across studies.
86. Studies of ETS exposure and the risks for delay in conception, spontaneous abortion, and perinatal mortality are few, and the results are inconsistent.

Appendix. Description of Epidemiologic Studies Relating to Total Mortality

Studies Measuring Death Rates

American Cancer Society Cancer Prevention Studies

The American Cancer Society (ACS) Cancer Prevention Studies I and II (CPS-I and CPS-II) are the largest prospective studies of smoking and mortality among women (Table 3.1). Because the two studies were similar with respect to selection and follow-up (Garfinkel 1985; Stellman and Garfinkel 1986; Garfinkel and Stellman 1988), they provide a longitudinal perspective on how smoking attributable risk changed among U.S. women from the late 1950s through the 1980s (U.S. Department of Health and Human Services [USDHHS] 1989b; Thun et al. 1995, 1997a). CPS-I covered 25 states (Hammond 1966); CPS-II was nationwide. Participants were recruited by ACS volunteers in the fall of 1959 and in the fall of 1982, respectively. Volunteers sought to recruit participants from among their friends, neighbors, and acquaintances and to interview all adults aged 30 years or older in the households. Compared with the general U.S. population, participants were older, had more years of education, and were more likely to be married and to be in the middle class. Whites made up 97 and 93 percent of CPS-I and CPS-II participants, respectively. At the start of the study, CPS-I included 391,748 women who had never smoked cigarettes and 152,228 who were current smokers. During the six years of follow-up, 28,922 deaths occurred (Table 3.1). Women in CPS-II included 355,518 women who had never smoked cigarettes (15,450 deaths), 126,794 current smokers (6,232 deaths), and 121,802 former smokers (4,663 deaths). During the six years of follow-up, 26,345 deaths occurred.

British Doctors'Study

The British doctors' study was a landmark prospective study of tobacco smoking and mortality (Doll and Hill 1966; Doll et al. 1980, 1994). In 1951, the British Medical Association mailed to all British physicians a questionnaire inquiring about smoking and other lifestyle habits; 6,194 female physicians and 34,439 male physicians responded to the survey. The women in this study represented 60 percent of female British physicians at the time. Updated information was obtained in 1961 and again in 1973 on all but 1.8 and 4.1 percent, respectively, of the surviving female physicians. Results from 1973, reflecting 22 years of follow-up, have been published (Doll et al. 1980); 1,094 deaths had occurred among the women (Table 3.1). Four of these deaths were excluded from the analyses because the participants smoked tobacco products other than cigarettes. Of the data from the 40-year follow-up, results for the men physicians have been published (Doll et al. 1994), but results for the women physicians have not been published.

Japanese Study of 29 Health Districts

In late 1965, 142,857 women and 122,261 men aged 40 years or older in Japan were enrolled in the Japanese study of 29 health districts (Hirayama 1990) (Table 3.1). Participants represented a range of 91 to 99 percent of adults in this age group in these districts. Information on tobacco smoking was obtained by a self-administered questionnaire at enrollment. After 6 years, reinterview of 3,728 randomly selected women showed that the percentage of smokers had decreased only slightly (from 10.4 to 9.7 percent). During 17 years of follow-up (through 1982), 23,544 deaths among women occurred (Table 3.1). This is the only large prospective study of smoking and mortality in a non-Western culture.

U.S. Nurses'Health Study

In 1976, in the U.S. Nurses' Health Study, 121,700 female registered nurses aged 30 through 55 years completed and returned a mailed questionnaire requesting information on current and past smoking habits (Kawachi et al. 1993a, 1997b). Follow-up questionnaires were subsequently mailed every 2 years to update information on smoking behavior, other cardiovascular risk factors, and development of major illnesses. During the first 12 years of follow-up (through April 30, 1988), deaths occurred among 2,847 of the 117,001 female nurses who, at the start of the study, were free from manifest coronary heart disease, stroke, and cancer (except nonmelanoma skin cancer) (Table 3.1) (Kawachi et al. 1993a, 1997b). Of the 2,847 nurses who died, 933 had never smoked, 799

were former smokers, and 1,115 were current smokers. The U.S. Nurses' Health Study is one of five prospective studies of smoking among women that have been started since 1975.

Kaiser Permanente Medical Care Program Study

Between 1979 and 1986, the Kaiser Permanente Medical Care Program obtained baseline information about tobacco smoking from 36,035 women and 24,803 men aged 35 years or older (Table 3.1) (Friedman et al. 1997). Participants in the program make up about 30 percent of the population in the areas it serves. Follow-up through 1987 identified 1,098 deaths among all women (308 current smokers, 165 former smokers, and 625 women who had never smoked). This study provides the only published data on premature death associated with cigarette smoking among African American women.

Leisure World Cohort Study

Information on tobacco use and other factors was collected in 1981 from questionnaires that were mailed and returned by 8,869 women and 4,999 men who lived in the affluent Leisure World Retirement community in southern California (Paganini-Hill and Hsu 1994). Participants who completed the questionnaire (61 percent of the community) had a median age of 73 years at the start of the study. During 9.5 years of follow-up (through December 1990), 1,987 deaths occurred among women and 2,015 among men (Table 3.1). This is one of two prospective studies of a population consisting primarily of older adults.

Study of Three U.S. Communities

From 1981 through 1983, 4,469 women and 2,709 men aged 65 years or older were enrolled in a study at three sites: East Boston, Massachusetts; rural Iowa; and New Haven, Connecticut (LaCroix et al. 1991). The participants were interviewed by telephone annually during the five years of follow-up, which was completed in 1988. Approximately 82 percent of the target population were enrolled in the study. There were 1,442 deaths from all causes, but the number among women was not specified. One objective of the study was to measure the impact of continued smoking on death rates among older adults.

Studies Measuring Probability of Death

Framingham Study

The Framingham study began in 1948 with a cohort of 5,209 white adults (2,873 women and 2,336 men) aged 30 through 62 years when they were first examined in Framingham, Massachusetts, between 1948 and 1952 (Freund et al. 1993). Information on smoking was obtained at the first examination. Surviving members of the original sample and volunteers were generally reexamined and reinterviewed about smoking at 2-year intervals. Deaths were identified from interviews with next of kin and death certificates. Results over the first 18 years of follow-up (through 1966) were expressed as cumulative incidence or probability of death (Table 3.1 and Figure 3.4) (Shurtleff 1974). During that time, 296 deaths occurred among women participants. Subsequent analyses of pooled biennial data were undertaken to determine annual death rates (Cupples and D'Agostino 1987; Freund et al. 1993). However, investigators could not control for the changing background cardiovascular death rates, and, therefore, data from those analyses are not included here.

Canadian Pensioners'Study

Beginning in 1955, the Department of National Health and Welfare, Canada, enrolled 14,226 women (mostly widows of veterans) and 77,541 men (veterans on pension) younger than age 30 years to over age 80 years in the Canadian pensioners' study—a study of smoking-related mortality (Best et al. 1961). During the six years of follow-up, 9,491 of the men and 1,794 of the women died. The association between smoking and all-cause mortality among women that is shown in Figure 3.4 is from the final report of this study (Canadian Department of National Health and Welfare 1966).

British-Norwegian Migrant Study

In October 1962, questionnaires on morbidity requesting information on personal and demographic characteristics, including cigarette smoking and symptoms of cardiorespiratory disease, were sent to approximately 32,000 British migrants and 18,000 Norwegian migrants to the United States. At that time, three-fourths of the British and Norwegian immigrants to the United States resided in 12 states

(Pearl et al. 1966). The questionnaires were sent to all British and Norwegian migrants, who made up a 25-percent random sample of all residents of those states for whom country of birth was recorded in the 1960 U.S. Census. The response rate was 86 percent. The respondents then were followed up for survival and cause of death for five years, from January 1, 1963, through December 31, 1967. Responses to the questionnaire were received from 9,057 female British migrants and 5,337 female Norwegian migrants (Table 3.1). During the five-year follow-up, 588 female British migrants and 354 female Norwegian migrants died. The cumulative probability ratios shown in Figure 3.4 were obtained from the 1980 Surgeon General's report on the health consequences of smoking among women (USDHHS 1980). The raw data are no longer available to calculate 95 percent confidence intervals.

Swedish Study

In 1963, questionnaires about smoking were mailed to a national probability sample of 55,000 Swedish adults (27,732 women) aged 18 through 69 years (Cederlöf et al. 1975). The response rate was 89 percent. On the basis of information about smoking status in 1963 and linkage with national death registries over the ensuing 10 years, RR for death was estimated among women who currently or formerly smoked cigarettes compared with women who had never smoked. The results for 10 years of follow-up were published in 1975 (Table 3.1).

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