

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; Bennis 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) [¶]	
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.[¶] ≥ 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 3.0 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, 10.0 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 a 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 estradiol 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-hydroxyestrogens, 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, progesterone, 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		0.5 ^Δ	0.6 ^Δ
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		0.9 ^Δ	1.0 ^Δ
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. A study 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 clinic-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	1.7*
						½-1 pack/day	1.7*
						1-2 packs/day	1.0
						>2 packs/day	0.4
Baron et al. 1986b	1,174/2,128	Hospital				1-14 packs/year	1.4*
						≥15 packs/year	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	1.1
						10-19 years	1.6*
						20-29 years	1.3
						30-39 years	1.5*
						≥40 years	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	1.7†
						≥15 cigarettes/day	1.8†
Peters et al. 1986	200/200	Neighbor				2-20 years	1.5†
						≥21 years	4.0*†
Nischan et al. 1988	225/435	Hospital	1.2 (0.8-1.7)			<10 years	0.7
						10-19 years	1.3
						20-29 years	1.7
						≥30 years	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	1.0
						10-19 years	1.0
						20-29 years	1.1
						30-39 years	0.6
						≥40 years	1.5
Licciardone et al. 1989	331/993	Other cancers			1.7 (1.0-2.9)	<1 pack/day	2.2*†
						≥1 pack/day	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	1.0§
						10-19 years	2.4*
						≥20 years	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 ^A	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		1.3 (0.7-2.3)	0.9 (0.2-3.8)
	Spain					2.0 (1.3-3.0)	1.8 (0.9-3.5)
	Colombia						
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.

^ACIN = 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