Carcinogenic Effects

7.0 INTRODUCTION It has been estimated that 22 percent of all cancer deaths in women and 45 percent of all cancer deaths in men can be attributed to personal smoking habits (Shopland *et al.*, 1991). Smoking is an established cause of cancers of the lung, larynx, oral cavity (including pharynx), esophagus, and bladder. It is a probable cause of cancers of the kidney, pancreas, and stomach in men and women, and of cervical cancer in women (IARC, 1986; U.S. DHHS, 1989). Environmental tobacco smoke (ETS) has been established as a cause of lung cancer in nonsmokers (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). This document explores the role of ETS in the etiology of cancers, including lung cancer and cancers other than lung, in nonsmokers.

In the first part of this review, available data is presented on the relationship between ETS and all cancers combined, in adults (Section 7.1.1), and in children (Section 7.1.2). Second, evidence is discussed regarding the role of ETS in the etiology of specific cancer sites. Section 7.2 presents the data on ETS and lung cancer. In Section 7.3, the evidence is discussed on ETS exposure and cancer sites other than lung which are causally linked to active smoking. The evidence on ETS and cancer sites where the role of active smoking is equivocal (*e.g.*, cancers of the breast, stomach, brain, and hematopoietic system) is discussed in Section 7.4. That section also includes the evidence on ETS exposure and risk of childhood cancers (specific sites). Individual studies are described briefly, and the results, including the point estimates of relative risks and corresponding 95 percent confidence intervals, are presented. Findings from the studies are evaluated, taking into account the quality of the studies with respect to their study design, sample size, assessment of exposure, adjustment for potential confounders, and consideration of sources of biases. For cancers that are causally associated with active smoking, we also compare the magnitude of the risk associated with ETS exposure versus that of active smoking.

7.0.1 Misclassification of Smoking Status The 1986 National Research Council report (NRC, 1986) and a subsequent paper, Wald *et al.* (1986) pointed out that because smokers tend to marry smokers, if a study contains smokers who are misclassified as nonsmokers, they are more likely to be classified as exposed to ETS. Therefore, the estimate of relative risk to ETS exposure will be exaggerated due to the association of lung cancer with active smoking for this group of misclassified subjects. Wald *et al.* (1986) estimated the proportion of ever-smokers who are misclassified as lifelong nonsmokers to be about 7 percent. This estimate was based on the percentage of self-

reported nonsmokers (2.1 percent) who have levels of nicotine and cotinine in the range of those of smokers and the percentage of smokers who, on subsequent re-interview, claimed to have never smoked (4.9 percent). Lee (1986, 1989, 1992) has argued that the extent of this misclassification bias is higher—about 12 percent. As discussed in detail below, two recent studies (Riboli *et al.*, 1995; Nyberg *et al.*, 1997) using different methodologies conclude that, while there is some misclassification of smokers as nonsmokers, the misclassification rate is low and is unlikely to explain the observed lung cancer risk from ETS exposure.

Riboli *et al.* (1995) reported the results of a multicenter (13 centers) international (10 countries) study organized by the International Agency for Research on Cancer (IARC) to validate self-reported exposure to ETS from different sources by analysis of urinary cotinine levels. Questionnaire data and urine samples were collected from 1,369 nonsmoking women who had not used any tobacco products for at least 2 years. Forty-seven women had urine cotinine levels above 50 ng/mg creatinine, a level used to discriminate smokers from nonsmokers in some previous studies. Further investigation of these 47 women showed that 27 had levels between 50-150 ng/mg while 20 had levels exceeding 150 ng/mg. In fact, the majority of women (16 of 27) with levels between 50-150 ng/mg had reported long daily exposure to ETS (>5 hours per day) 4 to 8 days prior to sample collection and were exposed to at least eight cigarettes per day. On the other hand, a significantly lower percentage of women with cotinine levels exceeding 150 ng/mg had long daily exposure to ETS or were exposed to at least eight cigarettes per day. These investigators concluded that most of the women with levels between 50 to 150 ng/mg were truly heavily exposed to ETS, while those with levels above 150 ng/mg were more likely to be deceivers and may have smoked. Thus the percentage of deceivers (1.5 percent, 20 of 1,369) in this cross-sectional study is quite comparable to that reported by Fontham *et al.* (1994) in which 0.6 percent of lung cancer cases (2 of 356) (prescreened for smoking status on the basis of medical history and other factors) and 2.3 percent of population controls (25 of 1,064) showed cotinine/creatinine concentrations of 100 ng/mg or higher. Results from this study also illustrate that cotinine levels of 50-150 ng/mg are quite plausible when nonsmokers are very heavily exposed to ETS.

Nyberg *et al.* (1997) investigated misclassification rates in two large Swedish cohorts in which smoking habits were assessed on two separate occasions some 6 to 10 years apart. Two types of misclassification rates were presented. The first misclassification rate was calculated based on the number of ever-smokers misclassified as never-smokers divided by the total population of ever-smokers. The second misclassification rate was calculated based on the number of reported never-smokers who really were smokers divided by the total population of never-smokers. In this study, the proportion of ever-smokers misclassified as never-smokers was 4.9 percent among men and 4.5 percent among women in the first cohort studies; the corresponding figures in the second cohort were 5.0 percent and 7.3 percent. The misclassification rate expressed as the proportion of never-smokers who really were smokers was 11.1 percent in men and 1.3 percent in women in

the first cohort study and 11.5 percent and 2.2 percent, respectively, in the second cohort study. Nyberg *et al.* (1997) noted that there is good agreement in most studies in terms of the first misclassification rate irrespective of geographic area or gender of subjects. On the other hand, the second misclassification rate is much more variable from study to study, and that rate can be misleading because it is dependent on the number of nonsmokers in a particular study. Aside from the rate of misclassification, these investigators also showed that in this, as in other study populations, most of the ever-smokers who were misclassified as nonsmokers had quit smoking some time earlier and smoked less than the average smokers. Thus, this study also suggested that there is limited smoker misclassification and that misclassification bias does not explain the observed lung cancer risk associated with ETS exposure.

Both of these studies suggest that to a large extent, misclassification of smokers as nonsmokers can be minimized if adequate screening questions are used to ensure that former smokers are identified and are excluded from studies of lifetime nonsmokers. Although cotinine is only a marker of recent tobacco exposure, it is still useful to be able to exclude current smokers from a study. In fact, multiple sources of information and questions designed to screen out current or former smokers were used in many of the newer studies of ETS and lung cancer (such as Fontham *et al.*, 1994) so that this source of misclassification bias has been minimized. Thus, the collective evidence from the newer studies (Riboli *et al.*, 1995; Nyberg *et al.*, 1997), as well as the studies reviewed by the U.S. EPA (1992), indicates that misclassification bias does not explain the observed lung cancer risk associated with ETS exposure.

7.1 ALL CANCERS (COMBINED)

Overall cancer related death rates for smokers are about two times higher than for nonsmokers (U.S. DHEW, 1979). Those nonsmokers who are exposed to tobacco smoke are exposed to the same toxic constituents of tobacco smoke as smokers (U.S. DHHS, 1986), although active smokers and those exposed to ETS may differ in the relative amounts of carcinogens to which they are exposed. Furthermore, the phase distributions of compounds differ between mainstream smoke and ETS. More of the constituents appear in the vapor phase (versus the particulate phases) in ETS compared to mainstream smoke, and particle sizes are smaller in ETS. Components also enter the vapor phase from the particulate phase as ETS ages. Therefore, the relative uptake and deposition of these components potentially differ between active and passive smokers (Guerin *et al.*, 1992). Because of these differences, it is not apparent which cancer sites may be most affected by ETS exposure. This section describes studies addressing the overall risk of cancer (all sites combined) from ETS exposure, in adults and in children.

7.1.1 All Cancers In Adults

Cancer risk in adult life may be due to an accumulation of exposures incurred transplacentally, during childhood, and during adult life. To study the potential role of ETS exposure in the etiology of various cancers in adults, most of the studies have focused on the association between adult exposure to ETS and subsequent risk (Hirayama,

1984; Sandler *et al.*, 1989; Reynolds *et al.*, 1987; Sandler *et al.*, 1985a), although the role of ETS exposure during childhood as a risk factor for adult cancers has also been investigated (Sandler *et al.*, 1985b).

7.1.1.1 Cohort Studies Risk of all cancers in nonsmokers exposed to ETS (based on spousal smoking) was evaluated in three cohort studies.

Hirayama (1984) In the first cohort study, the mortality of 91,540 nonsmoking wives in relation to the smoking habits of their husbands was investigated in Japan (Hirayama, 1984). Mortality of the cohort was monitored by review of death certificates and the annual census of residents. After 16 years of follow-up, there were a total of 2,705 cancer deaths (all sites) among the nonsmoking women. The relative risks (RRs) were 1.00, 1.12 (95% CI = 1.03-1.21), and 1.23 (95% CI = 1.12-1.35) for women whose husbands were nonsmokers, ex-smokers or smokers of 1-19 cigarettes per day, and smokers of 20 or more cigarettes per day, respectively, when adjustment was made for husband's age and occupation. In this population, the increased risk for all cancers combined was due mainly to the increased risk observed for cancers of the lung, nasal sinus, and brain. These respectively accounted for 7 percent, 1 percent, and 1 percent of the tumors in this population. Stomach cancer, representing 31 percent of the cancers in this population, was not associated with passive smoking (Hirayama, 1984). There was a small increased risk of cervical cancer in passive smokers (see Section 7.2.2) (Table 7.1).

Sandler et al. (1989) Using a cohort surveyed in 1963 in Western Maryland, Sandler *et al.* (1989) evaluated the all-cancer mortality in nonsmokers who lived with smokers. A total of 22,973 Caucasian men and 25,369 Caucasian women were enrolled; 4,162 men and 14,873 women were lifetime nonsmokers. In 1975, death records were reviewed to evaluate the risk of mortality, and specific causes of mortality, in passive smokers compared to nonsmokers not exposed to ETS. In brief, a score ranging from 0-12 was assigned to each adult in the household based on his/her smoking history. A total household smoking score was then calculated by summing the smoking contribution scores of all persons living in that household. Each individual's household ETS exposure was calculated by subtracting his or her own contribution from the total household score. Among nonsmokers, 1,248 men (30.0 percent) and 9,551 women (64.2 percent) were exposed to household tobacco smoke and were considered to be passive smokers. Exposure to ETS did not increase the risk for all cancers combined in nonsmoking men (RR = 1.01, 95% CI = 0.66-1.53) and nonsmoking women (RR = 1.00, 95% CI = 0.82-1.21) after adjusting for age, marital status, education, and housing quality. When the analysis was conducted separately for tumors related to smoking and tumors not related to smoking, exposure to ETS was associated with a small increased risk for smoking-related tumors in women (RR = 1.45, 95% CI = 0.88-2.40), but not in men (RR = 0.96, 95% CI = 0.66-1.53). In men and women, there was no association between ETS exposure and risk of non-smoking-related tumors (Table 7.1).

Table 7.1
Exposure to Spouse's Smoking and Relative Risk (RR) of all Cancers in Adults

Cohort Studies	# Cases	Exposure to Passive Smoking	RR (95% CI) for Spouse's Smoking
Hirayama, 1984		Husband's smoking	
All cancers[a]	634	Nonsmoking	1.00
	1,341	Ex-/1-19/day	1.12 (1.03-1.21)[b]
	730	20+/day	1.23 (1.12-1.35)
Sandler *et al.*, 1989	Males	Household smoking	
All cancers[a]	84	No	1.0
	31	Yes	1.01 (0.66-1.53)
	Females		
	211	No	1.00
	290	Yes	1.00 (0.82-1.21)
All cancers classified as:			
Smoking-related cancers	Males		
	24	No	1.0
	8	Yes	0.96 (0.43-2.62)
	Females		
	27	No	1.0
	49	Yes	1.45 (0.88-2.40)
Other cancers	Males		
	60	No	1.0
	23	Yes	1.03 (0.40-2.62)
	Females		
	184	No	1.0
	241	Yes	0.93 (0.76-1.54)
Reynold *et al.*, 1987		Husband's smoking	
All cancers[a]	71[c]	No	1.00
		Yes	1.68 (1.12-1.5)[b]
Smoking-related cancers	4[c]	No	1.00
		Yes	7.01 (1.05-47.0)

[a] *There were 200 lung cancers in Hirayama (1984); 2 lung cancers in Sandler et al., 1989; and an unspecified number in Reynold et al., 1987.*
[b] *90% CI confidence intervals.*
[c] *The distribution of the 71 cancers by husband's smoking was not presented; the specific cancer sites were not presented.*

Reynolds et al. (1987) Reynolds *et al.* (1987) reported results from a small cohort of 2,413 married women (46 percent had never smoked) who participated in a population-based survey in Alameda County, California in 1965. Smoking history was independently ascertained for each spouse. Based on 71 cancers diagnosed among the 1,111 nonsmoking women during the 17 years of follow-up, nonsmoking women whose husbands smoked showed a RR of 1.68 (90% CI = 1.1-2.5) for all cancers combined compared to women whose husbands did not smoke. The authors also reported a 7-fold increased risk (90% CI = 1.1-47.0) of smoking-related cancers in relation to husband's smoking (Table 7.1), but this was based on four cases only (smoking-related cancers included cancers of the lung, mouth, esophagus, bladder, pancreas, liver, kidney, and uterine cervix); the specific sites of the four cases were not presented.

7.1.1.2 Case-Control Studies

Sandler et al. (1985a and b) Overall cancer risk in relation to ETS exposure from spouses and parents was evaluated in a case-control study conducted by Sandler *et al.* (1985a). This study included all cancers (excluding skin cancers) diagnosed between ages 15 and 59, during July 1979 through March 1981, from the hospital-based tumor registry affiliated with the University of North Carolina. Of the 740 eligible cancer cases, 518 completed a mailed questionnaire which included information on ETS exposure during childhood and adult life. For 360 of the 518 cases, a friend/acquaintance of the same race, gender, and within 5 years of age of the case served as a control in the study. The remaining controls were identified by systematic telephone sampling using the telephone numbers of the cases as a starting point. Passive smoke exposure during childhood was based on whether their natural parents ever smoked, smoked before the subject's birth, smoked in the house for most of the years before the subject was 10 years old, and whether mothers smoked while pregnant with the index subject. Passive smoke exposure during adult life was based on the number of years of marriage during which a spouse smoked at least one cigarette per day for as long as 6 months. The average number of cigarettes smoked by spouses was also obtained. Among the 518 cases and controls, 231 cases and 235 controls were lifetime nonsmokers.

Among lifetime nonsmokers, there was a significant 2-fold increased risk (95% CI = 1.4-3.0) associated with spouses' smoking after adjustment for gender, race, and age. When the effect of ETS exposure was examined by age group, gender, and race, the effect was more apparent for subjects aged 40-49 (adjusted RR = 2.0, 95% CI = 1.4-2.9), females (adjusted RR = 2.0, 95% CI = 1.3-2.9), and non-whites (adjusted RR = 2.0, 95% CI = 1.4-3.0). However, no dose-response relationship was observed between risk and either the number of years married to a smoker or number of cigarettes husbands smoked per day (data not presented). The role of ETS exposure was also investigated by site of tumor. The increased risk was not limited to lung cancer and other smoking-related tumors, such as cervical cancer. Increased risks were also observed for breast and endocrine gland cancers—tumors not causally associated with active smoking.

In a second report of the same adult study population, Sandler *et al.*, (1985b) evaluated the association between ETS exposure from parents and risk of all cancers. Mothers and father's smoking habits were available on 438 cases and 470 controls; 197 cases and 223 controls were lifetime nonsmokers. Maternal and paternal smoking were each associated with a nonsignificant 20 percent increased risk for all cancers among nonsmokers. The effect of maternal and paternal smoking was evaluated for 'smoking-related' and 'non-smoking related' cancers. 'Smoking-related' cancers included tumors of the oral cavity and pharynx, esophagus, pancreas, respiratory and intrathoracic organs, urinary tract and cervix, and accounted for some 25 percent of tumors in nonsmokers. For 'smoking-related' tumors, the RR was 0.76 (95% CI = 0.25-2.30) for maternal smoking and 1.68 (95% CI = 0.86-3.29) for paternal smoking. For cancers not related to smoking, the RR was 1.24 (95% CI = 0.65-2.36) for maternal smoking and 1.13 (95% CI = 0.73-1.75) for paternal smoking.

7.1.1.3 Summary In summary, there is limited evidence from two cohort studies (Hirayama, 1984; Reynolds *et al.*, 1987) and one case-control study (Sandler *et al.*, 1985a) that exposure to spouses' smoking may increase overall risk of cancer in nonsmoking women. In one study, the increase is explained primarily by an elevated risk observed for lung cancer (Hirayama, 1984). However, in two studies, elevated risks were observed for sites not typically related to active smoking, as well as sites related to smoking (Reynolds *et al.*, 1987; Sandler *et al.*, 1985a). In the study by Reynolds *et al.* (1987), the strong association between husbands' smoking and smoking-related tumors was based on very few cases, accounting for only 6 percent of all cancers. In the study by Sandler *et al.* (1985a), increased risks were observed for both smoking-related (lung, cervix), and nonsmoking-related sites (breast and endocrine gland) after adjustment for age and education. Although the results on nonsmoking-related cancers are intriguing, they are difficult to interpret given that known risk factors for the specific cancers under study were not adjusted for (Sandler *et al.*, 1985a). Possible effects of potential confounders are a concern and should be more carefully researched in further studies. For example, sexual activity is a risk factor for cervical cancer and exposure to ETS may be associated with sexual activity. Alcohol intake is a risk factor for breast cancer and exposure to ETS may be positively associated with alcohol use.

7.1.2 All Cancers In Children

Exposure to ETS has been investigated as a risk factor for all childhood cancers combined and for specific childhood tumors (see Sections 7.3.3 to 7.3.6). Exposure to ETS may occur during the prenatal or postnatal period. Prenatally, the fetus may be exposed to tobacco smoke constituents when the mother smokes during pregnancy (*i.e.*, transplacental effects) or if the mother is exposed to someone else's smoking, most likely the father's smoking. Postnatally, the child may be exposed to ETS directly by inhalation. The main sources of postnatal ETS exposure for a child whose parents both smoke are likely to be from the mother, and to a lesser extent the father.

In this chapter, mothers' smoking during pregnancy is considered to be a surrogate measure of mothers' smoking postnatally (see below). However, since studies on childhood cancers included subjects who were diagnosed with cancer up to age 24, it is reasonable that tobacco smoke exposure both *in utero* and postnatally would be important. Thus, study findings require cautious interpretation.

The extent of information on passive smoke exposure varied in the different studies. Two case-control studies conducted in the 1950's asked about mothers' or fathers' smoking habits at the time of interview or study enrollment. In one study, this pertained to smoking habits of parents at the time of interview which was after the death of the subject under study (Stewart *et al.*, 1958). The other study focused on the mothers' smoking habits when study subjects were enrolled (Manning and Carroll, 1957). In more recent studies, mothers' smoking habits during pregnancy were available (Neutel and Buck, 1971; Stjernfeldt *et al.*, 1986a & b; Pershagen *et al.*, 1992; Severson *et al.*, 1993). Several studies offered more detailed information by including mothers' smoking habits 1-2 years before and during the pregnancy (Gold *et al.*, 1979; Van Steensel-Moll *et al.*, 1985; John *et al.*, 1991; Gold *et al.*, 1993). Mothers' smoking during pregnancy represents transplacental exposure to tobacco smoke constituents and may also be used as a proxy variable of postnatal ETS exposure of the child. There are data to support the assumption that mothers' smoking habits during pregnancy represent an unbiased estimate of their smoking habits after pregnancy. In a study of childhood cancers and maternal smoking (Stjernfeldt *et al.*, 1986a & b), comparison of mothers' smoking habits 5 years before, during, and after pregnancy showed that a similar percentage (8 percent) of cases' and controls' mothers reported they smoked after pregnancy when they had not smoked during pregnancy. In a study of childhood brain tumors (Gold *et al.*, 1993), comparable percentages of mothers of cases (72 percent) and of population controls (73 percent) who had ever smoked reported they were smoking during the birth year of the child. However, some women may quit during pregnancy and resume afterwards so there is potential misclassification when smoking status is based only on smoking habits during pregnancy.

Other studies on childhood cancers obtained information on both mothers' and fathers' smoking habits during the index pregnancy (Preston-Martin *et al.*, 1982; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Howe *et al.*, 1989; John *et al.*, 1991; Gold *et al.*, 1993; Kuijten *et al.*, 1990; McCredie *et al.*, 1994). Children whose nonsmoking mothers were exposed to spouses' smoking were thus considered exposed to ETS prenatally. In some studies, the effect of fathers' smoking was evaluated among children of nonsmoking mothers (John *et al.*, 1991; McCredie *et al.*, 1994; Gold *et al.*, 1993). None of the studies collected information on fathers' smoking postnatally. However, on the basis of the above-mentioned data that showed mother's smoking during pregnancy to be an unbiased estimate of her smoking postnatally (Stjernfeldt *et al.*, 1986a & b) or ever smoking (Gold *et al.*, 1993), it is assumed that father's smoking during pregnancy is also an unbiased proxy for father's smoking postnatally.

7.1.2.1 Biomarkers Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally

The effects of transplacental exposure to tobacco smoke constituents due to maternal active smoking during pregnancy are difficult to distinguish from those of postnatal ETS exposure. Recent studies investigating the levels of three different biomarkers of tobacco-smoke exposure in the offspring of mothers who smoke have demonstrated that the fetus (Coghlin *et al.*, 1991; Hammond *et al.*, 1993), the newborn (Eliopoulos *et al.*, 1994), and the young child (Crawford *et al.*, 1994) are all exposed to considerable amounts of tobacco products.

Eliopoulos et al. (1994) In one of the studies (Eliopoulos *et al.*, 1994), mothers were identified 1 to 3 days after delivery and five to seven hair shafts were obtained near the skull from both the mothers and their newborns for determination of nicotine and cotinine levels (Table 7.2a). Although previous studies typically measured cotinine and nicotine levels in saliva, serum, or urine, levels measured in hair samples provide more long-term assessment of ETS exposure. Nicotine and cotinine levels were highest in mothers who were active smokers, intermediate in nonsmokers who were passive smokers, and lowest in nonsmokers not exposed to ETS. The respective mean levels were 19.2, 3.2, and 1.2 for nicotine (ng/mg) and 6.3, 0.9, and 0.3. for cotinine (ng/mg). Newborns of smokers showed significantly higher mean levels of nicotine (2.4 ng/mg) than newborns of passive smokers (0.28 ng/mg) or nonsmokers (0.4 ng/mg). Nicotine levels in newborns of passive smokers were not higher than those of nonsmokers but the difference in levels was not statistically significant. On the other hand, mean levels of cotinine were highest in newborns of smokers (2.8 ng/mg), intermediate in passive smokers (0.6 ng/mg), and lowest in nonsmokers (0.26 ng/mg). The cotinine levels in newborns of passive smokers were significantly higher than levels in newborns of nonsmokers, and were significantly lower than levels in newborns of smokers. The authors explained that nicotine may be a less sensitive marker than cotinine because of its shorter half-life (1-3 hours for nicotine compared to 10-14 hours for cotinine).

Coghlin et al. (1991)
Hammond et al. (1993) In a study conducted by Coghlin *et al.* (1991), maternal-fetal exchange of a potent tobacco-related human carcinogen, 4-aminobiphenyl (4-ABP), was studied in smoking (n = 14) and nonsmoking (n = 38) pregnant women. N-hydroxy-4-ABP, the active metabolite of 4-ABP, forms chemical adducts with hemoglobin. Levels of 4-ABP hemoglobin adducts were detected in all maternal-fetal paired blood samples. The mean levels of such adducts were 183 (pg/g of hemoglobin) in smoking women, 92 in fetal blood samples from smokers, 22 in nonsmoking women, and 17 in fetal blood samples from nonsmokers. In a related study conducted by the same investigators (Hammond *et al.*, 1993), the relationship between levels of 4-ABP-hemoglobin adducts and exposure to ETS in nonsmoking women (based on nicotine levels measured by passive monitors) was investigated. The median level of 4-ABP adduct was 26 pg/g among nonsmoking women in the highest ETS exposure category (±2 $\mu g/m^3$ weekly average nicotine) compared to median levels of 15 pg/g among those with the lowest ETS exposure (<0.5 $\mu g/m^3$ weekly average nicotine). The levels of 4-ABP hemoglobin adducts in nonsmoking women

Table 7.2a
Hair Concentrations of Nicotine and Cotinine in Women and their Newborn Infants

	Mean (SEM)* Concentration of Nicotine (ng/ml)	Mean (SEM) Concentration of Cotinine (ng/ml)
Active smoking women (*n* = 36)	19.2 (4.9)	6.3 (4.0)
Newborn of active smoking women	2.4 (0.9)	2.8 (0.8)
Passive smoking women[a] (*n* = 23)	3.2 (0.8)	0.9 (0.3)
Newborn of passive smoking women	0.28 (0.05)	0.6 (0.15)[b]
Nonsmoking women (*n* = 35)	1.2 (0.4)	0.3 (0.06)
Newborn of nonsmoking women	0.4 (0.09)	0.26 (0.04)

Reference: Eliopoulos et al. (1994)
** (SEM) = Standard error of the mean.*
[a] *Defined as regular and steady gestational exposure to other person's cigarette smoke, either at home or in the workplace.*
[b] *$p < 0.01$ when compared to newborns of active smoking women and newborns of nonsmokers.*

Table 7.2b
4-Aminobiphenyl Hemoglobin Adduct Concentrations in Pregnant Women and Fetuses by Exposure to Tobacco Smoke

		Mean Concentration (pg/g of hemoglobin)	Standard Deviation
Nonsmoking pregnant women[a] (*n* = 40)		22	8
Smoking pregnant women (*n* = 15)		183	108
Nonsmoking women by levels of exposure to passive smoking based on nicotine concentrations[b,c]			
$\mu g/m^3$			
<0.5	(*n* = 7)	17.6	2.4
0.5-1.9	(*n* = 20)	20.8	2.0
≥2.0	(*n* = 9)	27.8	1.4
Fetuses of nonsmoking mothers[b] (*n* = 40)		17	13
Fetuses of smoking mothers (*n* = 16)		92	54

[a] *Reference: Coghlin et al. (1991)*
[b] *Reference: Hammond et al. (1993)*
[c] *This represented weekly average nicotine concentrations measured during the third trimester when each subject wore a lightweight monitor. Nonsmoking women in this study were the same nonsmoking pregnant women reported in Coghlin et al. 1991.*

Table 7.2c
Cotinine and PAH-Albumin Levels in Mothers and their Preshool Children

	Mean (SE) Cotinine Level (ng/ml)	Mean (SE) PAH-albumin Level (fmol/µg)
Active smoking women (*n* = 31)	170 (21.2)	0.80 (0.15)
Preschool children of active smoking women	4.14 (0.54)	0.35 (0.07)
Passive smoking women[a] (*n* = 32)	1.64 (0.97)	0.49 (0.08)
Preschool children of passive smoking women	0.87 (0.20)[b]	0.18 (0.04)[c]
Nonsmoking women (*n* = 24)	0.96 (0.79)	0.31 (0.08)
Preschool children of nonsmoking women	0.25 (0.12)	0.15 (0.02)

Reference: Crawford et al. (1994)
Abbreviations: PAH = polyaromatic hydrocarbon; SE = standard error
[a] *Exposure to ETS at home from other household members and visitors.*
[b] *Levels in preschool children in households with ETS exposure were significantly higher (p <0.01) than those in children in nonsmoking households.*
[c] *Levels in preschool children in households with ETS exposure were not significantly higher than those in children in nonsmoking households.*

were 12 percent of those in smokers whereas levels in fetuses of nonsmoking women were about 9 percent of those of smoking women. These two studies provided evidence that 4-ABP crosses the human placenta and binds to fetal hemoglobin in both nonsmoking and smoking mothers and that among nonsmoking women, the levels of 4-ABP adducts increased significantly with increasing levels of ETS exposure (Hammond *et al.*, 1993).

Crawford et al. (1994) In the third study, Crawford *et al.* (1994) evaluated levels of serum cotinine and polycyclic aromatic hydrocarbon (PAH)-albumin adducts in Hispanic and African-American preschool children and their mothers. In this study, mean serum cotinine levels were highest in mothers who smoked (170 ng/ml), intermediate in nonsmoking mothers exposed to passive smokers in the household (1.64 ng/ml), and lowest in nonsmoking mothers not exposed to ETS in the household (0.96 ng/ml). A similar gradient in serum cotinine was observed in preschool children whose mothers were smokers (4.14 ng/ml), passive smokers (0.87 ng/ml), and nonsmokers not exposed to household ETS (0.25 ng/ml). Levels of PAH-albumin adducts (fmol/µg) followed the same pattern in mothers who were smokers, passive smokers, and nonsmokers; the respective levels were 0.80, 0.49, and 0.31. In preschool children of smokers, passive smokers, and nonsmokers

not exposed to ETS, the corresponding levels of PAH-albumin adducts were 0.35, 0.18, and 0.15. Comparisons between the three groups of mothers and between the three groups of preschool children show that there were statistically significant differences in levels of cotinine and PAH-albumin adducts, with those in smokers (and their children) higher than those in passive smokers and nonsmokers not exposed to ETS (and their children). Although levels in passive smokers (and their children) were also higher than those in nonsmokers not exposed to ETS (and their children), the differences were not statistically significant. Levels of cotinine and PAH-adducts in children whose mothers were passive smokers (*i.e.*, exposed to household ETS) were lower than those of their mothers who were living in the same ETS-exposed households (levels were about one-third to one-half), presumably because mothers had more opportunities to be exposed to ETS outside the home than did their preschool children.

In this study, young children exposed to ETS via their mothers' smoking showed increases in cotinine and PAH-albumin adducts. These results suggest that exposed children can take up and metabolically activate respiratory carcinogens. Children with nonsmoking mothers who were exposed to ETS from other household members also showed increases in levels of cotinine and PAH-albumin adducts, although the increases were smaller.

7.1.2.2 Cohort Studies Two prospective studies and a case-cohort study investigated the effect of maternal smoking during pregnancy and risk of cancer in children (Table 7.3).

Neutel and Buck (1971) A study by Neutel and Buck (1971) was based on 89,302 births registered in Canada and the United Kingdom. The cohort included all births registered in ten Canadian hospitals between 1958 and 1961, as well as those registered in all hospitals in England and Wales during a one-week period. Smoking habits of mothers during pregnancy were recorded before or just after the birth of the child. For 74 percent of the cohort (n = 66,456), mothers were classified as nonsmokers, smokers of less than one pack per day, or smokers of one or more packs per day. In the remainder of the cohort, nonsmoking mothers and those smoking less than one pack per day could not be distinguished and thus are excluded from this discussion. A total of 65 cancer deaths (22 leukemias, 20 nervous system tumors, and 23 other sites) occurred before age 10 among the 66,456 births. There was a small increased risk for all cancers combined (RR = 1.31, 95% CI = 0.8, 2.2) among children whose mothers smoked compared to children whose mothers did not smoke. There were few cases in the heavy smoking category, and no consistent dose trend of increasing risk with increasing amounts smoked by mothers during pregnancy was observed.

Pershagen et al. (1992) A second cohort study was conducted by Pershagen *et al.* (1992) who utilized data from the Swedish Medical Birth Registry and the Swedish Cancer Registry. Cancer incidence in a cohort of 497,051 children born between 1982-1987 was determined and compared by maternal smoking at 2-3 months of pregnancy (none, <10 cigarettes/day, or >10 cigarettes/day). Relative risks were adjusted for potential confounders which included maternal age, birth order, year and county of birth of index sub-

Table 7.3
Maternal Smoking During Index Pregnancy and Risk of all Childhood Cancers Combined

Cohort Studies (Age of Subjects)	# Cases	Smoking Habits (cig/day)	Odds Ratio (95% CI) for Maternal Smoking
Neutel and Buck, 1970	34	No	1.0
(Age ≤ 10)	30	Yes	1.3 (0.8-2.2)
Pershagen *et al.*, 1992	230	No	1.0
(Age ≤ 5)	61	<10	1.04 (0.8-1.4)
	36	≥10	0.92 (0.6-1.3)
Case-Control Studies (Age of Subjects)	**# Cases/ # Controls**	**Smoking Habits (cig/day)**	**Odds Ratio (95% CI) for Maternal Smoking**
Stjernfeldt *et al.*, 1986a	177/220	0	1.0
(Age ≤ 16)	30/35	1-9	1.07 (0.6-1.8)
	73/58	10+	1.56 (1.1-2.3)
McKinney *et al.*, 1986	555/1,100[a]	0	1.0
(Age ≤ 15)		1-10	1.12 (0.9-1.5)
		11+	0.84 (0.7-1.1)
Buckley *et al.*, 1986	1,814/720[a]	0	1.0
(Age ≤ 15)		1-9	1.31 (0.9-1.9)
		10+	0.97 (0.8-1.2)
Golding *et al.*, 1990[b]	13/61	<5	1.0
(Age ≤ 10)	20/38	≥5	2.47 (1.2-5.1)
John *et al.*, 1991	223/196[a]	0	1.0
(Age ≤ 14)		1-10	1.4 (0.7-2.7)
		11+	1.5 (0.8-2.7)

[a] *Numbers represent total cases/controls. Case/control distribution of maternal smoking by case/control status was not presented.*
[b] *Case-cohort study.*

ject. There were a total of 327 cancers for which maternal smoking habits were known—198 solid tumors and 129 tumors of the lymphatic and hematopoietic system. There was no association between maternal smoking and risk of all cancers combined (adjusted RR = 0.99, 95% CI = 0.78-1.27). The lack of an association persisted when the analysis was conducted separately for solid tumors combined (adjusted RR = 0.96, 95% CI = 0.70-1.32), and for lymphatic and hematopoietic tumors combined (adjusted RR = 1.04, 95% CI = 0.71-1.52).

The study by Pershagen *et al.*, (1992) has several strengths, but also a major limitation. The compilation of the cohort of births was nearly complete (99 percent). Of the 422 childhood cancer cases identified in the Swedish Cancer Registry during this time period, 408 could be linked to a subject in the birth cohort (we assumed that 81 of 408 cases were excluded from the analysis because data on maternal smoking habits were missing). Data on mothers' smoking habits at 2-3 months of pregnancy were available on over 90 percent of children born between 1983 to 1987 and for about 50 percent of children born in 1982. The lower figure in 1982 was due mainly to logistical problems during this first year when the birth registry started to collect information on smoking. Results remained unchanged when births in 1982 were excluded from the analysis. The percentage of mothers who smoked in this study was also similar to that reported in other Swedish studies, so that underreporting of smoking during pregnancy cannot explain the lack of an association. The main limitation of this study is that the maximum follow-up was to 5 years of age, and thus an effect of maternal smoking on cancers occurring at older ages was not assessed; there were small numbers of cancers diagnosed among the 4-5 year olds.

Golding et al. (1990) A case-cohort study was conducted by Golding *et al.* (1990), who collected information prospectively on 16,193 infants delivered over a one-week period in 1970 in the United Kingdom. These children were followed up at ages 5 and 10; 80 percent and 94 percent respectively were successfully contacted. By 1980, 33 children had developed cancer (9 leukemia, 5 lymphoma, 8 brain, 5 Wilm's tumor, 6 other). For each cancer case, three controls were selected and matched to cases on factors including maternal age at birth of index subject, parity, and social class. Significantly more mothers of cases had smoked five cigarettes or more per day throughout pregnancy compared to the controls (RR = 2.47, 95% CI = 1.2-5.1). Maternal smoking remained statistically significant in logistic regression analysis when other risk factors were controlled for (*e.g.*, social class, X-ray in pregnancies, use of various medications).

7.1.2.3 Case-control Studies One of the first case-control studies to examine the role of parental smoking and risk of childhood cancers was a hospital-based study conducted in the U.S. (Manning and Carroll, 1957). Smoking habits of mothers (at time of study enrollment) of children with cancers (188 leukemias, 42 lymphomas, and 93 other cancers) were compared to mothers of children with orthopedic diseases (n = 50). There was no difference in the percentage of mothers of children with cancer who smoked ten or more cigarettes per day (37.4 percent) compared to mothers of controls (38.0 percent). A second study was conducted by Stewart *et al.* (1958) who included as cases all children in England and Wales who had died of leukemia or other cancers before their tenth birthday between 1953 and 1955. Controls were individually matched to cases on gender, age (plus or minus 6 months of the birth date of the cases), and locality of residence. A total of 1,416 case/control pairs were available for analysis. Fathers and mothers of the index subjects were classified as heavy, moderate, light, or nonsmokers. The smoking habits of fathers of children with cancer (82.9 percent smoked at least one cigarette or pipe per day) were similar to those

of fathers of control children (80.9 percent smoked). There was a small excess of mothers of cases who smoked (47.8 percent) compared to mothers of controls (43.8 percent) (OR = 1.09, $p = 0.04$), but this was not adjusted for potential confounding factors. The authors cautioned that since parents were interviewed after the death of the index patients, their smoking habits may be affected by bereavement.

Results from five case-control studies conducted since the 1980's offer better information on smoking habits of parents during pregnancy (Table 7.3).

Stjernfeldt et al. (1986a, 1986b, 1992) Stjernfeldt *et al.* (1986a, 1986b, 1992) conducted a population-based, nationwide case-control study of childhood cancer in Sweden. A total of 305 children, aged 16 or younger, diagnosed with cancer during 1978 and 1981 were identified by the Swedish Child Leukemia Group. Cases were compared to 340 control children with insulin-dependent diabetes mellitus. Families of cases and controls completed a self-administered questionnaire with an overall participation rate of about 95 percent in both groups. Controls were not individually- or frequency-matched to cases on age or gender, but these variables were controlled for in the analysis. Information on smoking habits of mothers was obtained on 92 percent of cases and controls for the 5-year period before pregnancy, during pregnancy, and postnatally to onset of disease in the index subject.

There was some suggestion of an increased risk for all cancers combined in relation to mother's smoking during pregnancy. Compared to children whose mothers were nonsmokers, children whose mothers smoked 1-9, and 10+ cigarettes per day showed RRs of 1.07 (95% CI = 0.63-1.80) and 1.56 (95% CI = 1.05-2.33) respectively. The increase in risk was not observed for solid tumors but was restricted to tumors of the reticuloendothelial system, primarily acute lymphoblastic leukemias. The authors did not present results separately for mother's smoking after birth of the index subject, but suggested that since mothers who smoked during pregnancy generally smoked after the child was born, it would be difficult to separate the effect of *in utero* exposure to tobacco smoke constituents versus postnatal ETS exposure.

Despite concerns raised regarding the choice of controls and possible selective recall bias among cases (McKinney and Stiller, 1986; Buckley *et al.*, 1986; Dahlquist and Wall, 1986; Li, 1986; Cunningham, 1986), none of these biases appear to explain the study's findings. It can be argued that mothers of diabetic children would recall more similarly to mothers of children with cancer if there is any recall bias associated with having a disease. Smoking habits of mothers of diabetic children were representative of the general population since their smoking prevalences were comparable to those of Swedish women surveyed in studies conducted during the same time period. Moreover, differences between cases and controls in ages at diagnosis, geographic location, and socioeconomic status could not explain the apparent findings (Stjernfeldt *et al.*, 1986b). The increased risk associated with maternal smoking was observed after adjustment for factors including maternal age, birth order of index subject, and parental occupation.

McKinney and Stiller (1986) In response to the findings of Stjernfeldt *et al.* (1986a & b), McKinney and Stiller (1986) published a letter to the editor and a more detailed paper (McKinney *et al.*, 1987) presenting data collected for the Inter-Regional Epidemiology Study of Childhood Cancer (IRESCC), a collaborative study conducted in three health regions in the United Kingdom (Yorkshire, West Midlands, and North West) between 1980 and 1983. Study subjects included 555 children (under age 15) diagnosed with childhood cancer. Two healthy, age- and sex-matched control children were identified for each case using the general practitioner lists and admissions to hospital for minor conditions. Parents of cases and controls were asked identical questions regarding the antenatal period of the index subject—*e.g.*, illness, use of medications, complications, smoking and drinking habits (McKinney *et al.*, 1987). Maternal smoking habits during pregnancy were not associated with risk for all cancers combined; the RRs were 1.0, 1.12 (95% CI = 0.85-1.47) and 0.84 (95% CI = 0.65-1.09), respectively for mothers smoking 0, 1-10, and 11+ cigarettes/day. Leukemias and lymphomas, which accounted for 44 percent of the childhood cancers in this population, were not associated with maternal smoking. However, maternal smoking was associated with nonsignificant increased risks for soft-tissue sarcomas and bone tumors (see Section 7.4.6.4: Bone and Soft-Tissue Sarcomas).

Buckley et al. (1986) Also in response to Stjernfeldt's findings, Buckley *et al.* (1986) investigated the role of maternal smoking during pregnancy and the risk of childhood cancer using data gathered by the US Children's Cancer Study Group. Since 1983, the parents of 1,814 children have completed a questionnaire which included smoking histories of the mother and father before and during the pregnancy of the index subject. Controls were drawn at random from approximately the same geographic regions as cases in the US and Canada. There was no association between maternal smoking during pregnancy and risk of all cancers combined; the RRs were 1.31, and 0.97 respectively, for mothers smoking 1-9, and 10+ cigarettes/day during pregnancy compared to nonsmokers. Acute lymphoblastic leukemia, representing 41 percent of cancers in this study, was not related to mother's smoking. Paternal smoking during the index pregnancy was also not associated with all childhood cancers combined (data were not presented). Adjustment for potential confounders (*e.g.*, birth year of the child, maternal age, illnesses during the pregnancy, and socioeconomic factors) did not alter the results.

John et al. (1991) John *et al.* (1991) investigated the role of parental smoking before and during pregnancy and the risk of childhood cancer in a population-based case-control study conducted in Colorado. The study included incident childhood cancers, diagnosed between 1976 and 1983 among children 14 years old or younger. Controls were selected by random-digit dialing and were individually matched to cases on age (±3 years), sex, and telephone exchange area. Of the 356 eligible cases, 252 (response rate of 70.8 percent) participated in the study compared to 222 controls (response rate of 62.8 percent). Structured interviews were administered to parents of index subjects and included questions on smoking habits of mothers, fathers, and other household members during the index pregnancy. In

addition, questions regarding the mother's cigarette smoking habits at three months prior to the index's conception and during each trimester of the pregnancy were asked. Questions on father's smoking included use of cigarettes, cigars, and pipes. Information on other smokers in the household was derived based on questions regarding the number of regular smokers at each residence from conception to the time of the child's diagnosis. The definition of nonexposed in this study is "not exposed to smoking by either parent or by other household members from the period starting 1 year before birth through the time of diagnosis." Data on the number of cases and controls who were exposed to other household members only (but not to parents' smoking) were not presented.

For all cancers combined, there was a small increased risk associated with exposure to mothers or fathers' smoking. The RRs for all cancers were 1.3 (95% CI = 0.8-2.0), 1.5 (95% CI = 1.0-2.5), and 1.4 (95% CI = 0.9-2.4), respectively, in relation to mothers who smoked during the 3 months prior to conception, the first trimester, and all three trimesters of the pregnancy. The OR for all cancers combined was 1.3 (95% CI = 0.9-2.0) in relation to any tobacco use by the father. The ORs for all cancers combined in association with mothers' smoking in the absence of father's smoking, fathers' smoking in the absence of others' smoking, and the combined effect of mothers' and fathers' smoking were 1.7 (95% CI = 0.7-4.3), 1.4 (95% CI = 0.9-2.3), and 1.5 (95% CI = 0.9-2.6), respectively. The data suggest an increasing trend in risk with increasing amounts smoked by mothers, but not by fathers. The positive association between ETS exposure and risk of all cancers is largely due to its effect on risk for acute lymphoblastic leukemia, lymphoma, and brain tumors. Father's education was a potential confounder in this study. The OR for all childhood cancers in relation to fathers' and mothers' smoking was 1.5 (95% CI = 0.9-2.6); this OR was reduced to 1.2 (95% CI = 0.7-2.1) when father's education was accounted for in the analysis.

7.1.2.4 Summary While in some studies increased risks overall in childhood cancers were observed, in others no such increases were seen. There are several limitations in both the studies finding an association and those finding no association between ETS exposure and risk of childhood cancers. The cohort study of Pershagen *et al.* (1992) is limited in that it can only examine the effect of ETS exposure on tumors diagnosed up to 5 years of age, whereas all the other studies included cancers up to 10 or 16 years of age. Causes of childhood cancers in very young children may differ from those of older children. The two large case-control studies which found no association with maternal smoking were collaborative studies of childhood cancers conducted in the United Kingdom (McKinney and Stiller, 1986) and the U.S. (Buckley *et al.*, 1986). Selection bias of cases cannot be ruled out in these studies. Childhood cancer patients admitted to academic institutions were enrolled in these studies and may be unrepresentative of all childhood cancers in the population (*e.g.,* higher social class). The denominator of childhood cancers was not presented, and thus participation rates could not be calculated. Because of the association between social class/education and smoking habits, selection bias associated with social class/education

cannot be precluded. Prevalence of smoking habits of mothers/fathers was not presented in these two studies. On the other hand, the strongest positive finding reported in the case-cohort study by Golding *et al.* (1990) was based on a small number of cases and classification of mother's smoking as less than five versus greater than five cigarettes/day. The choice of the less than five cigarettes/day as the baseline category was not explained, and it is unclear whether this cut-off was an *a priori* decision. Presenting the results using nonsmoking mothers as the baseline group would have been a useful comparison to other studies. The results by Stjernfeldt *et al.* (1986a & b) have also been questioned because of the choice of controls (children with diabetes). Finally, there is some suggestion that inadequate adjustment for paternal education (as a surrogate for social class) may have produced an association between parental smoking and risk of childhood cancer that is artificially strengthened (John *et al.*, 1991).

In summary, the evidence for a role of parental smoking and childhood cancers is inconclusive. One (Neutel and Buck, 1971) of two cohort studies reported an elevated risk which is not statistically significant (OR = 1.3, 95% CI = 0.8-2.2). Two (Stjernfeldt *et al.*, 1986; Golding *et al.*, 1990) of five recent case-control studies (conducted in the 1980s) reported significant associations between mother's smoking during pregnancy and risk of childhood cancers. A third case-control study (John *et al.*, 1991) which reported elevated risks that were not statistically significant was the only study in which fathers' smoking during pregnancy in the absence of mothers' smoking was evaluated; the investigators found a statistically nonsignificant increased risk associated with fathers' smoking alone (OR = 1.4, 95% CI = 0.9-2.3). The positive findings are due largely to the significant association between maternal smoking and acute lymphoblastic leukemia in these studies. No other cancer site appeared to be significantly affected by maternal or paternal smoking.

7.2 ETS AND LUNG CANCER

Active smoking is firmly established as a causal factor for lung cancer. The Surgeon General (U.S. DHHS, 1986), National Research Council (NRC, 1986), and U.S. EPA (1992) have reviewed epidemiologic studies investigating the role of ETS exposure as a cause of lung cancer in nonsmokers. Our review focuses on studies published since the latest review—three large U.S. population-based case-control studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1991 and 1994), a fourth, considerably smaller, hospital-based case-control study (Kabat *et al.*, 1995), and a recent U.S. cohort study (Cardenas *et al.*, 1997).

7.2.1 Epidemiologic Studies Published Prior to 1991

In 1981, the first epidemiological studies of ETS exposure and lung cancer were published (Hirayama, 1981; Trichopoulos *et al.*, 1981). These studies found that nonsmokers married to smokers showed a significantly higher risk of lung cancer than nonsmokers married to nonsmokers. Some 30 epidemiological studies have since been published. Most of the individual studies found a small increased risk, and a few found statistically significant results; however, all the studies published in the 1980s had small sample sizes which lacked statistical power to detect small associations. The Surgeon General (U.S. DHHS, 1986), NRC (1986), and U.S. EPA (1992) conducted compre-

hensive reviews of the epidemiological literature and concluded that ETS exposure was causally associated with lung cancer. Their conclusions were based on the total weight of evidence and not on any individual study.

The U.S. EPA (1992) report reviewed a total of 30 epidemiologic studies (four prospective follow-up and 26 case-control studies) from eight countries. All the studies examined the risk of lung cancer in nonsmokers in relation to spousal smoking habits. Each study was examined in detail and then the studies were examined collectively. Because none of the studies were exactly alike, and the individual studies had different methodologic strengths and weaknesses, the U.S. EPA report ranked the studies in four tiers and gave special consideration to the 15 studies in the two highest tiers. The U.S. EPA report concluded that ETS is responsible for approximately 3,000 lung cancer deaths per year in U.S. nonsmokers.

In order to gain a more accurate estimate of the association between ETS exposure and lung cancer, a meta-analysis approach has been used to pool results of comparable studies. Numerous meta-analyses have been published on this subject (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992; Fleiss and Gross, 1991; Arundel *et al.*, 1987; Kilpatrick, 1992; Pershagen, 1992; Vainio and Partensen, 1989; Repace and Lowry, 1990; Spizer *et al.*, 1990; Wells *et al.*, 1991; Wells, 1993). A widely disseminated and reviewed meta-analysis was conducted by the U.S. EPA (U.S. EPA, 1992; Farland *et al.*, 1994; Jinot and Bayard, 1994). Despite careful considerations of many methodologic issues of concern in the meta-analysis of ETS exposure and lung cancer (*e.g.*, measurement of ETS exposure, misclassification bias of nonsmoker status and disease status, adjustment for potential confounders), the U.S. EPA report was criticized (LeVois and Layard, 1994; Gori, 1994a & b). Some of the concerns centered around issues that were specific to the study of ETS exposure and lung cancer, including misclassification bias of smokers as nonsmokers and the extent of such misclassification. On the other hand, other issues were generic to meta-analysis techniques, and they include possible publication bias of positive studies and the difficulty in obtaining adjusted risk estimates (Gori, 1994a & b) for meta-analysis. The issue of publication bias has been reviewed in detail by Bero *et al.* (1994), who concluded that there is no publication bias against statistically nonsignificant results on ETS in the peer-reviewed literature.

The U.S. EPA's (1992) reporting of 90 percent confidence intervals has gained much attention and is worth addressing here. The U.S. EPA report uses a one-tailed test of statistical significance (with $p = 0.05$) and reports the corresponding 90 percent confidence intervals, consistent with the one-tailed test. Use of a one-tailed statistical test could be considered to increase the probability of accepting an association (for an individual study) that occurs by chance. A one-tailed test is a standard statistical methodology used when there is prior evidence that the effect of an agent is likely to be in one specific direction. In this case, the Surgeon General (U.S. DHHS, 1986), NRC (1986), and an International Agency for Research on Cancer work group (IARC, 1986) all previously concluded that ETS exposure increased lung cancer risk. The established causal association between active smoking and lung cancer and the chemical similarity between main-

stream smoke and ETS were considered by the U.S. EPA (1992) to provide prior evidence that any effect of ETS on lung cancer would be likely to be positive (*i.e.*, to increase the risk); thus, the one-tailed significance test was the appropriate method for evaluating the hypothesis of an effect of ETS on lung cancer risk (U.S. EPA, 1994). Had the EPA used a two-tailed statistical significance test (with corresponding 95 percent confidence intervals) instead of a one-tailed test (with 90 percent confidence intervals), the overall conclusions regarding causality and degree of risk would have been the same (U.S. EPA, 1994).

7.2.2 Case-Control Studies Published Since 1991

Three large U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer have been published since 1991; they confirm and extend the results of the pooled U.S. studies presented in the U.S. EPA report. These studies were conducted in Florida (Stockwell *et al.*, 1992), Missouri (Brownson *et al.*, 1992), and in five geographic areas of the U.S.—New Orleans, Louisiana; Atlanta, Georgia; Houston, Texas; Los Angeles County, California; and San Francisco Bay Area, California—referred to as the U.S. multicenter study (Fontham *et al.*, 1991 and 1994). Preliminary findings from the U.S. multicenter study (Fontham *et al.*, 1991) were included in the U.S. EPA (1992) report. A fourth study, which is a considerably smaller, hospital-based case-control study, was published in 1995 (Kabat *et al.*, 1995). In addition, three other studies which provide some information on ETS exposure as part of investigations of lung cancer and indoor air pollution in Guangzhou, China (Liu *et al.*, 1993), familial risk factors in Detroit (Schwartz *et al.*, 1996), and various suspected risk factors in Kaohsiung, Taiwan (Ko *et al.*, 1997) are also briefly reviewed in this section.

The case-control studies will be reviewed, and their respective study designs and the main findings will be described. In the evaluation of the methodologic issues related to the study of ETS exposure, the focus will be on the sources of cases and controls, the methods used to obtain information on the exposures of interest, the verification of the exposures of interest and of the diagnosis of lung cancer, and the consideration of potential confounding variables in the analysis of ETS exposure.

To minimize confusion, the ORs and confidence intervals will be cited exactly as theywere reported in the original papers. This means that some numbers are reported to one decimal place whereas others are reported to two decimal places. Odds ratios that had to be calculated for this review are labeled as such in the text and tables—*e.g.*, "calculated odds ratio"—and these estimates are referred to as "crude odds ratios." In some instances, the numbers of cases and controls (presented in the tables) by various intensity of ETS exposure (*i.e.*, pack-years, years of exposure) did not add up to the total numbers of subjects included in the individual studies, and it is assumed that these differences in numbers are due to missing information on specific parameters of intensity of ETS exposure or on the covariates included in the adjustments (the variables that were adjusted for in the different analyses are described as footnotes in the various tables). The meas-

ures of intensity of exposure were generally in terms of years (or smoke-years) or pack-years of exposure, number of cigarettes (or tobacco products) smoked per day, or the number of smokers in the household.

7.2.2.1 Four U.S. Case-Control Studies of ETS and Lung Cancer

Stockwell et al. (1992)

Stockwell *et al.* (1992) conducted a population-based case-control study of women in 28 counties in central Florida (Table 7.4). Eligible cases included women diagnosed with a histologically confirmed primary lung cancer between April 1, 1987, and February 28, 1991, and were identified through the Florida Statewide Cancer Registry and the tumor registries of area hospitals. Age criteria for the study subjects were not specified. Population controls were selected by random-digit dialing; it is unclear whether cases and controls were frequency-matched on any criteria. All cases and control subjects were lifetime nonsmokers, defined as having smoked for a total of less than 6 months or less than 100 cigarettes in their lifetime. The nonsmoking status of the study subjects was verified by checking medical records and checking with physicians' offices (for cases) and by inquiry at the time the subjects were contacted to set up the interview as well as at the beginning of the interview (for cases and controls). The response rate for lung cancer cases was 83 percent; it was not specified for controls.

A combination of telephone (51 percent for cases; 46 percent for controls) and in-person (41 percent for cases; 54 percent for controls) interviews and mailed questionnaires (8 percent for cases; 0.3 percent for controls) were used to obtain information from study subjects. Interviews of surrogate respondents (primarily husbands and children) were necessary for 66.7 percent of the case patients who were too ill to be interviewed or were deceased. Information was obtained on a total of 210 lung cancer patients and 301 controls.

Subjects were asked about their exposure to ETS from husbands, mothers, fathers, siblings, and other household members and at the workplace. Compared to unexposed individuals who had no household ETS exposure, women who were exposed to husbands' smoking had ORs of 1.6 (95% CI = 0.8-3.0) for those who had ever been exposed and 2.2 (95% CI = 1.0-4.9) for those with 40 or more smoke-years of exposure after adjustment for age, race, and education. Similar odds ratios were observed for exposure to smoking by husbands and other household members in adult life (Table 7.5). Exposure to ETS from mothers, fathers, and siblings was associated with an increased risk of lung cancer, although none of the individual increases in risks were statistically significant. Stockwell *et al.* (1992) also considered ETS exposure from different sources during childhood/adolescence in terms of years of exposure. Women who experienced 22 years or more of ETS exposure from all household members combined during childhood/adolescence showed a significantly elevated OR for lung cancer (2.4, 95% CI = 1.1-5.4) (Table 7.6). When ETS exposures from both childhood/adolescence and adulthood (*i.e.*, from husbands and other household members) were considered jointly, women who reported 40 or more years of exposure experienced an elevated risk of lung cancer (OR = 2.3, 95% CI = 1.1-4.6) compared to women who had fewer than 22 years of

exposure (data not shown). These investigators noted that there was no statistically significant association in this study between ETS exposure at work or during social activities and risk of lung cancer (actual results were not presented in Stockwell *et al.*, 1992).

The elevated risks associated with ETS exposure (during childhood/adolescence, adulthood, and all lifetime combined) were observed for all lung cancer cell types; the risk was stronger for cell types other than adenocarcinoma of the lung. Analysis by respondent type showed that the risk estimates for ETS exposure varied by the source of case information. For example, ETS exposure from husbands was a stronger risk factor for lung cancer when the respondents were the case patients (OR = 3.1, 95% CI = 0.9-10.6) or their husbands (OR = 3.1, 95% CI = 0.7-13.7). When the surrogate respondent was a family member other than the patient's husband, ETS exposure was not associated with elevated risk (OR = 0.9, 95% CI = 0.4-1.9).

It should be noted that the distribution of study subjects by ETS exposure was not presented; only the odds ratios were presented. The "unexposed" reference category was comprised of individuals with no household ETS; presumably this same reference category was used in all analyses for cases and controls.

Brownson et al. (1992) Brownson *et al.* (1992) conducted a population-based case-control study of women in Missouri (Table 7.4). Females aged 30 to 84 years who were diagnosed with primary lung cancer between January 1986 and June 1991, and were identified from the Missouri Cancer Registry, were considered eligible. Population controls were identified from a sample of the state driver's license files and Health Care Finance Administration listings. The case group included both lifetime nonsmokers and ex-smokers who had stopped smoking at least 15 years before diagnosis or who had smoked less than 1 pack-year. The definition of lifetime nonsmokers was not specified explicitly. The control group was matched by age group to case patients at about a two to one ratio. Tissue slides were reviewed to confirm the histologic classification for 468 (76 percent) of the 618 lung cancer cases.

The response rate was 95 percent for cases and 75 percent for controls, nonsmokers and ex-smokers combined. Information was collected on a total of 618 lung cancer cases of whom 432 were lifetime nonsmokers and 186 were ex-smokers. Of the lung cancer patients, 402 interviews were conducted with surrogate respondents and 216 interviews were with the lung cancer patients themselves. A total of 1,400 control subjects were interviewed, all of whom were self-respondents; 1,166 controls were lifetime nonsmokers.

All case and control interviews were conducted by telephone at which time the nonsmoking status was verified. Questions on ETS exposure pertained to exposures in both childhood (17 years and younger) and adult life (18 years and older). For each time period, respondents were questioned about the source of exposure (*e.g.*, a parent or spouse) including both household and workplace exposure. After an individual source was deter-

Table 7.4
Study Characteristics of the Four U.S. Case-Control Studies of Lung Cancer and ETS Published Since 1991

	Stockwell *et al.* (1992)	**Brownson *et al.* (1992)**	**Fontham *et al.* (1994)**	**Kabat *et al.* (1995)**
Area	Central Florida	Missouri	5 U.S. metropolitan areas	4 U.S. cities
Accrual period	1987-1991	1986-1991	1985-1991	1983-1990
Sample size[1]				
cases	210 (F)	432 (F)	653 (F)	69 (F), 41 (M)
controls	301 (F)	1166 (F)	1253 (F)	187 (F), 117 (M)
Ages	NA (% by birth year groupings provided)	30-84	20-79	not specified
Source of cases	Florida Cancer Registry	Missouri Cancer Registry	All hospital/registries in specific geographic areas	6 hospitals in the 4 cities
Source of controls	RDD	DMV, HCFA	RDD, HCFA	other hospital patients
Matching variables of lifetime nonsmoking controls	NA	age	age, area, & race	age, race, hospital, date of interview
Percent of self-respondents				
cases	33	34*	63	100
controls	100	100	100	100
Mode of data collection	in-person, telephone, mailed questionnaires	telephone	in-person	in-person
% Histologic confirmation	100%	76%**	100%**	100%
% adenocarcinoma	61%	66%	76%	NA
Definition of lifetime nonsmoker	smoked for a total of <6 months or <100 cigarettes in their lifetime	not described	<100 cigarettes, no use of other tobacco for >6 mos	<365 cigarettes over lifetime
Verification of nonsmoking status	multistep-medical record, physician, at initial contact & interview	at interview	multistep-medical record, physician, at initial contact & interview	at interview
Biological markers	none	none	urinary cotinine***	none

[1] *Sample size of lifetime nonsmokers in study*
* *Presented for nonsmokers and ex-smokers combined*
** *Confirmed by independent histologic review*
*** *On 81% of self-respondent cases and 85% of controls*
Abbreviations: F-females, M-males, NA-not available, RDD-random digit dialing, DMV-Department of Motor Vehicle, HCFA-Health Care Financing Administration

Table 7.5
Association Between Risk of Lung Cancer in Lifetime Nonsmoking Females and Exposure to Spousal Smoking

Study	Exposure Status	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse	Odds Ratio (95% CI) for yrs. exp./amt. smoked by spouse
Stockwell *et al.* (1992)	Spouse smoked[a] no yes	AOR[a] 1.0 1.6 (0.8-3.0)	Smoke-years in adult household (spouse and others)[a] <22 23-39 40+	AOR[a] 1.6 (0.8-3.2) 1.4 (0.7-2.9) 2.4 (1.1-5.3)
Brownson *et al.* (1992)	Spouse smoked / Cases* / Controls* never 213 568 ever 218 598	AOR[b] 1.0 1.0 (0.8-1.2)	Cigarette pack-years / cases / controls 0 213 568 0-15 32 128 15-40 54 200 40+ 110 216	AOR[b] 1.0 0.7 (0.5-1.1) 0.7 (0.5-1.0) 1.3 (1.0-1.7)

Table 7.5 (Continued)

Study	Exposure Status			Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse			Odds Ratio (95% CI) for yrs. exp./amt. smoked by spouse
Fontham *et al.* (1994)	Spouse smoked	cases exposed/ total cases	controls exp/ total controls	AOR[c]	By pack-years of exposure to spouses	cases*	controls*	AOR[c]
	any type				0	267	562	1.00
	tobacco	433/651	766/1,253	1.29 (1.04-1.60)	<15.0	146	300	1.08 (0.86-1.39)
	cigarettes	366/648	691/1,253	1.18 (0.96-1.46)	15.1-39.9	92	190	1.04 (0.76-1.42)
	cigars	85/641	138/1,253	1.25 (0.92-1.71)	40.0-79.9	80	126	1.36 (0.97-1.91)
	pipes	86/640	158/1,253	1.19 (0.88-1.60)	80.0+	24	27	1.79 (0.99-3.25)
Kabat *et al.* (1995)	**Males**				**Males**			
	Spouse smoked:	cases/controls*		AOR[d]	Spouse smoked:	cases/controls*		AOR[d]
	no	28/79		1.0	1-10 cigs/day	5 / 17		0.74 (0.24-2.23)
	yes	11/19		1.60 (0.67-3.82)	11+ cigs/day	5 / 2		7.48 (1.35-41.36)
	Females				**Females**			
	Spouse smoked:	cases/controls*			Spouse smoked:	cases/controls*		
	no	26/ 71		1.0	1-10 cigs/day	17 / 50		0.82 (0.42-1.61)
	yes	41/102		1.08 (0.60-1.94	11+ cigs/day	12 / 28		1.06 (0.49-2.30)

[a] *Distribution of cases and controls was not presented; ORs adjusted for age, race, and education; ORs are from Table 2 of Stockwell et al. (1992).*

[b] *Adjusted for age, previous lung disease; ORs are from Table 2 of Brownson et al. (1992).*

[c] *Adjusted for age, race, study area, education, fruits & vegetables & supplemental vitamin index, dietary cholesterol, family history of lung cancer, and employment in high-risk occupations; ORs are from Table 3 of Fontham et al. (1994).*

[d] *Adjusted for age, years of education, and type of hospital; ORs are from Table 4 of Kabat et al. (1995).*

* *The number of cases and controls by intensity of exposure may not add up to the total numbers of subjects due to missing values.*

Table 7.5b
Risk of Lung Cancer in Nonsmoking Women and Men: a Cohort Analysis

Study	Exposure Status	No. of Lung Cancer Deaths	Multivariate RR[a]	Multivariate CI
Cardenas *et al.* (1997)	Among women			
	-- who never smoked	54	--	
	-- husband ever smoked	96	1.0	0.8-1.6
	-- current smoker	44	1.2	0.8-1.8
	-- former smoker	52	1.1	0.8-1.6
	By cigarettes per day smoked by husbands			
	never	30	1.0	--
	1 to 19	9	1.1	0.5-2.2
	20 to 39	22	1.2	0.7-2.2
	40+	13	1.9	1.0-3.6
	By years in marriage to smoker			
	0	30	1.0	--
	1-17	13	1.5	0.8-2.9
	18-29	14	1.5	0.8-2.8
	30+	17	1.1	0.6-2.1
	By pack-years of exposure			
	0	30	1.0	--
	1-16	10	1.0	0.5-2.1
	17-35	16	1.5	0.8-2.7
	36+	18	1.5	0.8-2.6
	Among men			
	-- who never smoked	79	1.0	
	-- wives ever smoked	18	1.1	0.6-1.8
	-- current smoker	8	1.0	0.5-2.0
	-- former smoker	10	1.1	0.6-2.2

[a] *Adjusted for age, race, education, dietary intake of vegetables and total fat, occupation, and history of lung disease.*

Table 7.6
Association Between Risk of Lung Cancer and ETS Exposure from Parents and Other Household Members

Study & Study area	Sex	ETS exposure	Cases/ Controls		Odds Ratio (95% CI) for exposed
STUDIES CONDUCTED IN THE UNITED STATES					
Janerich *et al.* (1990) New York	M, F	Smoker-years in childhood/adolescence			
		0	57	68	1.0
		1-24	82	94	1.09 (0.68-1.73)
		25+	52	29	2.07 (1.16-3.68)
Stockwell *et al.* (1992) Central Florida	F	(Distributions by exposure	210	301	
		not presented)			
		mother			1.6 (0.6-4.3)
		father			1.2 (0.6-2.3)
		siblings			1.7 (0.8-3.9)
		During childhood/adolescence from parents and siblings			
		(in yrs) <18			1.6 (0.7-3.6)
		18-21			1.1 (0.5-2.6)
		22+			2.4 (1.1-5.4)
Brownson *et al.* (1992) Missouri	F	During childhood from parents			
		never	357	877	1.0
		ever	74	289	0.7 (0.5-0.9)
		During childhood from any household members			
		never	323	802	1.0
		ever	108	364	0.8 (0.6-1.1)
Fontham *et al.* (1994) Five U.S. areas	F	During childhood			
		father			
		no	304	669	1.00
		yes	299	556	0.83 (0.67-1.02)
		mother			
		no	76	161	1.00
		yes	548	1,079	0.86 (0.62-1.18)
		Childhood household exposure			
		(in yrs.) 0	148	444	1.00
		1-17	95	291	0.99 (0.73-1.35)
		18+	146	485	0.88 (0.67-1.16)

Table 7.6 (Continued)

Study & Study area	Sex	ETS exposure	Cases/ Controls		Odds Ratio (95% CI) for exposed
Kabat *et al.*		Childhood exposure			
(1995)	M	no	15	41	1.00
Four U.S. cities		yes	25	76	0.90 (0.43-1.89)
		#smokers: 1	18	53	1.12 (0.46-2.70)
		#smokers: 2+	7	22	1.13 (0.34-3.75)
	F	no	22	81	1.00
		yes	47	106	1.55 (0.95-2.79)
		#smokers: 1	39	82	1.75 (0.91-3.35)
		#smokers: 2+	8	23	1.27 (0.43-3.78)
		Adulthood household exposure			
	M	no	28	83	1.00
		yes	13	34	1.13 (0.53-2.45)
		#smokers: 1	6	28	0.64 (0.19-2.13)
		#smokers: 2+	7	5	4.15 (1.34-12.87)
	F	no	26	68	1.00
		yes	43	119	0.95 (0.53-1.67)
		#smokers: 1	34	93	0.96 (0.50-1.84)
		#smokers: 2+	9	25	0.94 (0.34-2.63)
Wu *et al.* (1985)	F	Parents smoked			
Los Angeles		no	18	29	1.0
		yes	11	33	0.6 (0.2-1.7)
Kabat and		Current ETS exposure at home			
Wynder (1984)	M	no	19	20	1.00
U.S.A.		yes	6	5	1.26 (0.33-4.83)*
	F	no	37	36	1.00
		yes	16	17	0.92 (0.40-2.08)*
STUDIES CONDUCTED IN ASIA					
Sobue (1990)	F	During childhood			
Japan		father			
		no	35	143	1.00
		yes	109	588	0.79 (0.52-1.21)
		mother			
		no	127	668	1.00
		yes	17	63	1.33 (0.74-2.37)
		Other household member			
		no			
		yes	113	587	1.00
			31	114	1.18 (0.76-1.84)

Table 7.6 (Continued)

Study & Study area	Sex	ETS exposure	Cases/ Controls		Odds Ratio (95% CI) for exposed
Shimizu *et al.* (1988) Japan	F	During childhood and/or adult life (distribution of exposure presented for controls)			
		father			1.1[a]
		mother			4.0 ($p < 0.05$)
		father-in-law			3.2 ($p < 0.05$)
		mother-in-law			0.8
		brother(s) or sister(s)			0.8
		son(s) or daughter(s)			0.8
Gao *et al.* (1987) Shanghai	F	Lived with a smoker during childhood			1.1 (0.7-1.7)
Koo *et al.* (1987) Hong Kong	F	# cohabitants who smoked (included spouse, parents, in-laws, children, or other cohabitants)			
		0	27	49	1.0
		1	48	68	1.73 (0.6-6.4)
		2+	13	20	1.35 (0.6-5.0)
Wu-Williams *et al.* (1990a) North China	F	father smoked			
		no	235	352	1.0
		yes	182	250	1.1 (0.8-1.4)*
		mother smoked			
		no	298	410	1.0
		yes	119	192	0.9 (0.6-1.1)*
STUDIES CONDUCTED IN EUROPE					
Pershagen *et al.* (1987) Sweden	F	parental smoking			
		neither parent smoked	38	NA[b]	1.0
		one or both parents smoked	9	NA	1.0 (0.4-2.3)[b]
Svensson *et al.* (1989) Sweden	F	father smoked			
		no	19	98	1.0
		yes	12	71	0.9 (0.4-2.3)
		mother smoked			
		no	19	98	1.0
		yes	3	5	3.3 (0.5-18.8)

* *Calculated from data provided in the study publication*

[a] *Shimizu et al. reported p-values for findings, but did not report confidence intervals, and confidence intervals could not be calculated from the reported information.*

[b] *The numbers presented are shown in Table 5 of Pershagen et al. (1987). Although the numbers (and %) of cases and controls with at least one parent who smoked are shown in Table 2 of Pershagen et al. (1987), we cannot reproduce the OR of 1.0 shown in their Table 5 if we impute the number of controls by parental smoking habits.*

mined, a series of detailed questions were asked on the type of tobacco used, duration of exposure, intensity of exposure, and average number of hours per day exposed. In the analyses restricted to lifetime nonsmokers, adjustment included age and history of previous lung diseases. Although initially examined, adjustment was not made for dietary beta-carotene and dietary fat because these factors did not confound the associations in this study.

In an analysis restricted to lifetime nonsmokers, there was no increase in risk associated with "ever-exposed" to spousal ETS (adjusted OR = 1.0, 95% CI = 0.8-1.2) or exposure to fewer than 40 pack-years (see Table 7.5). However, analysis of the highest category of exposure to spouses' smoking (greater than 40 pack-years) yielded an OR of 1.3 (95% CI = 1.0-1.7) (Table 7.5). Analyses by histologic type showed the largest increase in risk for other/mixed-cell types and for small-cell carcinomas, but these results were for lifetime nonsmokers and ex-smokers combined. Results were not presented separately for self-respondents and surrogate respondents. There was no association between risk of lung cancer and ETS exposure from parents (adjusted OR = 0.7, 95% CI = 0.5-0.9) or other household members (adjusted OR = 0.8, 95% CI = 0.6-1.1) during childhood (Table 7.6). These investigators also noted that there was no overall elevated lung-cancer risk in this study associated with any ETS exposure in the workplace. However, lifetime nonsmokers showed an increase in risk at the highest quartile of workplace ETS exposure (OR = 1.2, 95% CI = 0.9-1.7) (Table 7.7). Although the extent of exposure among the highest quartile of workplace was not specified, this OR is similar to the U.S. EPA report's risk estimate for spousal smoking obtained from the meta-analysis.

Fontham et al. (1991 and 1994) Fontham *et al.* (1991 and 1994) conducted a population-based case-control study of women in five geographic areas in the U.S.—New Orleans, Louisiana; Atlanta, Georgia; Houston, Texas; Los Angeles County, California; and San Francisco Bay Area, California—referred to as the U.S. multicenter study (Table 7.4). Eligible cases included women with microscopically confirmed primary carcinoma of the lung that were diagnosed between December 1, 1986, and November 30, 1988, among residents of Atlanta and Houston, and during 2 additional years—1989 and 1990—among residents of New Orleans, Los Angeles County, and San Francisco Bay Area. Additional eligibility criteria included age at diagnosis (20 to 79 years), language (English, Spanish, Chinese), history of previous cancer (none), and lifetime non-tobacco use (fewer than 100 cigarettes smoked and no use of any other form of tobacco for more than 5 months). One pathologist independently reviewed and confirmed histologic classification of 85 percent of the lung tumors in this study.

A population-based control group was selected by random-digit dialing and supplemented by random sampling from the U.S. Health Care Financing Administration files for women 65 years and older. Controls were frequency matched to cases on race and age in a two to one ratio of controls to cases and met the same residence, language, and tobacco-use criteria as cases. In-person interviews were completed for 665 of 800 incident lung cancer cases and 1,278 of 1,826 population controls; the respec-

tive response rate was 83 percent and 70 percent. The proportion of interviews conducted with self-respondents was 63 percent for lung cancer patients and 100 percent for controls. The considerably higher percentage of self-respondents in this study compared to the studies conducted by Stockwell *et al.* (1992) and Brownson *et al.* (1992) may be due to the more rapid identification of patients and thus contact of lung cancer cases in this multicenter study.

The lifetime nonsmoking status of study subjects was confirmed using a multistep procedure which included checking: 1) medical records, 2) with physicians' offices, 3) at the time of contact to set up the interview, and 4) at the beginning of the interview. In addition, the subjects' current nonsmoking status was corroborated by measurement of urinary cotinine levels. Cotinine, a sensitive and specific biologic marker of recent tobacco exposure (Haley *et al.*, 1983) was measured on 81 percent of self-respondent cases and 83 percent of controls. Levels of urinary cotinine/creatinine exceeding 100 ng/mg were found in 0.6 percent of cases and 2.3 percent of controls, indicating a low percentage of misclassification of smokers as nonsmokers (Fontham *et al.*, 1994).

The in-person interviews followed an extensive structured questionnaire designed to obtain information on household, occupational, and other exposures to ETS during each subject's lifetime, as well as other exposures associated with lung cancer. Exposure to ETS was examined by source during childhood (father, mother, and other household members who lived in the home for at least 6 months) and during adult life (spouse, other household members, occupational, and social exposures).

Spousal smoking was associated with a statistically significant increased risk of lung cancer; adjusted ORs of 1.29 (95% CI = 1.04-1.60) for ever exposed to spouses' smoking and 1.79 (95% CI = 0.99-3.25) (p for trend = 0.03) for 80 or more pack-years of exposure to spouses' smoking were observed (Table 7.5). Exposure to other sources of ETS during adult life was also associated with an increased risk of lung cancer. Adjusted ORs of 1.39 (95% CI = 1.11-1.74) for ever exposed to ETS at the workplace and 1.86 (95% CI = 1.24-2.78) for 31 or more years of exposure at the workplace were observed (Table 7.7). In addition, increased risks were associated with ETS exposure in social settings (see section 7.2.4.3). When all sources of ETS exposure during adult life were considered jointly as years of exposure, women with 48 years or more of exposure showed an OR of 1.74 (95% CI = 1.14-2.65) compared with women with no ETS exposure (data not shown). The increased risks associated with ETS exposure from spouses, at the workplace, and other social settings were observed for adenocarcinomas as well as other histologic types of lung cancer.

The findings for ETS exposure were similar when the analysis was restricted to self-respondents only. For example, among self-respondents only, an OR of 1.67 (95% CI = 1.03-2.70) was found for women with 48 years or more of exposure for all sources combined in adult life compared with women with no exposure (the OR was 1.74 for all respondents combined—data not shown). These results for ETS exposure were observed after

Table 7.7
Studies on ETS Exposure at the Workplace and Lung Cancer Among Lifetime Nonsmoking Subjects

Study/ Year of study	Questions on ETS exposure	#unexposed/ #exposed cases	#unexposed/ #exposed controls	OR (95% CI) for exposed
STUDIES IN THE UNITED STATES				
Kabat & Wynder (1984) 1961-1980	current or last job			
	males	7/18	14/11	3.3 (1.0-10.4)
	females	27/26	22/31	0.7 (0.3-1.5)
Garfinkel *et al.* (1985) 1971-1981	#hrs/day exposed to smoke of others at work: Past 5 years	80/14	262/52	0.88 (0.7-1.2)
	Past 25 years	42/34	135/118	0.93 (0.7-1.2)
Wu *et al.* (1985) 1981-1982	# years exposed at each job	13/16	31/31	1.3 (0.5-3.3)
Janerich *et al.* (1990) 1982-1984	# smokers at work (lifetime), amount of time working with smokers	NA	NA	no association 0.9 (0.8-1.04)
Brownson *et al.* (1992) 1986-1991	current/most recent job, exposed to other's smoke	NA	NA	no association overall 1.2 (0.9-1.7)[a]
Stockwell *et al.* (1992) 1987-1991	not described	NA	NA	no association
Fontham *et al.* (1994) 1985-1991	# years exposed at each job (lifetime years of exposure at work)	224/385	491/756	1.39 (1.1-1.7)[b]
	By years of exposure	cases	controls	
	0	224	491	1.00[c]
	1-15	213	450	1.30 (1.01-1.67)
	16-30	118	223	1.40 (1.04-1.88)
	31+	54	83	1.86 (1.24-2.78)[b]
Kabat *et al.* (1995) 1983-1990	four (4) jobs that lasted 1 year or more			
	males	18/23	52/65	1.02 (0.50-2.09)
	females	23/35	64/85	1.15 (0.62-2.13)

Table 7.7 (Continued)

Study/ Year of study	Questions on ETS exposure	#unexposed/ #exposed cases	#unexposed/ #exposed controls	OR (95% CI) for exposed
STUDIES IN THE UNITED KINGDOM AND GREECE				
Lee *et al.* (1986) 1977-1982	timing of job not specified, exposure as no, little, a lot			
	males	3/7	40/57	1.61 (0.4-6.6)
	females	12/3	113/47	0.63 (0.2-2.3)
Kalandidi *et al.* (1990) 1987-1989	#smokers at work current/last job:	24/65	40/78	1.39 (0.8-2.5)[d]
STUDIES IN ASIA				
Koo *et al.* (1984) 1981-1983	any ETS exposure at work (all jobs)	NA	NA	0.91 (0.15-5.37)
Shimizu *et al.* (1988) 1982-1985	most recent/current job, any smokers at work	NA	NA	1.2
Wu-Williams *et al.* (1990) 1985-1987	exposure at each job	187/228	301/301	1.2 (0.9-1.6)[e] 1.06 (0.8-1.4)[f]

[a] *For highest quartile of exposure*
[b] *$p < 0.01$*
[c] *Trend, $p = 0.001$*
[d] *Calculated from entries on exposure at work in Table 2 of publication*
[e] *Adjusted for center, age, and education*
[f] *Adjusted for center, age, education, previous lung disease, and heating practices*

adjustment for age, race, study area, education, intake of fruits and vegetables and use of supplemental vitamins, dietary cholesterol, family history of lung cancer, and employment in high-risk occupations.

In this study, ETS exposure during childhood/adolescence from father, mother, or other household members was not associated with risk of lung cancer. The OR for any childhood exposure to ETS (*i.e.*, any household member) was 0.89 (95% CI = 0.72-1.10) (Table 7.6) (data from table 4 of Fontham *et al.* (1994)). However, there was some suggestion that the risk associated with adult ETS exposure varied according to childhood ETS exposure. Significantly elevated risks associated with adult ETS exposures were observed in women with and without childhood exposures. The elevations in risk for women exposed during childhood were twice as high as for those

without childhood exposures. For example, at the highest level of ETS exposure (48 adult smoke-years or more), the authors reported an adjusted OR of 3.25 (95% CI = 1.42-7.46) among women reporting childhood exposures compared to 1.77 (95% CI = 0.98-3.19) for those reporting no childhood exposure (data not shown).

Kabat et al. (1995) Kabat *et al.* (1995) conducted a hospital-based case-control study of women and men between 1983 and 1990 as part of a long-standing study of tobacco-related cancers. This study was carried out in six hospitals located in four U.S. cities (New York City, New York; Chicago, Illinois; Detroit, Michigan; and Philadelphia, Pennsylvania). Newly diagnosed, histologically confirmed cases of primary cancer of the lung were ascertained in the collaborating hospitals. For each case enrolled, up to three control patients who were lifetime nonsmokers matched on age ($\pm$5 years), sex, race, hospital, and date of interview (within 2 months) were interviewed. Control patients were admitted for various cancer and noncancer outcomes. About 30 percent of the controls were diagnosed with cancer of the stomach/intestine, genitourinary tract, or lymphatic and hematopoietic system, cancer sites which may be positively associated with tobacco use (see Sections 7.3.3, 7.4.2, and 7.4.4). Thus, the ETS exposure among some controls may be higher than the general population, leading to a bias towards the null.

Subjects were considered lifetime nonsmokers if they had never consumed as much as one cigarette per day for a year, or had smoked fewer than 365 cigarettes over their lifetime. In the structured interview, detailed questions regarding the initiation of smoking early in life were included and provided a basis for excluding ex-smokers who quit decades prior to diagnosis but had smoked more than this minimum amount. The proportion of never-smokers among all lung cancer cases in this study was 3 percent in males and 8 percent in females.

All subjects were interviewed in person in the hospital. The questionnaire included a detailed history of exposure to ETS, during childhood and adult life. Questions were also asked about adult ETS exposures inside and outside the home (at work, in cars and other forms of transportation, and in social settings). Interviews were conducted with 41 male and 69 female never-smoking lung cancer cases and 117 male and 187 female never-smoking controls.

There were no significant associations between spouses' smoking and risk of lung cancer in male (OR = 1.60, 95% CI = 0.67-3.82) or female (OR = 1.08, 95% CI = 0.60-1.94) subjects (Table 7.5). The calculated OR for lung cancer in males and females combined was calculated to be 1.19 (95% CI = 0.76-1.87) in association with spousal ETS exposure. Wives' smoking 11+ cigarettes/day was associated with a significant increased risk (OR = 7.48, 95% CI = 1.35-41.36) of lung cancer in men (Table 7.5). However, this result was based on small numbers and thus unstable, and a similar result was not observed in women associated with their husbands' smoking. For males and females combined, the calculated OR for having a spouse who smoked 11+ cigarettes/day was 1.57 (95% CI = 0.81-3.07). The OR for lung cancer

associated with spouses who smoked in the bedroom was slightly higher than that associated with any smoking by spouses, but this association was not statistically significant in males (OR = 5.02, 95% CI = 0.72-35.01) or females (OR = 1.09, 95% CI = 0.49-2.42) (data not shown)(the crude OR for males and females combined was 1.20, 95% CI = 0.6-2.4).

Results for any household ETS exposure during adult life were similar to the results described above for spousal ETS exposure; household exposure was not significantly associated with risk of lung cancer (Table 7.6). The exception was that, among males, there was a statistically significant increased risk (OR = 4.15, 95% CI = 1.34-12.87) of lung cancer associated with two or more smokers in the adult household, but this was not observed among females (OR = 0.94, 95% CI = 0.34-2.63).

Sources of ETS exposure outside of the home during adult life were also evaluated, including ETS exposure at the workplace, in social situations, and inside cars. Workplace ETS exposure was not associated with increased risk of lung cancer in males or females (Table 7.7) in this study. There were small increased risks for lung cancer associated with ETS exposures in social situations and inside cars (see 7.2.4.3). The elevated risk associated with ETS exposure inside cars was statistically significant in an analysis which combined male and female subjects (see 7.2.5.3).

Exposure to ETS during childhood was not associated with any increased risk in males (OR = 0.90, 95% CI = 0.43-1.89), but in females it was associated with an increased risk which was of borderline statistical significance (OR = 1.55, 95% CI = 0.95-2.79) (Table 7.6). There were no significant dose-response relationships between number of smokers in childhood households and risk of lung cancer in male or female subjects in this study.

7.2.2.2 Other Case-Control Studies Providing Information on ETS and Lung Cancer

Liu et al. (1993)

Liu *et al.* (1993) present the results of a hospital-based case-control study of indoor air pollution and lung cancer in Guangzhou, China. Newly diagnosed cases of primary lung cancer selected from eight major hospitals over a one-year period were included. Controls were individually matched to cases on age, sex, residential district, and date of diagnosis or hospital admission. Six of the eight hospitals (excluding the Tumor Hospital and Chest Hospital) which provided cases also provided controls for this study. Patients with certain diseases were excluded as eligible controls, but the diagnoses of controls included in the study were not presented. Of the 327 lung cancer cases identified, a total of 224 male and 92 female incident lung cancer cases and an equal number of individually matched male and female hospital controls were interviewed.

The main objective of the study was to investigate the role of indoor air pollution and ventilation on risk of lung cancer in smokers and nonsmokers. Questions on spouse's smoking habits were also asked. An unmatched analysis was conducted to examine the effect of ETS exposure among the 38 female cases and 69 female controls who had never smoked. Compared to nonsmoking women who were not exposed to husbands' smoking, women exposed to 1-19 and 20+ cigarettes per day of husbands' smoking showed

ORs of 0.7 and 2.9, respectively (p for trend = 0.03) after adjusting for education, occupation, and living area. Risk of lung cancer was increased in association with living in a house with poor air circulation. The crude OR comparing women ever exposed to those with no exposure to husbands' smoking was 1.66 (95% CI = 0.73-3.78). No air circulation and lack of a separate kitchen were other significant risk factors for lung cancer in this study. There is no discussion of whether the analysis of ETS exposure in nonsmokers considered air circulation or presence of a separate kitchen as adjustment variables.

Schwartz et al. (1996) The main objective of this case-control study was to investigate the role of familial risk factors in the etiology of lung cancer. Cases and controls in this study had previously participated in the Occupational Cancer Incidence Surveillance Study (OCISS). OCISS subjects were identified among metropolitan Detroit area residents with specific cancers which included lung cancers. Population controls (without cancers) selected by random digit dialing were identified for the original OCISS study. For this analysis, all lung cancer cases who did not smoke cigarettes, cigars, and/or pipes (it was, however, never specified whether they were lifetime nonsmokers) were eligible. Controls represented a random sample, approximately one-third of all eligible nonsmoking controls, and they were frequency-matched to nonsmoking lung cancer cases by 5-year age group, sex, race, and county of residence. The final eligible sample included 314 cases and 345 controls, of whom 257 case and 277 control interviews were obtained. Some 72 percent of the case and 64 percent of the control subjects were females.

Telephone interviews were conducted. Because of the high case fatality associated with lung cancer, 83 percent of the case interviews had to be conducted with proxies which included spouses, siblings, offspring, or parents. In contrast, 22 percent of the control interviews were completed with proxies. After adjustment for age, race, and sex, exposure to ETS at home was not a significant risk factor for lung cancer (OR = 1.1, 95% CI = 0.8-1.60), while exposure to ETS at work was of borderline statistical significance (OR = 1.5, 95% CI = 1.0-2.2). However, it is unclear whether ETS exposure at home included exposures during childhood and/or adult life. It was also not specified whether ETS exposure at all jobs or the most current or longest job was asked. Limitations of this study include the fact that almost all the information on cases was obtained from proxy interviews and that relevant details regarding ETS exposure variables were not described. This study was not designed to investigate the role of ETS exposure in the etiology of lung cancer in nonsmokers.

Ko et al. (1997) This was a hospital-based case-control study conducted in Kaohsiung, Taiwan, a heavily industrialized city. All eligible lung cancers were identified during a 2-year period in a leading teaching hospital in this study area. Of the 128 eligible female lung cancer patients identified, 117 were interviewed while they were in the hospital. Control women were ophthalmic patients (n = 62) or women admitted for a health check (n = 55), and they were matched to cases on age and date of interview. The study was designed to investigate various suspected risk factors for lung

cancer including active and passive smoking, previous lung diseases, cooking practices, and indoor environment. Questions on ETS exposure asked about smoking habits of parents, husbands, cohabitants and coworkers. There were 11 cases and 3 controls who were active smokers. The analysis on ETS exposure was conducted among the 105 case-control pairs of nonsmokers. In matched analyses adjusted for socioeconomic status, residential area, and education, risk of lung cancer in nonsmoking women was not associated with ETS exposure from parents (OR = 0.8; 95% CI = 0.4-1.6), cohabitants (OR = 1.0; 95% CI = 0.4-2.3), or coworkers (OR = 1.1; 95% CI = 0.4-3.0), but there was a small nonsignificant increased risk associated with ETS exposure from spouses (OR = 1.3; 95% CI = 0.7-2.5). It was not specified whether exposure from parents and other cohabitants covered exposures during both childhood and adult life. It was also not specified whether exposure from coworkers covered all jobs or the last or longest job. ETS exposure was one of several sources of indoor air pollution investigated in this study. It is not clear whether information on extent (*i.e.*, duration or amount) of ETS exposure was obtained.

7.2.3 A U.S. Cohort Study Published Since 1991

Cardenas et al. (1997)

The analysis by Cardenas *et al.* (1997) utilized data from the CPS-II, which enrolled approximately 1.2 million men and women in 1982. By December 1989, 91.2 percent (1,080,689) were still living, 8.6 percent (101,519) had died, and the remainder had unknown vital status. Death certificates were obtained for 96.8 percent of subjects known to have died.

Among never-smokers in this study, two analyses on ETS exposure and risk of lung cancer were conducted. The main and more complete analysis on long-term ETS exposure was based on information on active smoking habits of spouses obtained directly from spouses who were linked to the index never-smoker. With less than 2 percent of subjects excluded due to missing data, a total of 150 lung-cancer deaths in 192,234 never-smoker women and 97 lung-cancer deaths in 96,542 never-smoker men were available for this analysis. In approximately half of the never-smoker women, information on amount smoked by husbands and years in marriage to husbands who smoked was also available (*i.e.*, for 74 lung-cancer deaths in 92,222 never-smoker women). A second and less complete analysis was based on self reporting of current ETS exposure at home, at work, or in other areas. Thirteen percent of male to 30 percent of female subjects had missing information in one of the three questions on sources of recent ETS exposure. Based on the assumption that individuals with missing data on one of the sources of ETS exposure had no exposure from that source, these analyses included 246 lung cancer deaths in 281,536 never smoking women and 116 lung cancer deaths in 110,687 never smoking men. The analyses were conducted with adjustment for the main confounders which included age, race, years of education, occupation, dietary intake of various fruits, vegetables and fat, and history of previous lung diseases.

In the analyses based on spousal smoking habits (Table 7.5b), never-smoking women married to smokers showed a small increased risk of lung cancer (RR = 1.20, 95% CI = 0.8-1.6); the risk was 1.2 (95% CI = 0.8-1.8)

associated with husbands who were current smokers and 1.1 (95% CI = 0.6-1.6) for husbands who were former smokers. There was an increasing trend of risk associated with number of cigarettes smoked by spouses; the ORs were 1.0, 1.1, 1.2, and 1.9, respectively, for 0, 1-19, 20-39, and 40+ cigarettes smoked per day (p for trend = 0.03). Similarly, there was an increasing trend of risk with increasing pack-years smoked by spouse (p for trend = 0.10). There was, however, not a smooth trend of increasing risk with increasing years of ETS exposure. The ORs were 1.0, 1.5, and 1.1, respectively, associated with 0, 1-17, 18-29, and 30+ years of exposure (p for trend = 0.5). Based on fewer lung-cancer deaths in men and a lower prevalence of men married to smokers, the risk of lung cancer among never smoking men married to smokers was 1.1 (95% CI = 0.6-1.8); the risk was 1.0 (95% CI = 0.5-2.0) associated with wives who were current smokers and 1.1 (95% CI = 0.6-2.2) for wives who were former smokers.

Cardenas *et al*. (1997) reported that none of the self-reported current ETS exposure measures (any exposure or total hours of exposure) was associated with increased lung cancer risk. The multivariate RRs among women who reported 0, 1-2, 3-5, or 6+ hours of ETS per day in all settings were 1.0, 0.8, 0.7, and 1.1, respectively. The corresponding RRs in men were 1.0, 0.6, 1.0, and 1.3.

There are several notable advantages of this cohort study. Possible selective recall bias and information bias with the use of surrogate respondents, concerns raised by some regarding case-control studies, are avoided. Because the main analysis identified only married couples, this precluded any bias introduced as a result of married and unmarried persons describing ETS exposure differently. Moreover, this cohort analysis has an added advantage compared to previous cohort studies in that a large number of potential confounders were accounted for in the analysis and an association with ETS exposure from spouses was present.

The main limitations of this study are the relatively small number of lung cancer deaths available for analysis. In addition, information on amount smoked by husbands and years of marriage to smokers was available on approximately half of the never-smoker women. These investigators calculated that approximately 1,000 expected cases are needed to achieve 80 percent statistical power (assuming an RR of 1.2, alpha of 0.05, 2-sided, and an ETS exposure rate of 60 percent). A second limitation is that spousal ETS exposure was based on the smoking habits of current spouse and that information on ETS exposure from previous marriages or from other household members was not available. Even for current spouses, information on amount smoked and duration of smoking was available on only about half of the never-smokers in this study.

7.2.4 ETS Exposure from Spouses

The results from the recent U.S. studies are compatible with the pooled estimate of the U.S. EPA (1992) report, which found a summary OR of 1.19 (90% CI = 1.04-1.35) for ever exposed to ETS from spouses (for U.S. studies). Results from the largest population-based study, the U.S. multicenter study (OR = 1.29, 95% CI = 1.04-1.60, for ever exposed) (Fontham *et al*., 1994) were closest to the pooled estimate from

the U.S. EPA report. Of the two other population-based studies, the association found in the Florida study (Stockwell *et al.*, 1992) was stronger (OR = 1.6, 95% CI = 0.8-3.0; although it did not achieve statistical significance except for the highest exposure category: OR = 2.4, 95% CI = 1.1-5.3), and that from the Missouri study (Brownson *et al.*, 1992) was weaker (overall OR = 1.0, 95% CI = 0.8-1.2; for highest exposure category of spousal smoking, OR = 1.3, 95% CI = 1.0-1.7) than the pooled estimate result. Although the authors of the fourth study—the hospital-based case-control study (Kabat *et al.*, 1995)—reported their findings as unsupportive of an association between ETS exposure and risk of lung cancer, the odds ratio were elevated for males (OR = 1.60, 95% CI = 0.67-3.82) and females (OR = 1.08, 95%CI = 0.60-1.94), though not statistically significant, and the results of this small study do not contradict an increased risk on the order of 20 percent. The cohort study by Cardenas *et al.* (1997) also showed a small increased risk of lung cancer (RR = 1.2, 95% CI = 0.8-1.6) associated with being married to a smoker. In addition, positive increasing trends in risk of lung cancer in nonsmokers were observed for increasing ETS exposure indices in all three of the population-based studies (Table 7.5) and in the U.S. cohort study (Table 7.5a). The concordance in these study results gives further credibility to the finding of a causal association between spousal ETS exposure and risk of lung cancer described in the U.S. EPA (1992) report.

The sample sizes of the three population-based U.S. studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1994) were considerably larger than previously published case-control studies in the U.S. (Correa *et al.*, 1983; Buffler *et al.*, 1984; Kabat and Wynder 1984; Dalager *et al.*, 1986; Wu *et al.*, 1985; Garfinkel *et al.*, 1985; Humble *et al.*, 1987; Brownson *et al.*, 1987; Janerich *et al.*, 1990). Spousal ETS exposure was not associated with a significant increased risk of lung cancer in males and females in the Kabat *et al.* (1995) study. However, this study was considerably smaller than the other three U.S. studies published in the 1990s and had limited statistical power to detect a significant association. The recent cohort study (Cardenas *et al.*, 1997) was limited by the relatively small number of lung cancer deaths available for analysis.

Another important feature of the post-1991 studies is that they addressed many of the criticisms (Mantel, 1983; Lee, 1986 and 1989; Katzenstein, 1992) directed at previous studies of ETS exposure and lung cancer. Although the extent to which these criticisms were addressed in each of the four case-control studies varied, the concerns were addressed collectively in these studies. Specifically, concerns regarding selection bias, misclassification bias of smokers as lifetime nonsmokers, misclassification of some non-lung cancers as lung cancers, misclassification of ETS exposure, and the lack of adjustment for potential confounders were addressed. Concerns regarding possible selective recall bias and information bias of case-control studies are avoided in the cohort study by Cardenas *et al.* (1997). Moreover, because the main analysis included only married couples who reported their own smoking habits, misclassification of ETS exposure due to reporting bias is also avoided.

The three population-based studies were careful to minimize the possibility of selection and misclassification biases. Selection bias associated with cases from selected hospitals is eliminated since, in all three population-based studies, lung cancer patients were identified from the cancer registries and hospitals covering a specific study area. The use of population-based controls instead of other patients as controls is also advantageous, since ETS exposure of patients with certain diagnoses may be higher and not representative of the exposure distribution of the source population from which cases were drawn. In addition, the U.S. multicenter study (Fontham *et al.*, 1991) examined the issue of differential recall between lung cancer cases and controls by interviewing colon cancer patients as a second control group during the first three years of the study. The findings on ETS exposure were comparable when lung cancer patients were compared to population controls and to colon cancer controls, suggesting that recall bias resulting from having a diagnosis of cancer could not explain the observed association with ETS.

Another source of misclassification bias that is of concern (Wald *et al.*, 1986; Lee, 1989) pertains to the misclassification of smokers as nonsmokers. In two of the four case-control studies (Fontham *et al.*, 1994; Stockwell *et al.*, 1992), the definition of lifetime nonsmokers was limited to individuals who had smoked fewer than 100 cigarettes and had no more than 6 months of tobacco use in their lifetime. In one study (Kabat *et al.*, 1995), subjects were considered lifetime nonsmokers if they had never consumed as much as one cigarette per day for a year, or had smoked fewer than 365 cigarettes over their lifetime. Both the U.S. multicenter study (Fontham *et al.*, 1994) and the Florida study (Stockwell *et al.*, 1992) used multiple sources of information to verify the lifetime nonsmokers' status. In addition, the U.S. multicenter study corroborated the subjects' self-reported current nonsmoking status using the urinary cotinine level. These results showed a very low percentage of cases (0.6 percent) and controls (2.3 percent) had levels of urinary cotinine exceeding 100 ng/mg, suggesting minimal misclassification of smokers as nonsmokers (Fontham *et al.*, 1994). Although the urinary cotinine/creatinine concentration only assesses current smoking (there are currently no biomarkers that allow assessment of past tobacco exposure), these results provided an additional verification of the current nonsmoking status.

Misclassification of lung cancer is also minimized by the requirement of microscopic diagnosis (Stockwell *et al.*, 1992; Fontham *et al.*, 1994; Kabat *et al.*, 1995) and an independent review of diagnostic material (Brownson *et al.*, 1992; Fontham *et al.*, 1994). In the three population-based studies with data by cell type (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1994), adenocarcinoma of the lung was the predominant cell type of lung cancer in nonsmoking women, accounting for over 60 percent of the lung tumors.

Because of the high fatality rate of lung cancer, all three U.S. population-based studies interviewed surrogate respondents to obtain information on a percentage of lung cancer cases who could not participate because they were too ill or were deceased. In all three studies, controls were self-

respondents. The percentage of lung cancer self-respondents was considerably higher for the U.S. multicenter study (63 percent) compared with the other two U.S. studies (33 percent for the Florida and 34 percent for the Missouri study). Since a surrogate's knowledge of the ETS exposure of an index subject is variable and dependent on their relationship and the exposure period of interest, it is likely that the quality of information on ETS exposure is higher in studies in which a high percentage of interview is conducted with self-respondents. On the other hand, the use of surrogate respondents was avoided in the U.S. hospital-based study since all interviews were conducted with the lung cancer cases and hospital patient controls while the subjects were still in the hospital (Kabat *et al.*, 1995).

Another criticism of previous studies of ETS exposure and lung cancer is that a small increased risk associated with ETS exposure may be due to lack of adjustment for potential confounding factors. In particular, it has been suggested that nonsmokers living with smokers have lower dietary intakes of specific micronutrients (Koo *et al.*, 1988; Hebert and Kabat, 1990; Sidney *et al.*, 1989; Le Marchand *et al.*, 1991; Matanoski *et al.*, 1995), including beta-carotene, which may be protective for lung cancer. However, there is little evidence of confounding by dietary factors in the U.S. multicenter study (Fontham *et al.*, 1994) or in a study conducted in Greece (Kalandidi *et al.*, 1990). In fact, similar trends of increased risk of lung cancer associated with increasing duration of exposure were observed at all levels of dietary factors (including intake of fruits and vegetables, supplemental vitamin use, and dietary cholesterol) (Fontham *et al.*, 1994). Other factors including employment in high-risk occupations (Fontham *et al.*, 1994) and previous lung diseases (Brownson *et al.*, 1992; Wu *et al.*, 1995) were examined, and they did not confound the association of ETS exposure and lung cancer. Thus, the recent large, well-conducted study (Fontham *et al.*, 1994) assessed all potential confounders that should be considered in evaluating the association of ETS with lung cancer in nonsmokers; the association was observed with adjustment for these potential confounders.

7.2.5 Other Sources of ETS Exposure

Because of the importance of obtaining a comprehensive measure of lifetime ETS exposure (Cummings *et al.*, 1989), all four U.S. case-control studies included questions to assess ETS exposure at home (from spouses, parents, and other household members during childhood and adult life), at the workplace and in other social settings. However, the exact questions asked and the level of detail obtained varied in these studies. Only a subset of the studies published prior to 1991 included questions on ETS exposures from sources other than spouses.

7.2.5.1 ETS Exposure From Parents and Other Household Members (Other Than Spouses)

Table 7.6 summarizes the case-control studies conducted since 1981 in the U.S. (n = 7) and outside of the U.S. (n = 7) that included questions on ETS exposure from household members other than spouses—represented mainly by exposure from parents during childhood—but also including other household members during childhood and adult life. The study by Akiba *et al.* (1986), which reported "no association," was not included in Table 7.6 since no information on the association or the distribution of subjects by exposure status was provided.

Among the U.S. studies, the strongest evidence for an effect of parental smoking is from studies conducted by Janerich *et al.* (1990) and Stockwell *et al.* (1992). In the study by Janerich *et al.* (1990), exposure during childhood up to age 21 accounted for about one-third of the lifetime duration (expressed in smoker-years) of ETS exposure. The highest level of childhood exposure (25 or more smoker-years) was associated with a statistically significant increased risk (OR = 2.07, 95% CI = 1.16-3.68), although there was no statistically significant elevated risk with 1-24 years of exposure. In the study by Stockwell *et al.* (1992), exposure to ETS from mothers, fathers, and siblings during childhood/adolescence was associated with a 10 to 70 percent increase in risk. Women who experienced 22 years or more of exposure to ETS from all household members combined during childhood/adolescence showed a significantly elevated risk of 2.4 (95% CI = 1.1-5.4) (Table 7.6). On the other hand, risk of lung cancer in nonsmokers was not associated with ETS exposure during childhood in the U.S. multicenter study (Fontham *et al.*, 1994), the Missouri study (Brownson *et al.*, 1992), the U.S. hospital-based study (Kabat *et al.*, 1995), or a small study conducted in Los Angeles County (Wu *et al.*, 1985). However, in the U.S. multicenter study, subjects who were exposed to ETS exposure during both childhood and adult life showed the highest increase in risk of lung cancer (Fontham *et al.*, 1994). In a hospital-based study conducted in the 1970's (Kabat and Wynder, 1984) and a subsequent one conducted in the 1980's (Kabat *et al.*, 1995), smoking by family members during adult life was not associated with risk of lung cancer in nonsmoking males and females.

In two studies conducted in Japan (Shimizu *et al.*, 1988; Sobue, 1990), an increased risk of lung cancer was associated with mothers' smoking; the result was statistically significant in one study (Shimuzu *et al.*, 1988) but not the other (Sobue, 1990). A significantly increased risk of lung cancer was also associated with smoking by the father-in-law in one Japanese study (Shimizu *et al.*, 1988). In Shanghai, China (Gao *et al.*, 1987) and in Northern China (Wu-Williams *et al.*, 1990), exposure to ETS during childhood did not differ significantly between lung cancer cases and controls. In a study conducted in Hong Kong, risk of lung cancer in nonsmokers was increased in households with smokers, although there was not a smooth trend of increasing risks with increasing number of smokers in the household (Koo *et al.*, 1987). In Sweden, no association between parents' smoking and risk of lung cancer was reported in one study (Pershagen *et al.*, 1987), whereas in another study, a statistically nonsignificant 3-fold increased risk of lung cancer was found for mothers' smoking (Svensson *et al.*, 1989).

Quality of information on parents' smoking (or other household members) during childhood may be compromised in some studies, particularly those in which this information is provided by surrogate respondents. Although there is generally good agreement of responses on ETS exposure when subjects themselves were asked on two different occasions whether specific household members smoked, the level of agreement diminished on quantitative aspects of smoking by household members (Pron *et al.*, 1988; Coultas *et al.*, 1989; Brownson *et al.*, 1993a). Studies which show high

concordance on the reporting of exposure to ETS during childhood and parents' smoking habits (Coultas *et al.*, 1989; Brownson *et al.*, 1993a) were based on responses obtained from the subjects themselves. The degree of agreement when the responses on smoking habits of the other household members are provided by surrogate respondents is not known. The fact that exposures from household members other than spouses are reported less reliably may partially explain the inconsistent results regarding the association between the risk of lung cancer and ETS exposure from these household members (*i.e.*, other than spouses); it may also explain the failure of most studies to observe stronger associations with exposure from household members other than from spouses.

7.2.5.2 Workplace ETS Exposure Table 7.7 summarizes case-control studies which included questions on ETS exposure at the workplace. Indicators of workplace ETS exposure varied (the actual questions asked were not provided). In some studies, the indicators of workplace ETS exposure were limited to the most recent job or the last job (Kabat and Wynder, 1984; Shimizu, 1988; Kalandidi *et al.*, 1990; Brownson *et al.*, 1992), at other specific times (Garfinkel *et al.*, 1985), or the timing of the question was not specified (Lee *et al.*, 1986; Stockwell *et al.*, 1992). In one study, number of smokers at work (lifetime) and amount of time working with smokers was assessed (Janerich *et al.*, 1990). In other studies, questions were asked regarding ETS exposure at each workplace of at least 3 months (Koo *et al.*, 1987) or the last four jobs of at least 1 year duration (Kabat *et al.*, 1995). In three other studies, lifetime occupational history was obtained and exposure to ETS was assessed for each job (Wu *et al.*, 1985; Wu-Williams *et al.*, 1990; Fontham *et al.*, 1994).

Studies in which the assessment of workplace exposure to ETS was complete (covering all jobs) with considerable ETS exposure of subjects in the studies are generally supportive of an association between workplace ETS exposure and risk of lung cancer (Wu *et al.*, 1985; Wu-Williams *et al.*, 1990; Fontham *et al.*, 1994). In particular, results from the U.S. multicenter study (Fontham *et al.*, 1994) suggested a trend of increasing risks with increasing duration of ETS exposure at the workplace. Compared to women who had no ETS exposure at the workplace, women who reported exposure for 1-15, 16-30, and 30 or more years showed adjusted odds ratios of 1.30, 1.40, and 1.86, respectively (p for trend = 0.001) (Table 7.7). In a subsequent analysis that selected workers only and adjusted for other adult ETS exposure sources, the RRs associated with workplace exposure were modestly enhanced (Reynolds *et al.*, 1996). The overall odds ratios associated with any reported workplace exposure increased from 1.39 in the earlier analysis to 1.56 (95% CI = 1.21-2.02) and the corresponding point estimates for 1-15, 16-30, and 30 or more years of exposure were likewise elevated; the adjusted odds ratios were 1.46, 1.58, and 2.08, respectively. Occupational exposure to carcinogens is an important confounder for lung cancer in nonsmokers, and the U.S. multicenter study (Fontham *et al.*, 1994) is the only one which adjusted for such exposures.

In addition to the incomplete assessment of exposure to ETS at the workplace in some studies, respondents, particularly surrogate respondents, may be less able to provide information on the subjects' exposure to ETS at the workplace. In a study in which a test-retest design was used to examine the reliability of passive smoke histories reported in personal interviews, self-respondents more reliably reported residential exposure than exposure at work (Pron *et al.*, 1988). This may be a particularly important problem in studies in which the proportion of surrogate respondents was high (Brownson *et al.*, 1992; Stockwell *et al.*, 1992).

Despite some of the above-mentioned difficulties in obtaining histories of lifetime ETS exposure at the workplace, there is reason to believe this source of ETS exposure also increases the risk of lung cancer, as does ETS exposure from spouses. The workplace has been a major source of ETS exposure outside the home (Cummings *et al.*, 1989 and 1990; Emmons *et al.*, 1992; Siegel, 1993), although the relative importance of workplace ETS exposure may be declining in California as the result of increasing restrictions on smoking in the workplace. In the International Agency for Research on Cancer (IARC) ten-country, collaborative study which correlated urinary cotinine levels to self-reported recent exposure to ETS at home (from spouses), in the workplace, and other social settings, Riboli *et al.* (1990) found that exposure to ETS at the workplace was a significant predictor of cotinine levels, similar to ETS exposure from spouses.

7.2.5.3 ETS Exposure in Other Settings Two of the four U.S. case-control studies published since 1991 (Fontham *et al.*, 1994; Kabat *et al.*, 1995) also asked questions about ETS exposure in social settings (other than the workplace) or in modes of transportation. In the U.S. multicenter study, increased risks were associated with ETS exposure in social settings. Women who were exposed for 1-15, 16-30, and >30 years at other social settings compared to no exposure showed adjusted ORs of 1.45, 1.59, and 1.54, respectively (p for trend = 0.002) (Table 6 of Fontham *et al.*, 1994). In the U.S. hospital-based study, associations with ETS exposure in social situations and risk of lung cancer were not statistically significant in males (OR = 1.39, 95% CI = 0.67-2.86) or females (OR = 1.22, 95% CI = 0.69-2.15) (Table 2 of Kabat *et al.* (1995)); the calculated OR for males and females combined was 1.26 (95% CI = 0.81-1.95). ETS exposure in cars was associated with non-significant increased risks of lung cancer in both males (OR = 1.55, 95% CI = 0.63-3.78) and females (OR = 1.84, 95% CI = 0.96-3.53) in the Kabat *et al.* (1995) study. Although the risks for males and females considered separately were not significantly different from controls, the calculated risk for males and females combined was significantly elevated (OR = 1.73 (95% CI = 1.03-2.92). No male cases were exposed to ETS in other modes of transportation, whereas there was a significant excess of female cases compared to female controls who reported such exposures (OR = 5.17, 95% CI = 1.46-18.24). ETS exposure in other modes of transportation was associated with an OR of 2.23 (95% CI = 0.83-5.99) for lung cancer in males and females combined in the Kabat *et al.* (1995) study.

7.2.6 Summary Despite the compelling biologic plausibility of an effect of ETS exposure on risk of lung cancer, detection of an effect has been difficult because a small excess in risk is difficult to establish in a single epidemiologic study. The U.S. EPA (1992), NRC (1986), and Surgeon General (U.S. DHHS, 1986) all undertook comprehensive reviews of the literature and determined on the basis of the overall evidence that ETS exposure causes lung cancer. Since the publication of the most recent authoritative review of lung cancer and ETS exposure (U.S. EPA, 1992), three large U.S. population-based studies (Stockwell *et al.*, 1992; Brownson *et al.*, 1992; Fontham *et al.*, 1991 and 1994), a smaller hospital-based case-control study (Kabat *et al.*, 1995), and a cohort study (Cardenas *et al.*, 1997) have been published. The three population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized (*i.e.*, small sample size, possible selection bias, possible misclassification biases, inadequate adjustment for potential confounders). Results from these studies and the cohort study are consistent with the conclusions of the U.S. EPA (1992), NRC (1986), and Surgeon General (U.S. DHHS, 1986) reports. Each of the three population-based studies shows a statistically significant increased risk of lung cancer in nonsmokers associated with long term exposure to ETS as well as increasing risk with increasing ETS exposure. The smaller hospital-based study lacked the statistical power to find the effect observed in the other studies. The results of the cohort study, though not statistically significant, were similar to the risk estimated by the U.S. EPA. Taken together, the recent studies provide additional evidence that ETS exposure is causally associated with lung cancer. The consistency of the findings in the five recent studies and the meta-analysis result of the U.S. EPA indicate about a 20 percent increased risk of lung cancer in nonsmokers.

7.3 ETS AND CANCER SITES OTHER THAN LUNG THAT ARE ASSOCIATED WITH ACTIVE SMOKING: NASAL SINUS, CERVICAL AND BLADDER

Active smoking is firmly established as a causal factor for cancers of the lung, larynx, oral cavity, esophagus, bladder, and nasal sinus cavity; in addition, evidence exists which suggests that smokers are at increased risk for kidney and cervical cancer. As reviewed above, the role of ETS exposure and risk of cancers in nonsmokers has been investigated mainly for lung cancer (U.S. DHHS, 1986; NRC, 1986; U.S. EPA, 1992). There are some data on the role of ETS for other cancer sites, including cancers of nasal sinus cavity, cervix, and bladder (U.S. DHHS, 1982 and 1989; IARC, 1986).

7.3.1 Nasal Sinus Cancer

Cancers of the nasal cavity and paranasal sinuses are extremely rare, accounting for 0.2 percent of all invasive incident cancers and 1.4 percent of all newly diagnosed respiratory cancers in the U.S. Use of tobacco products, various occupational exposures (*e.g.*, wood dust), and history of nasal polyps, have been implicated as risk factors for these tumors (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992). Although the risk associated with any use of tobacco is modest (OR about 1.5), up to a 5-fold increased risk has been observed with

7.3.1.1 Active Smoking and Nasal Sinus Cancer

heavy smoking (Elwood *et al.*, 1981). The evidence suggests that the effect of smoking, particularly current or recent tobacco use, is stronger for squamous cell carcinoma than for other cell types (mainly adenocarcinomas) of nasal sinus cancer (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992). The proportion of squamous cell nasal sinus cancers included in the different studies may influence the overall strength of the relationship between active smoking and all nasal sinus cancers combined. Studies which did not find a significant association between active smoking and nasal sinus cancer were generally small studies (*i.e.*, <50 cases and controls) (Tola *et al.*, 1980; Merler *et al.*, 1986), or had included few squamous cell carcinomas of the nasal sinus. For example, the study by Merler *et al.* (1986) included less than 20 percent squamous cell carcinomas compared to at least 40 percent of this cell type in other studies finding a positive association with smoking (Elwood *et al.*, 1981; Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Tola *et al.*, 1980; Zheng *et al.*, 1992).

7.3.1.2 ETS and Nasal Sinus Cancer The role of ETS exposure in the etiology of nasal sinus cancer in nonsmokers has been investigated in one cohort and two case-control studies (Table 7.8).

Hirayama (1983 and 1984) Using data from a Japanese prospective study (see Section 7.1 for detailed description), Hirayama (1983 and 1984) reported an increased risk of para-nasal sinus cancer (based on 28 nasal sinus cancer deaths) among nonsmoking women exposed to husbands' smoking. Relative risks increased with amount husbands smoked: compared to women married to nonsmokers, the RR was 1.7 (95% CI = 0.7-4.2), 2.0 (95% CI = 0.6-6.3), and 2.6 (95% CI = 1.0-6.3, $p \leq 0.05$), for women whose husbands smoked 1-14, 15-19, and 20+ cigarettes per day respectively, when husbands' age and occupation were adjusted for. The dose-dependent increase in risk was statistically significant ($p < 0.03$). Active smoking was not associated with nasal sinus cancer in this study; the OR was 0.9 (90% CI = 0.5-1.4) for males and females combined (Hirayama, 1990). Cell type distribution of nasal sinus cancer in nonsmokers and smokers was not available in this Japanese cohort study.

Fukuda and Shibata (1988 and 1990) The second study was conducted by Fukuda and Shibata (1988 and 1990) in Japan using a case-control study design. The 1988 report presented preliminary findings, and the 1990 report included results on 169 (125 men and 44 women) squamous cell maxillary sinus cancer cases and 338 controls (250 men and 88 women). Controls were selected from the general population. All subjects were interviewed directly. Nine of 125 male cases and 48 of 250 male controls had never smoked. Active smoking was a significant risk factor in men; the RR was 4.6 for smoking >39 cigarettes per day compared to nonsmokers. Based on a small number of nonsmoking men, exposure to ETS was associated with a small, nonsignificant increased risk of nasal cancer. Most of the female cases and controls in this study were nonsmokers (35 of 44 cases and 74 of 88 controls had never smoked). Active smoking was associated with a nonsignificant increased risk of nasal cancer in women. Among nonsmoking

Table 7.8
Association Between Passive Smoke Exposure and Risk of Nasal Sinus Cancer in Nonsmokers

Studies	Exposure to Passive Smoking		Relative Risk (95% CI)	
Cohort Studies				
Hirayama (1984)	Spouse's smoking in cig/day:			
	No	(5)[a]	1.0	
	Ex-smoker or Smokers			
	1-14	(9)	1.7	(0.7-4.2)
	15-19	(4)	2.0	(0.6-6.3)
	20+	(10)	2.6	(1.0-6.3)
Case-Control Studies				
Fukuda and Shibata (1990)	# Smokers in household			
	0	(11/35)[b]	1.0	
	1	(15/34)	1.4	(0.6-3.5)
	2+	(9/5)	5.7[c]	(1.7-19.4)
	1+	(24/39)	2.0	(0.8-4.5)
Zheng et al. (1993)	Ever exposed[d]			
	No		1.0	
	Yes		3.0	(1.0-8.9)

[a] *Number of nasal sinus cancer deaths.*
[b] *Number of cases/controls.*
[c] *p for trend = 0.02.*
[d] *Number of cases/controls by exposure category was not presented.*

women, domestic exposure to ETS, represented by the number of smokers in the household, was a significant risk factor. Compared to nonsmoking women with no reported ETS exposure, nonsmoking women who reported one, and two or more smokers in the household showed RRs of 1.4 and 5.7, respectively (95% CIs = 0.6-1.5 and 1.7-19.4; *p* for trend = 0.02). The OR associated with any passive smoke exposure (*i.e.*, none versus any exposure) is 1.96 (95% CI = 0.8-4.5). Information on duration or intensity of ETS exposure was not reported. The effect associated with passive smoking persisted with adjustment for other risk factors including sinusitis and/or polyps, nasal trauma, and woodworking.

Zheng et al. (1993) The third study was a case-control analysis of cancer of the nasal cavity and sinuses among white men in the U.S. using data from the 1986 National Mortality Followback Survey (Zheng *et al.*, 1993). The study included a total of 147 cases (76 maxillary sinus, 11 nasal cavity, 4 auditory

and middle ear, 56 other accessory sinuses cancer) and 449 controls who died of other causes. All information was obtained from a surrogate who responded to a mailed questionnaire. There was an increased risk of nasal cancer among cigarette smokers, with a nearly 2-fold increased risk among heavy or long-term smokers for all nasal cancer sites. Compared to nonsmokers, heavy smokers showed an OR of 2.7 (95% CI = 1.2-6.4) for maxillary sinus cancers and an OR of 1.3 for other nasal cancer (95% CI = 0.5-3.3). Twenty-eight cases and 99 controls had never smoked. Among nonsmokers, more cases than controls had a wife who smoked cigarettes (OR = 3.0, 95% CI = 1.0-8.9, $p \leq 0.05$), but the authors stated there was not a smooth trend of increasing risks as the number of cigarettes smoked by the spouse increased (data on dose-response were not presented). The 3-fold risk associated with having a wife who smoked is somewhat surprising since more than half (15 of 28) of the tumors in nonsmokers were other nasal sinus cancer and this subgroup was less strongly associated with active smoking. However, the histologic cell type of nasal sinus cancer among smokers and nonsmokers was not available in this study, making it difficult to make direct comparisons of findings in smokers and nonsmokers.

7.3.1.3 Summary Existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. The results have been observed in studies in white American males and Japanese females, in cohort and case-control study designs, and with some adjustment for possible confounders. The risks associated with ETS exposure ranged from 1.7 to 3.0.

Future studies need to confirm the magnitude of risk associated with ETS exposure, to characterize the risk by the source of ETS exposure (*i.e.*, spouse, other household members, coworkers) and by timing of ETS exposure (current versus past exposure), and to establish the dose-response relationship. It is also important that future studies examine the association between ETS and nasal sinus cancer by histologic type and subsite of nasal sinus cancers, and the role of other potential confounders in the association. Studies designed to investigate the mechanism(s) of action of active smoking and ETS exposure will help to elucidate their respective roles in the development of nasal sinus cancer.

7.3.2 Cervical Cancer

7.3.2.1 Active Smoking and Cervical Cancer Numerous epidemiologic studies conducted in different populations of varying age groups exhibiting different degrees of cervical lesions have provided supportive evidence that women who smoke cigarettes are more likely to develop cervical cancer than women who do not (Winkelstein, 1990). The statistical association between active smoking and cervical cancer is reduced with adjustment for sexual activity variables (*e.g.*, number of partners, age at first intercourse) or infection with human papilloma virus (HPV), which has been accepted as the sexually transmitted etiological factor in cervical cancer (Brinton, 1990; Schiffman *et al.*, 1993; Munoz *et al.*, 1994; zur Hausen, 1986). However, an association between smoking and cervical cancer/intraepithelial neoplasia (CIN) has been found in case-con-

trol studies that have been able to control for these behavioral risk factors (Buckley *et al.*, 1981; Hellberg *et al.*, 1983; Brinton *et al.*, 1986; Clarke *et al.*, 1982; La Vecchia *et al.*, 1986; Becker *et al.*, 1994).

In most studies, the excess risk of cervical cancer for smokers is about 2-fold, with the highest risks generally observed for heavy or current smokers, suggesting that tobacco smoke may have a late-stage effect on cervical cancer development. The data also suggest that tobacco smoke may be a cofactor in the development of particularly high-grade CIN (Brinton and Hoover, 1992; Schiffman *et al.*, 1993) by acting with or enhancing other infectious agents, such as cervical HPV (zur Hausen, 1986; Burger *et al.*, 1993) in the promotion of cervical neoplasia. A possible mode of action of tobacco smoke is to compromise immune function (Barton *et al.*, 1988).

In addition to the epidemiological evidence, an association between smoking and cervical cancer is biologically plausible since carcinogens in tobacco smoke can be absorbed in the lung and transported to distant sites by the blood. Tobacco constituents, including cotinine and nicotine, have been detected in the cervical mucus of smokers (see below). Higher levels of DNA adducts in cervical biopsies of smokers compared to nonsmokers have also been reported (Simons, 1994, see below). Among women with cervical dysplasia, higher levels of mutagenicity in the cervical mucus of smokers compared to nonsmokers have been found (Holly *et al.*, 1986), although this result has not been observed in studies of women without cervical dysplasia (Schiffman *et al.*, 1987; Holly *et al.*, 1993).

7.3.2.2 ETS Exposure and Cervical Cancer

The relationship between ETS exposure and cervical cancer was investigated in one cohort and three case-control studies (Table 7.9).

Hirayama (1981)

As part of the Japanese cohort study, Hirayama (1981) presented results on risk of cervical cancer in women by husbands' smoking habits. Based on 250 cervical cancer deaths in nonsmokers, the RRs were 1.15, and 1.14 for women whose husbands were ex-smokers or smoked 1-19 cigarettes/day, and >20 cigarettes/day, respectively, compared to women whose husbands were nonsmokers (p value for trend = 0.25). In the same study, women who ever smoked showed a high risk of cervical cancer compared to nonsmokers (RR = 1.6, 90% CI = 1.3-1.9), and there was some suggestion of increasing risks with increasing amounts smoked (the RRs associated with smoking 1-9, 10-19, and 20+ cigarettes/day were 1.7 (90% CI = 1.3-2.2), 1.3 (90% CI = 1.0-1.8) and 2.4 (90% CI = 1.4-3.9), respectively (Hirayama, 1990)). The findings on active smoking and passive smoking were not adjusted for potential confounders including subjects' or husbands' sexual activity.

Sandler (1985a)

A case-control study which provided some data on the role of ETS exposure and risk of cervical cancer in nonsmokers (see Section 7.1.1 for details) was a study on childhood and adult life ETS exposure and risk of various cancer outcomes (Sandler, 1985a). Because this study included different cancer outcomes, information typically obtained in studies of a specific cancer site (*e.g.*, sexual activity in studies of cervical cancer) was not

Table 7.9
Relationship Between Active and Passive Smoke Exposure and Risk of Cervical Cancer

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking			Passive Smoking (Among Never Smokers)		
				Adj. OR[a]			Adj. OR[a]
Hirayama (1981, 1990)	Total number of cervical cancer deaths was 589; number of cervical cancers in never smokers was 250	Ever smoked 1-9 cigarettes/day 10-19 20+		1.6 (1.3-1.9) 1.7 (1.3-2.3) 1.3 (1.0-1.8) 2.4 (1.4-3.9)	NS Ex/1-19/day ≥20/day		1.0 1.15 1.14[b]
Sandler *et al.* (1985a & b)	56 cervical cases among nonsmokers -data on nonsmoking controls not presented (there were a total of 330 female controls)				Exposed to Spouse's smoking	CA/CO NA	2.1 ($p < 0.05$)
					Mother smoking	no 37/196[c] yes 3/24	1.0 0.7 (0.2-2.3)
					Father smoking	no 15/120 yes 19/91	1.0 1.7 (0.8-3.4)
			CA/CO	Adj. OR[d]	Hrs/day[e]	CA/CO	Adj. OR[d]
Slattery *et al.* (1989)	266 cases/408 controls (cases: 78% carcinoma *in situ*, 22% invasive cancer)	Never Ex-smoker Current smoker	81/305 37/48 148/55	1.0 1.4 (0.8-2.5) 3.4 (2.1-5.6)	None 0.1-0.9 1.0-2.9 ≥3.0	NA NA NA NA	1.0 1.1 (0.5-2.9) 1.6 (0.5-4.7) 3.4 (1.2-9.5)

Table 7.9 (Continued)

Study	# Cases/# Controls Cervical Cytology (among cases)	Active Smoking			Passive Smoking (Among Never Smokers)		
			CA/CO	Adj. OR[f]	At Home Yrs Exposure	CA/CO	Adj. OR[f]
Coker *et al.* (1992)	103 cases/268 controls (All biopsy-confirmed cervical intraepithelial neoplasia, class II or III)	Never	37/170	1.0	Not exposed	9/49	1.0
		Ever smoked	66/96	1.7 (0.9-3.3)	<17 yrs	18/52	1.5 (0.5-4.0)
		Current smoker	66/49	3.4 (1.7-7.0)	≥18 yrs	9/69	0.4 (0.1-1.3)
					At Work Yrs Exposure	CA/CO	Adj. OR
					Not exposed	28/132	1.0
					1-4 yrs	6/21	1.7 (0.5-5.1)
					≥5 yrs	2/16	0.4 (0.1-2.5)

[a] *90% CI.*
[b] *p value was 0.25.*
[c] *Number of cases and controls was calculated from Table 4 of Sandler et al., 1985e.*
[d] *Adjusted for age, church attendance, education, and number of sexual partners of the women.*
[e] *Number of hours of exposure per day inside and outside of the home.*
[f] *Adjusted for age, years of education, race, number of pap smears, number of partners, and genital warts.*

Abbreviations: NA = not available, CA/CO = cases/controls, OR = odds ratio.

collected. There were a total of 518 cancer patients; 101 had cervical cancers, of which 56 occurred in women who had never smoked. The 56 nonsmokers with cervical cancer were compared to 235 nonsmoking control women. Spouses' smoking habits were associated with an increased risk of cervical cancer in nonsmokers (OR = 2.1, 95% CI = 1.2-3.9) after adjustment for age, race, education, and smoking habits of parents. In the same study, husbands' smoking also increased risk of cervical cancer in women who were smokers (OR = 2.0, 95% CI = 0.9-4.1); the effect was observed after adjustment for the above-mentioned variables as well as personal smoking habits of women. Sandler *et al.* (1985b) also examined the association between parental smoking during childhood and risk of cervical cancer. Maternal smoking was not associated with risk of cervical cancer (OR = 0.66, 95% CI = 0.19-2.29) whereas paternal smoking was associated with a statistically nonsignificant increased risk (OR = 1.67, 95% CI = 0.81-3.45). The difference in results for mothers' versus fathers' smoking is likely due to chance; among controls the prevalence of mothers who smoked was low (11 percent) compared to fathers who smoked (43 percent).

Slattery et al. (1989) A second case-control study on this subject was designed to investigate the role of active smoking and passive smoking in the etiology of cervical cancer. This study included 266 women with cervical cancer and 408 population controls, selected by random-digit dialing in Utah (Slattery *et al.*, 1989). Eighty-one cases and 305 controls had never smoked. Women were asked whether they were exposed to "a lot, some, a little, or no" tobacco smoke inside or outside their homes and the number of hours of exposure per day, during the 5 years before interview. Among nonsmokers, ETS exposure inside and outside of the home was associated with a significantly increased risk with adjustment for potential confounders which included age, education, church attendance, and number of sexual partners of the woman. A 3-fold increased risk (OR = 3.4, 95% CI = 1.2-9.5) was observed for three or more hours of exposure per day. The increased risks associated with ETS exposure among nonsmoking women were comparable to the risks associated with active smoking in this study (Table 7.5). Although specific information on HPV infection and partners' sexual activity was not available, the effect of active smoking was strongest among women who had a few (none to one) sexual partners (OR = 14.2, 95% CI = 9.2-38.9) and weakest for women with four or more partners (the highest category of partners in this study, OR = 2.3, 95% CI = 1.4-3.9). The authors interpreted this finding to suggest that cigarette smoking, and presumably ETS exposure, as risk factors for cervical cancer may be more important among women who have not experienced other major risk factors for this cancer (*i.e.*, HPV infection).

Coker et al. (1992) Another case-control study which was designed to examine the role of active and passive smoking included 103 CIN cases (40 percent CIN II, 60 percent CIN III) and 268 controls; 37 CIN cases and 170 controls had never smoked (Coker *et al.*, 1992) (Table 7.9). All subjects had attended a family practice clinic, and controls were women with normal cervical cytology at enrollment. Subjects were asked about tobacco smoke exposure at the workplace and whether they had ever lived with a smoker who had

smoked for at least 1 year. The total number of years of exposure and the relationship of the smoker to the index subject were also asked. For nonsmokers, after adjusting for potential confounders, there was no significant or consistent association between ETS exposure at work or at home and risk of CIN. Analysis by source of ETS exposure showed no association with parents' smoking (OR = 0.4, 95% CI = 0.1-1.2), a positive association with husbands' smoking (OR = 1.5, 95% CI = 0.3-6.2) or others' smoking (OR = 1.8, 95% CI = 0.4-8.4) after adjustment for age, education, race, number of Pap smears, number of partners, and genital warts. The crude OR was calculated for any smoking by husbands (*i.e.*, combine smoking of husband only and of parent) is 2.2 (95% CI = 0.9-5.7); the crude OR for any parents' smoking (*i.e.*, combine smoking of parents only and of parent and husband) is 0.9 (95% CI = 0.4-2.1) (calculated based on Table 5 of Coker *et al.*, 1992). In this study, active smoking was a risk factor irrespective of HPV status; its effect was stronger among women classified as HPV-negative than those classified as HPV-positive.

Additional epidemiological information on cervical cancer Data from several other studies on cervical cancer show that husbands of women with cervical cancer are more likely to be smokers than husbands of control women, although the effect of husband's smoking generally diminished with adjustment for a woman's smoking. In a study conducted by Buckley *et al.* (1981), husbands' smoking was associated with an increased risk even after adjustment for wives' smoking habits although its effect diminished. There were too few nonsmoking women to evaluate the role of husbands' smoking in this subgroup. In a study by Hellberg *et al.* (1983 and 1986), the effect of husbands' smoking diminished and was no longer statistically significant after adjustment for wives' smoking habits, whereas the effect of wives' smoking persisted with adjustment for husbands' smoking. There was, however, a statistically nonsignificant excess of husbands who smoked among nonsmoking wives (Hellberg *et al.*, 1986). In a third study, Zunzunegui *et al.* (1986) reported an excess of husbands who smoked. Although this excess risk was not adjusted for wives' smoking habits, the authors argued that there was a deficit of smokers among wives and thus wives' smoking is an unlikely explanation for the finding on husbands' smoking.

Two case-control studies of cervical cancer, one conducted in Spain, a low risk area (Bosch *et al.*, 1996) and one conducted in Cali, Columbia, a high risk area (Munoz *et al.*, 1996) offered some additional information on the role of husbands' smoking in the etiology of wives' risk of cervical cancer. The study in Spain included 306 cases and 327 controls, while the study in Cali included 210 cases and 262 controls. Prevalence of active smoking among cervical cancer cases and controls was not presented in either study. In the study conducted in Spain, in all women, after adjustment for the woman's own active smoking habits, there was a significant trend of increasing risk in association with spouse's smoking. The ORs for cervical cancer were 1.0, 1.8, 2.1, and 2.5 associated with no, 0.1-3.2, 13.3-26.1, ≥26.2 pack-years of spouse's smoking (Bosch *et al.*, 1996). In the Cali study, although husbands' smoking was also associated with an increased risk of cervical cancer in wives, this result was not statistically significant

after adjustment for wives' smoking habits (Munoz *et al.*, 1996). Both studies are limited in that they did not present results on nonsmoker controls and nonsmoker cervical cancer patients.

7.3.2.3 Biomarkers of Cervical ETS Exposure

In addition to questionnaire-based data, several small studies have been conducted to determine whether there are measurable levels of tobacco-smoke constituents in cervical epithelial cells of nonsmokers. Detectable levels of nicotine and cotinine were found in the cervical mucus of nonsmokers; the levels ranged from <1 to about 6 percent of those of active smokers (Sasson *et al.*, 1985; Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992, see Table 7.10). In three of these studies (Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992), data were presented separately for nonsmokers exposed to ETS and those with no reported exposure to ETS. In two studies (Hellberg *et al.*, 1988; McCann *et al.*, 1992), levels of nicotine/cotinine in cervical mucus were not distinguishable between nonsmokers with and without ETS exposure, whereas in a third study, higher levels of nicotine were found in women with ETS exposure compared to those with no reported exposure (Jones *et al.*, 1991) (Table 7.10). None of the studies on cervical cancer has examined risk of cancer in relation to presence or absence of nicotine/cotinine in the cervical mucus, but this evidence from cross-sectional clinical studies supports the hypothesis that cervical exposure to tobacco constituents occurs from exposure to tobacco smoke.

The presence of carcinogen-DNA adducts in human tissues has been used as evidence of smoking-induced DNA damage. Using ^{32}P-postlabelling techniques, a linear relationship between cigarette consumption and levels of aromatic DNA adducts has been demonstrated in human bronchial epithelium (Phillips *et al.*, 1990a) and other tobacco-related sites, including the cervical epithelium (Phillips *et al.*, 1990b; Cuzick *et al.*, 1990). Recently, Simons (1993) measured levels of DNA adducts in cervical biopsies of 39 women admitted for hysterectomy for benign disease or colposcopy. In this group, 18 were smokers (11 current, 4 ex-smokers who stopped in the last 6 months, 3 longer-term ex-smokers) and 21 had never smoked. Of the nonsmokers, 75 percent (n = 16) reported exposure to ETS at work or in the home. Urinary cotinine/creatinine levels were also available on these subjects; a ratio of 0.06 or greater was used to indicate active smoking in the previous 24-48 hours.

The median DNA adduct level (per 10^8 nucleotides) was 4.62 in self-reported smokers, which was significantly higher than that in self-reported nonsmokers (3.47). Seven self-reported nonsmokers showed a urinary cotinine/creatinine ratio of 0.06 or greater, and they were reclassified as smokers (n = 25). The median DNA adduct level in self-reported and reclassified smokers was 4.45 compared to 3.52 (p = 0.07) in confirmed nonsmokers (*i.e.*, urinary cotinine/creatinine <0.06). The presence of adducts in cervical epithelium and the correlation with smoking habits strongly suggest that the adducts are a consequence of exposure to tobacco constituents. These results provide direct biochemical evidence that potentially carcinogenic agents may affect the DNA of cervical epithelial cells. It is notable that all

Table 7.10
Nicotine and Cotinine Measured in the Cervical Mucus of Smokers, Passive Smokers and Nonsmokers

Study	Levels (ng/ml) of Nicotine	Cotinine	
Sasson *et al.*, 1985[a]			
Smokers (*n* = 10)	740	316	
Nonsmokers (*n* = 8)	16	3	
Hellberg *et al.*, 1988[a]			
Smokers (*n* = 17)	1,056	1,061	
Nonsmokers with ETS exposure			
Yes[b] (*n* = 4)	20	51	
No (*n* = 14)	43	78	
	Levels of Nicotine (ng/ml)		
	Mean	Median	Range
Jones *et al.*, 1991[c]			
Smokers (*n* = 31)	34.3	11.8	2.8-383.4
Nonsmokers with ETS exposure[d]			
at home (*n* = 32)	0.1	0.8	<0.2-8.2
outside of home (*n* = 42)	NA[f]	0.4	<0.2-5.2
none (*n* = 70)	NA	0.2	<0.2-3.8
McCann *et al.*, 1992[c]			
Smokers (*n* = 25)	107.2	56	4-358
Nonsmokers with ETS exposure[d]			
Yes[e] (*n* = 12)	3.6	3.5	<0.2-12
No (*n* = 12)	3.9	3.5[g]	<0.2-14

[a] *Cervical mucus collected using aspiration methods.*
[b] *Exposed at home or work, time of passive smoke exposure relative to specimen collection not specified.*
[c] *Cervical mucus collected using cervical flush techniques.*
[d] *Passive smoke exposure in the last 24 hours.*
[e] *Nonsmokers with ETS exposure at home or at work.*
[f] *NA = not available.*
[g] *Excluded one outlier who was usually exposed to passive smoking several hours/day, but had no exposure within the last 24 hours.*

the women in the study had detectable proportions of DNA adducts regardless of their smoking status. The relatively high DNA adduct levels in nonsmokers may reflect exposure to ETS, reported by 75 percent of nonsmokers in this study. Future studies on DNA adduct levels by self-reported exposure to ETS in nonsmokers are needed to confirm these suggestive results.

7.3.2.4 Summary There is supportive evidence from epidemiological and biochemical studies implicating a role for ETS exposure in the etiology of cervical cancer in nonsmokers. A positive, but nonsignificant association was reported in one cohort study (Hirayama, 1981) and a significant, positive association was observed in two (Sandler *et al.*, 1985a; Slattery *et al.*, 1989) of three case-control studies. In the third case-control study, conducted by Coker *et al.* (1992), spousal ETS was associated with an increased the risk of cervical cancer/intraepithelial neoplasia in nonsmokers although the result was of borderline statistical significance. Any exposure to ETS (*i.e.*, parents and spouses combined) was not a risk factor in the study by Coker *et al.* (1992); this finding is not too surprising since risk of cervical cancer appears to be most affected by current tobacco use. In one of three biochemical studies, levels of nicotine in the cervical mucus of nonsmokers exposed to ETS were reported to be higher than levels in those with no exposure. Demonstration of detectable levels of nicotine and cotinine in cervical mucus of nonsmokers suggests that constituents of cigarette smoke may reach more distant sites such as the cervix and play a direct mutagenic role in the etiology of cervical cancer. In addition, the presence of DNA adduct levels in the cervical epithelium of nonsmokers supports the hypothesis that carcinogenic constituents of tobacco smoke may adversely effect the cervical epithelium.

Little is known about the transport of nicotine and cotinine throughout the body and about its metabolism in distant organ sites. Mutagenicity of semen due to smoking is plausible, and direct cervical contact with semen of smoking partners may represent another source of exposure to tobacco constituents. It is important to confirm these findings, to determine the importance of recent exposure to ETS (*i.e.*, within recent 5 years) versus lifetime exposure to ETS, and to determine the effect of exposure from spouses versus other household members or coworkers. It is also important to evaluate the effect of passive smoking by stage of cervical cancer (*e.g.*, invasive and pre-invasive), and by history of potential confounding factors, including HPV infection. Measurement of levels of cotinine/nicotine in cervical mucus as well as DNA adducts in cervical epithelium of nonsmokers will complement the epidemiological findings from questionnaires, although such measurements may not be available for cervical cancer cases who are enrolled in studies after surgical treatment for their cancers.

7.3.3 Bladder Cancer

7.3.3.1 Active Smoking and Bladder Cancer Active smoking is firmly established as a cause of bladder cancer; the relative risks for active smoking ranged from 2 to 10 in different studies (IARC, 1986). The estimated attributable risk for bladder cancer due to smoking is 47 percent in men and 38 percent in women (Shopland *et al.*, 1991). The range in relative risk estimates has been explained partly by the different types of tobacco smoked in different countries and the differences in carcinogenicity of tobacco types. Black tobacco products, commonly smoked in countries such as Italy and Argentina, are associated with higher risks of bladder cancer (Vineis *et al.*, 1984; Iscovich *et al.*, 1987) than blond tobacco products, smoked in the U.S. and Canada (Hartge *et al.*, 1990; Burch *et al.*, 1989). Black tobacco, compared to blond tobacco, contains higher concen-

trations of various aromatic amines, including 4-aminobiphenyl, an established bladder carcinogen (Patrianakos and Hoffmann, 1979; IARC, 1972).

7.3.3.2 ETS and Bladder Cancer

Risk of bladder cancer in nonsmokers in relation to ETS exposure was evaluated in two studies (Table 7.11).

Kabat et al. (1986)

The first study was conducted by Kabat *et al.* (1986) as part of a large on-going case-control study of smoking and cancer. Between 1976 and 1983, a total of 948 bladder cancer cases (751 male and 197 female) were interviewed, 152 of whom (76 male and 76 female) were lifetime nonsmokers (*i.e.*, smoked less than one cigarette, cigar, or pipe per day for 1 year). Hospital controls who were also lifetime nonsmokers were matched to each case on age, sex, race, hospital, and year of interview. There were a total of 492 nonsmoking controls (238 male and 254 female). Questions on ETS exposure were added to the questionnaire in 1979; this information was available on only 40 of 152 cases and 75 of 492 controls interviewed. Questions were asked regarding exposure to ETS inside the home, represented by spouses' smoking, and exposure outside of the home, including exposure at work or in transportation. Results were presented in terms of hours of ETS exposure per week.

The findings on the relationship between ETS exposure and bladder cancer were inconsistent by gender and by source of exposure. For nonsmoking males, there was a nonsignificant increased risk of bladder cancer associated with ETS exposure at home but not at work, whereas among nonsmoking females, a nonsignificant increased risk was observed for ETS exposure at work but not at home (Table 7.11). This study has several limitations, however. The most serious ones include the small sample size of nonsmokers and the fact that controls were selected from among hospital patients. Although controls were diagnosed with presumably non-tobacco-related diseases (specific diagnoses were not specified), many malignant and non-malignant diseases are causally related to tobacco smoke. Hence, it is quite conceivable that hospital controls may be more likely to be exposed to ETS than the general population.

Burch et al. (1989)

A second study was conducted by Burch *et al.* (1989) in Canada between 1979 and 1982. This study included 826 histologically-confirmed bladder cancers and 792 randomly selected controls (Table 7.11). Of these, 142 cases and 217 controls were nonsmokers (defined as having smoked fewer than 185 cigarettes in total). Subjects were asked about their exposure to the tobacco smoke of others at home and at work. For all subjects and for nonsmokers, there was no association between risk of bladder cancer and ETS exposure at home or at work. The authors suggested that because of the modest risk associated with active smoking (RR = 2.7) in this study, any association between ETS and bladder cancer in nonsmokers may be too weak to be detectable in questionnaire-based epidemiologic studies.

7.3.3.3 Biomarkers of Exposure to Bladder Carcinogens from ETS Exposure

Aside from questionnaire-based epidemiologic studies, some data are available from biochemical measurement studies which evaluated the effect of ETS and risk of bladder cancer in nonsmokers. These studies measured hemoglobin (Hb) adducts of 4- or 3-aminobiphenyl (4-ABP or 3-ABP) which are

Table 7.11
Passive Smoking and Bladder Cancer Among Nonsmokers

Study	Males		Females	
	# Exposed Cases/Controls	OR (95% CI)	# Exposed Cases/Controls	OR (95% CI)
Kabat *et al.* (1986)[a]				
Exposed to passive smoking				
At home	6/10	1.5 (0.5-4.5)	6/13	0.6 (0.5-1.2)
At work or in transportation	11/25	0.7 (0.2-1.8)	6/5	2.5 (0.6-10.1)
Burch *et al.* (1989)[b]				
Exposed to passive smoking				
At home	37/72	0.9 (0.5-2.0)	66/90	0.8 (0.3-1.7)
At work	25/45	1.0 (0.5-1.9)	26/38	0.9 (0.5-1.8)

[a] *Total number of nonsmokers were: males-23 cases, 44 controls; females-17 cases, 28 controls.*
[b] *Total number of nonsmokers were: males-61 cases, 112 controls; females-81 cases, 105 controls.*

formed over the 120-day lifespan of the erythrocyte and therefore may serve as dosimeters of average exposure over the previous 4 months. As mentioned above, the aromatic 4-ABP is a potent human bladder carcinogen (IARC, 1972).

In one study, concentrations of adducts of 4- and 3-ABP were measured in 57 nonsmokers. Subjects who reported exposure to ETS and had detectable serum cotinine levels showed higher median and mean levels of both adducts than subjects who reported no exposure to ETS and had no detectable cotinine levels. The result was of borderline significance for 4-ABP-Hb and was statistically significant for 3-ABP-Hb (MacClure *et al.*, 1989) (Table 7.12). In a second study, Barstch *et al.* (1990) extended the investigation of 4-ABP-Hb levels in smokers and nonsmokers by N-acetylation phenotype, a marker of susceptibility for bladder cancer (Table 7.13). It has been established that at the same level of exposure to active smoking and other exposures to xenobiotics, slow acetylators are at higher risk of bladder cancer than fast acetylators (Cartwright *et al.*, 1982; Vineis *et al.*, 1990). Among nonsmokers in this study, those with ETS exposure showed higher levels of ABP adducts than those with no ETS exposure. However, the relative increase in ABP adducts differed for "slow" and "fast" acetylators. Among nonsmokers with no ETS exposure, the ABP levels were at least two times higher among "slow" than "fast" acetylators. However, the ABP levels among nonsmokers with ETS exposure were comparable for "fast" and "slow" acetylators. Thus, the increase in ABP levels in relation to ETS exposure was more apparent for "fast" than "slow" acetylators (Table 7.13). It is of note that in both studies, nonsmokers showed levels of hemoglobin adducts of 4-ABP that were 28-35 percent of those of smokers, and the levels of 4-ABP were somewhat higher in nonsmokers exposed to

ETS than those not exposed. Levels of 4-ABP were 7 percent higher in nonsmokers exposed to ETS compared to nonsmokers not exposed in one study (MacClure *et al.*, 1989). In a second study, 4-ABP levels were 14 percent higher in nonsmokers exposed than nonsmokers not exposed among "slow" acetylators, and were almost two times higher among exposed "fast" acetylators compared to non-exposed "fast acetylators."

Future studies need to confirm and better characterize the relationship between levels of hemoglobin adducts in nonsmokers and their exposure to ETS by acetylator status.

7.3.3.4 Summary In summary, the evidence from questionnaire-based epidemiologic studies of ETS and bladder cancer is inadequate. There have been two case-control studies to date, both showed no significant increased risk associated with ETS exposure. These studies, however, had serious limitations including small sample sizes and crude assessment of exposure to ETS. On the other hand, the evidence from two biochemical studies is suggestive. In both studies, nonsmokers exposed to ETS showed higher levels of hemoglobin adducts of an established bladder carcinogen than nonsmokers not exposed to ETS, providing supporting evidence that nonsmokers exposed to ETS may be at increased risk of bladder cancer.

7.4 ETS AND CANCER SITES WHERE EVIDENCE FOR THE ROLE OF ACTIVE SMOKING IS EQUIVOCAL

7.4.1 Breast Cancer

7.4.1.1 Active Smoking and Breast Cancer

A large number of epidemiologic studies have investigated the association of active smoking and risk of breast cancer (Baron, 1984; MacMahon, 1990; Palmer and Rosenberg, 1993; Calle *et al.*, 1994; Baron *et al.*, 1996), and the results are inconclusive. A few case-control (Williams and Horm, 1977; Vessey *et al.*, 1983; O'Connell *et al.*, 1987) and cohort studies (Hammond, 1966) have found a protective effect associated with smoking. However, the majority of studies have found no association (Smith *et al.*, 1984; Adami *et al.*, 1988; Baron *et al.*, 1986; Rosenberg *et al.*, 1984; Porter and Jick, 1983; Brinton *et al.*, 1986; London *et al.*, 1989; Schechter *et al.*, 1989; Vatten and Kvinnsland, 1990; Field *et al.*, 1992) or a weak positive association with smoking (Le *et al.*, 1984; Rohan and Baron, 1989; Palmer *et al.*, 1991; Schechter *et al.*, 1985; Brownson *et al.*, 1988; Stockwell and Lyman, 1987; Calle *et al.*, 1994). The case-control studies which have found an increased risk with smoking tended to have selected cases and controls from cancer screening programs (Schechter *et al.*, 1985; Brownson *et al.*, 1988) or have found the increased risk among premenopausal women (Schechter *et al.*, 1985; Rohan and Baron, 1989; Brownson *et al.*, 1988); other studies found effects for selective smoking variables such as starting at an early age (Brinton *et al.*, 1986; Palmer *et al.*, 1991) or among former smokers (Hiatt *et al.*, 1988; Baron *et al.*, 1996). Meara *et al.* (1989) showed that bias in selection of cases and controls in hospital-based series would spuriously show a decreased risk of breast cancer with increasing amounts smoked. On the other hand, bias associated with selecting subjects from a cancer-screening population would spuriously produce an increased risk of breast cancer with increasing amounts smoked.

In the one prospective study which found a small, significant increased risk of fatal breast cancer with current smoking, the authors hypothesized that these findings could reflect either a poorer prognosis among breast cancer cases who smoke or a delayed diagnosis among current smokers (Calle *et al.*, 1994).

The above epidemiologic studies investigated the risk of breast cancer in active smokers compared to all nonsmokers in the baseline group. A recent study (Morabia *et al.*, 1996) investigated the effect of active smoking compared to nonsmokers not exposed to ETS. Data were also presented which allowed comparison of the effect of active smoking compared to all nonsmokers and to nonsmokers not exposed to ETS. We calculate that compared to all nonsmokers (126 cases and 621 controls), the crude ORs associated with ever smoking 1-9, 10-19, and 20+ cigarettes per day were 1.1, 1.5, and 1.6, respectively (p trend = 0.007). The corresponding adjusted ORs when compared to nonsmokers not exposed to ETS (28 cases and 241 controls) were 2.4, 3.6, and 3.7 (p trend = 0.09; from Table 2 of Morabia *et al.*, 1996). Similar results were obtained when current active smokers were compared to all nonsmokers and to nonsmokers not exposed to ETS.

7.4.1.2 ETS and Breast Cancer

A role of passive smoking in the etiology of breast cancer was first hypothesized by Horton (1988), who noted that countries with high mortality rates of lung cancer in males generally had high rates of breast cancer, whereas countries with low rates of lung cancer had low rates of breast cancer. Based on this observation, Horton then (1988 and 1992) tested the hypothesis and found that passive smoking (using male lung cancer rates as a proxy variable) is a risk factor for female breast cancer. There was, however, little support for this hypothesis in another correlational study which investigated the relationship between female breast cancer and male lung cancer within five countries (Williams and Lloyd, 1989). Deleterious effects of smoking on the breast are plausible since carcinogens in smoke (*e.g.*, 3-4 benzo[a]pyrene) or their metabolites are absorbed systemically (Kotin *et al.*, 1959), and have been detected in nipple aspirates of non-lactating women (Petrakis *et al.*, 1980).

Four analytic epidemiologic (one cohort and three case-control) studies have investigated the association between ETS exposure and risk of breast cancer among nonsmokers. Known risk factors for breast cancer (*i.e.*, reproductive factors, alcohol intake, social class) were not accounted for in the analysis of ETS exposure in the first two studies (Hirayama, 1984; Sandler *et al.*, 1985a) but they were accounted for in the two recent studies (Smith *et al.*, 1994; Morabia *et al.*, 1996). Only one study (Morabia *et al.*, 1996) was designed specifically to investigate the role of ETS and breast cancer.

Hirayama (1984) The first study was a Japanese cohort study (Hirayama, 1984) which included 115 breast cancer deaths in never-smoking women. Nonsmoking women whose husbands smoked showed a small, nonsignificant increased risk of breast cancer (RR = 1.3, 95% CI = 0.8-2.0).

Sandler et al. (1985a) In a case-control study conducted in North Carolina, husbands' smoking was associated with an increased risk of breast cancer (RR = 1.9, 95% CI = 0.9-4.2). The association was observed among pre-

Table 7.12
Mean Levels of Hemoglobin Adducts of 4- AND 3- Aminobiphenyls in nonsmokers

Population	4-ABP (pg/g Hb)	3-ABP (pg/g Hb)
Ex-smokers (at baseline)	130.4	16.0
Ex-smokers (after stopping smoking for two months)	33.3	1.7
Nonsmokers		
ETS exposure (-)[a] and Cotinine level (-)	45.9	1.2
ETS exposure (+)[b] and Cotinine level (+)	49.2	1.9

Reference: Maclure et al. (1989)

[a] *Based on 44 subjects-15 subjects had low levels of self-reported ETS exposure and no detectable cotinine levels; 29 subjects had no reported ETS exposure and no detectable cotinine levels.*

[b] *Based on 13 subjects-7 subjects had low levels of self-reported ETS exposure and detectable cotinine levels, 6 subjects had high levels of self-reported ETS exposure and detectable cotinine levels. The 6 subjects who reported high exposure to ETS showed the highest mean levels of 4-ABP (54 pg/g) and 3-ABP (2.4 pg/g) and median levels of 4-ABP (48 pg/g) and 3-ABP (2.6 pg/g).*

Table 7.13
Mean Levels of 4-ABP Hemoglobin Adducts (PG/G of Hemoglobin) Among Smokers and Nonsmokers by Acetylator Phenotype

Population	Acetylator Phenotype Slow	Fast
Black-tobacco smokers (*n* = 16)	175.0	117.5
Blond-tobacco smokers (*n* = 31)	111.8	86.4
Nonsmokers (*n* = 50)	31.7	19.4
Exposed to ETS		
No (*n* = 35)	30.4	12.3
Yes (*n* = 15)	34.8	33.6

Reference: Bartsch et al. (1990)

menopausal women (RR = 7.1, 95% CI = 1.6-31.3), but not among postmenopausal women (RR = 0.9, 95% CI = 0.4-2.2) (Sandler *et al.*, 1985a; Wells, 1991). In a further analysis of the case-control data from North Carolina, Wells (1992) reported that compared to nonsmoking women married to never-smokers, the age-adjusted RRs were 1.62 among nonsmoking women married to smokers, 0.64 among smoking women married to nonsmokers, and 1.51 among smoking women married to smokers.

Smith et al. (1994) The role of active and passive smoking was investigated in a case-control study conducted among young (diagnosed before the age of 36) breast cancer patients who were diagnosed between 1982 and 1985 and were residents in one of 11 health regions in the UK (Smith *et al.*, 1994). This study was designed specifically to study the role of reproductive factors, oral contraceptives, active smoking, and use of alcohol and caffeine. Questions on passive smoking were added and were administered to respondents who resided in three of the 11 participating health regions. In this study, one control was matched to each case interviewed. Each case/control pair were patients of the same general practitioner; the control was randomly selected from the list of patients of the general practitioner who cared for the case and was matched to the case on age (date of birth within 6 months). A mailed questionnaire was used to gather information on passive smoking exposure after the subjects had already participated in an in-person interview for the main study. The main study included a total of 755 breast cancer cases and an equal number of controls. A subset of 409 women (208 breast cancer cases and 201 controls) of whom 94 cases and 99 controls were nonsmokers, provided information on ETS exposure.

Active smoking was not associated with risk of breast cancer in this study; the crude OR for having ever smoked was 1.04, and the adjusted OR was 1.01 (adjustment included age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history, use of oral contraceptives, alcohol use, and biopsy for benign breast disease). Based on calculations that 114 of the 208 cases and 102 of the 201 controls who responded to questions on ETS exposure had ever smoked, the effect of active smoking was similar in the subset of subjects who responded to questions on passive smoke exposure (crude OR = 1.18 for women who had ever smoked) and for all subjects combined (*i.e.*, OR = 1.04).

Results on the association between passive smoking and risk of breast cancer were presented for smokers and nonsmokers combined. There was some suggestion that risk was highest among individuals who were exposed to ETS during both childhood and adult life. Compared to women who were not exposed to ETS, exposure during childhood only, adult life only, and during both childhood and adult life were associated with ORs of 1.98 (95% CI = 0.35-11.36), 2.65 (95% CI = 0.80-8.83), and 3.13 (95% CI = 1.05-9.38), respectively. Although there was an increased risk of breast cancer associated with childhood ETS exposure, adult exposure to ETS from partners, from other smokers at home and at work, and total lifetime exposure, there was no consistent dose trend of increasing risks with increasing levels of any of these sources of ETS exposure. However, the investigators noted

that the passive smoking findings among nonsmokers were similar to those for smokers and nonsmokers combined. The relative risks were consistently elevated, but again there was no evidence of a significant dose response for any exposure variable.

Morabia et al. (1996) A population case-control study conducted in Geneva, Switzerland (Morabia *et al.*, 1996) offered additional information on the role of active smoking and passive smoking in the etiology of breast cancer. In this study, 244 of 344 breast cancer patients aged less than 75 and diagnosed over a 2-year period consented to an in-person interview. Using an age-stratified random sampling scheme, population controls were identified from a listing which included all residents in Geneva. A total of 1,032 of the 1,473 eligible controls participated in this study.

All participants were asked specific questions on active and passive smoking including passive smoke exposure at home, at work, and during leisure time. Active and passive smoking exposure were recorded year by year, between the age of 10 years and the date of the interview. An episode of exposure is defined as at least 6 months of exposure when the woman was passively or actively exposed to tobacco smoke. For each episode of exposure, the woman was asked the age at which she was exposed and the corresponding calendar years. The number of hours per week of each passive smoking episode was recorded. An active smoker had smoked at least 100 cigarettes in her lifetime. Passive smokers were women who reported having been exposed to passive smoke at least 1 hour per day for at least 12 consecutive months during their lifetime.

Of the 244 breast cancer patients and 1,032 controls who were interviewed, 126 cases (51 percent) and 621 (60 percent) controls were lifetime nonsmokers. We calculate that compared to nonsmokers, the crude RRs for breast cancer associated with being a former smoker and a current smoker were 1.78 and 1.15, respectively. Among the 126 nonsmoking cases and 621 nonsmoking controls, 28 cases and 241 controls reported no ETS exposure. This group of nonsmokers with no ETS exposure comprised the baseline comparison group in the analyses reported by Morabia *et al.* (1996). Risk of breast cancer was elevated in nonsmokers who were exposed to ETS exposure from spouses and from all sources combined (*i.e.*, including from spouses). Compared to nonsmoking women who were not exposed to any ETS, the OR was 2.6 (95% CI = 1.6-4.3) for women who were exposed to passive smoking from spouses and 2.3 (95% CI = 1.5-3.7) for women who were ever exposed to passive smoking from all sources combined. The OR associated with high exposure (>50 hours/day-years) from spouses (OR = 2.7, 95% CI = 1.5-4.7) was essentially the same as lower exposure (1-50 hours/day-years) from spouses (OR = 2.3, 95% CI = 1.3-5.0). The OR associated with high exposure (>50 hours/day-years) from all sources combined (OR = 2.5, 95% CI = 1.5-4.2) was also similar to that associated with lower exposure (1-50 hours/day-years, OR = 2.2, 95% CI = 1.3-3.7).

Using nonsmokers never exposed to passive smoking as the baseline group, the magnitude of risks associated with ETS exposure were similar to the risks associated with active smoking. The risk of breast cancer was

increased among active smokers who smoked <20 pack-years (OR = 2.2, 95% CI = 1.2-4.3) and 20+ pack-years (OR = 3.2, 95% CI = 1.8-5.9). These findings on ETS exposure and active smoking were adjusted for age, education, body mass index, age at menarche, age at first birth, oral contraceptive use, and family history of breast cancer.

7.4.1.3 Summary All four studies on ETS exposure and breast cancer suggest that exposure to ETS is associated with an increased risk of breast cancer. Despite the consistency of this apparent observation, these results cannot be considered conclusive and must be interpreted cautiously for several reasons. In two studies, the associations with ETS exposure were present in select subgroups, younger women in one study (Hirayama, 1984) and premenopausal women in another study (Sandler *et al.*, 1985a; Wells, 1992). In three studies (Wells, 1992; Smith *et al.*, 1994; Morabia *et al.*, 1996), there is either no association between active smoking and risk of breast cancer or the effect of active smoking is weaker or comparable to the effect of passive smoking. Given that active smokers are also passively exposed to tobacco smoke, these findings on ETS exposure need to be reconciled. Moreover, in all the studies, there is no indication of increasing risk of breast cancer with increasing dose or measures of intensity of passive smoking. The apparent findings may be due to a deficit of cases who reported they had never been exposed or an excess of controls who reported they had been exposed to passive smoking, but at this time, there are also no obvious explanations why this would have occurred in each of the four studies. Results from a recent study suggest that tobacco smoke may influence the risk of breast cancer only in certain susceptible groups of women (Ambrosone *et al.*, 1995 and 1996).

7.4.2 Stomach Cancers The epidemiological evidence in support of active smoking as a risk factor for stomach cancer is equivocal. The 1982 Surgeon General's Report (U.S. DHHS, 1982) and the 1986 IARC report (IARC, 1986) concluded that tobacco smoke is associated with an increased risk of stomach cancer, but it is uncertain whether the relationship is causal. The hypothesis that tobacco smoke is a causal risk factor for stomach cancer is biologically plausible, since high concentrations of N-nitroso compounds are found in both mainstream and sidestream smoke. Exposure to N-nitroso compounds has been established as important in the development of stomach cancers (Preston-Martin and Correa, 1989).

Results from a cohort study conducted in Japan (Hirayama, 1984) are not supportive of an association between ETS exposure and risk of stomach cancer in nonsmokers. In this study, the risk of stomach cancer in nonsmokers married to nonsmoking husbands was similar to that of nonsmokers married to husbands who were ex-smokers or smoked 1-19 cigarettes/day (RR = 1.03) and those married to husbands who smoked greater than 20 cigarettes/day (RR = 1.05). The RR for stomach cancer in relation to active smoking in the same cohort was 1.3 for females and 1.6 for males (Hirayama, 1979). However, these associations with active smoking were not adjusted for dietary or other risk factors of stomach cancer. In

summary, thus far there is no epidemiologic evidence for an association between ETS exposure and stomach cancer, but research on this issue has been extremely limited.

7.4.3 Brain Tumors The age-incidence curve for brain tumors displays a bimodal distribution, peaking at ages 5 and 60. Brain tumors are a heterogeneous disease with different types of tumor occurring in the cranial cavity or in the spinal canal. The most common types of brain tumors are gliomas and meningiomas. Causes of brain tumors are not known, but exposure to N-nitroso compounds and certain occupations have been suspected (Preston-Martin and Correa, 1989). The hypothesis that ETS exposure increases the risk of brain tumors in adults and children is biologically plausible, since precursors of endogenously formed N-nitroso compounds are present in ETS. Moreover, in animal studies, neurogenic as well as other tumors were induced after transplacental exposure to a number of compounds present in tobacco smoke, including several nitrosamines (Preston-Martin and Correa, 1989). Some data suggest that active smoking may be related to brain tumors in adults, but the evidence is not consistent (Burch *et al.*, 1987).

7.4.3.1 In Adults A possible role of passive smoking in the etiology of brain tumors was first suggested in a prospective study conducted in Japan (Hirayama, 1984) (see Section 7.1.1 for study details). Based on 34 brain tumor deaths, there was an increased risk associated with ETS exposure. Nonsmoking women married to men who smoked 1-14, 15-19, and 20+ cigarettes per day showed RRs of 3.0 (95% CI = 1.1-8.6), 6.3 (95% CI = 2.0-19.4), and 4.3 (95% CI = 1.5-12.2), respectively, when the age and occupations of husbands were adjusted for in the analysis. Smokers showed a statistically nonsignificant increased risk of brain tumors compared to nonsmokers (RR = 1.2, 90% CI = 0.80-1.9) risk estimates by amount smoked were not presented (Hirayama, 1990).

In a case-control study which included all cancer outcomes, Sandler *et al.* (1985b) investigated the association between parental smoking and risk of brain tumors in adults (ages 15-59 years). Based on 11 cases among nonsmokers, there was a nonsignificant increased risk associated with father's smoking (OR = 1.65, 95% CI = 0.44-6.24), but not with mother's smoking (OR = 0.82, 95% CI = 0.10-6.64).

Ryan *et al.* (1992) published a case-control study on meningiomas and gliomas. This Australian study was one of 10 studies on adult brain tumors coordinated by the IARC. Classification of ETS exposure status was based on whether subjects were regularly exposed to smoking of parents, spouses, or coworkers. The authors reported an effect due to ETS, particularly for meningiomas. However, it is difficult to interpret these results because the analysis included all subjects who were not exposed to ETS in the baseline group, irrespective of the subject's active smoking habits. Thus, although there was an increased risk associated with ETS exposure for meningioma (RR = 2.5, 95% CI = 1.0-6.1) and for glioma (RR = 1.3, 95% CI = 0.6-2.7), it is not possible to rule out the effect of active smoking among those exposed to ETS.

7.4.3.2 In Children/ Young Adults

The effect of passive smoking and risk of brain/nervous system tumors in children has been evaluated in ten studies (Table 7.14). Five studies were designed specifically to identify risk factors for all brain tumors combined (Gold *et al.*, 1979; Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; Gold *et al.*, 1993; McCredie *et al.*, 1994), one study was focused on astrocytoma (Kuijten *et al.*, 1990), and four studies included all childhood cancers and results were presented for cancers of the brain or nervous system (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; John *et al.*, 1991; Pershagen *et al.*, 1992) (see Section 7.1.2 for study details).

Findings from four studies on childhood brain tumors (Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; John *et al.*, 1991; McCredie *et al.*, 1994) show a small increased risk in relation to paternal smoking (Table 7.14); results were statistically significant in two studies (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). Each of the four studies shows no association between maternal smoking during pregnancy and risk of childhood brain cancers.

Gold et al. (1979) Gold *et al.* (1979) conducted a hospital-based case-control study in Baltimore, MD which included all children under the age of 20 years, diagnosed with primary malignant brain tumors during the period 1965-1975. Children with brain tumors were compared to two types of controls; normal controls selected from birth certificates and controls with malignancies other than brain tumors. Each control was individually matched to children with brain tumors on sex, date of birth (plus or minus 1 year), race, and age at diagnosis (for cancer controls only). The response rate was 66 percent for brain tumor cases, 63 percent for cancer controls, and 21 percent for normal controls. There were a total of 73 matched-pairs of children with brain tumors and normal controls and 78 matched pairs of children with brain tumors and other cancer controls. Parents of cases and controls were interviewed. Maternal smoking prior to the index pregnancy did not differ between mothers of children with brain tumors and mothers of control children. However, mothers of children with brain tumors were more likely to have continued to smoke during the pregnancy compared to mothers in either control group (RR = 5.0, $p = 0.22$ for normal controls; RR = ∞, $p = 0.13$ for cancer controls). This finding, however, was not confirmed in a later study by the same investigators (Gold *et al.*, 1993, see below). Neither study presented data on the percentage of mothers who stopped smoking during pregnancy, and there is no apparent explanation for the discrepancy in findings.

Preston-Martin et al. (1982) Preston-Martin *et al.* (1982) conducted a population-based case-control study of brain tumors in Los Angeles County. Eligible subjects had a histologically confirmed brain tumor, diagnosed at or under 25 years of age between 1972 and 1977. Of the 317 eligible cases identified, mothers of 226 patients were interviewed. For each case interviewed, a friend ($n = 153$) or a neighborhood control ($n = 56$) was interviewed. Case and control mothers did not differ significantly in consumption of cigarettes during the index pregnancy (OR = 1.1, $p = 0.42$). However, there was a significant excess of case mothers who lived in a household with someone else who smoked (OR = 1.5, $p = 0.03$) compared to controls.

Howe et al. (1989) Howe *et al.* (1989) conducted a hospital-based case-control study of childhood brain tumors in southern Ontario between 1977 and 1983. Eligible cases consisted of all cases of brain tumors diagnosed in children under age 20 at two main hospitals in Toronto. Of the 123 cases identified, 74 were interviewed (60 percent). Up to two randomly selected controls, matched to each case by sex, date of birth (within 2 years), and area of residence, were identified from population lists maintained by the Ontario government. The study included a total of 74 cases and 138 controls. Maternal (OR = 1.42, $p = 0.36$) and paternal smoking (OR = 1.13, $p = 0.69$) during index pregnancy was associated with a small, nonsignificant increased risk of brain tumor.

Gold et al. (1993) Gold *et al.* (1993) conducted a large multi-centered population-based case-control study on childhood brain tumors. Cases were identified from eight population-based registries under the Surveillance, Epidemiology, and End Results (SEER) program; cases were 18 years of age or younger at the time of diagnosis of a histologically confirmed brain tumor between January 1977 and December 1981, and they resided in the catchment areas of the registries at the time of diagnosis. Three control children, selected mainly by random-digit dialing, were matched to each case by age, sex, and mother's racial/ethnic classification, as well as by area code and telephone prefix. In-person, structured interviews were conducted with parents of 361 cases and 1,083 controls. The participation rate was 85 percent for both cases and controls. Smoking habits of mothers and fathers during preconception, prenatal, and early postnatal periods were available. Most of the paternal information was supplied directly by the fathers (71 percent of interviews) and the remainder was supplied by the mothers (26 percent). In addition, information on various potential confounders (*e.g.*, intake of alcohol, coffee and tea, parental educational level), histologic type, and location of tumor were obtained.

There was no association between risk of childhood brain tumor and maternal or paternal smoking at any time, specifically during the year the index child was born, or in the 2 years before the index child was born (Table 7.14). Compared to children whose parents were both nonsmokers, the ORs for brain tumors was 0.95 (95% CI = 0.66-1.36) when both parents smoked, 0.94 (95% CI = 0.66-1.33) when only fathers smoked, and 1.06 (95% CI = 0.82-1.37) when only mothers smoked. The results were unchanged when analyses were stratified by histologic type of tumor (astrocytoma, medulloblastoma, other) and location of tumor (supratentorial, infratentorial, other), or when adjustment was made for potential confounders. Information on parental smoking before, during, and after the index pregnancy was obtained—there was no increase or decrease in the percentage of case and control parents who did not smoke in the year during which the index subject was born compared to the two previous years, and only minor changes in the percentage of case and control fathers and mothers who smoked less than a pack/day versus greater than a pack/day during these two time periods. Smoking habits during the early postnatal periods were not presented separately but were included as part of the year the index child was born. Thus, the effects of maternal or paternal smoking before, during, or after the index pregnancy could not be distinguished.

Table 7.14
Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	Father
		continued smoking during pregnancy[a]	
Gold *et al.*, 1979 (Age < 20)	84/73 (population) 84/78 (hospital)	5.0 ∞	No data
		During pregnancy	During pregnancy
Preston-Martin *et al.*, 1982 (Age < 25)	209/209	1.1	1.5[a]
		# cig/day during pregnancy	
Stjernfeldt *et al.*, 1986 (Age ≤ 16)	43/340	0 1-9 10+ cig/day 1.0 1.0 0.9	No data
		# cig/day during pregnancy	
McKinney and Stiller, 1986 (Age ≤ 15)	78/156	0 1-9 10+ cig/day 1.0 1.1 1.0	No data
		During pregnancy	During pregnancy
Howe *et al.*, 1989 (Age ≤ 20)	74/132	1.4	1.1
		During first trimester	12 months prior to birth
John *et al.*, 1991 (Age ≤ 14)	48/196	1.0	1.4
		Mother's smoking alone	Father's smoking alone
		*	1.9 (0.9-4.2)
		at 2-3 mos of pregnancy	
Pershagen *et al.*, 1992 (Age ≤ 5)	81[b]	0 <10 10+ cig/day 1.0 0.9 1.1	No data
McCredie *et al.*, 1994 (Age ≤ 14)	82/104	During pregnancy 1.3	During pregnancy 2.2[a] 4.2[c] 1.1[d]
Kuijten *et al.*, 1990 (Age ≤ 14)	163[e]/163	During pregnancy 1.0	During pregnancy 0.8

Table 7.14 (Continued)

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	Father
Gold *et al.*, 1993 (Age ≤ 18)	361/1083	Ever smoked 0.9	Ever smoked 1.1
		During yr of birth 0 <1 pack/day pack/day 1.0 0.8 1.0	During yr of birth 0 <1 pack/day pack/day 1.0 0.7 1.1
		2 yrs before birth 0 <1 pack/day pack/day 1.0 0.8 1.0	2 yrs before birth 0 <1 pack/day pack/day 1.0 0.9 1.2
		Mother's smoking alone 1.1	Father's smoking alone 0.9

[a] *p < 0.05*
[b] *cohort study*
[c] *OR if data obtained from mother*
[d] *OR if data obtained from father*
[e] *Cases restricted to astrocytoma*
* *0 exposed cases, 8 exposed controls*

McCredie et al. (1994) McCredie *et al.* (1994) conducted a population-based case-control study of incident primary malignant brain tumors diagnosed in children aged 0-14 years in New South Wales, Australia from 1985 to 1989. Each case was aged matched (±3 to 12 months of age) to two controls selected from electoral rolls. The response rate was 85 percent for cases and 60 percent for controls, resulting in completed personal interviews with mothers of 82 cases and 164 controls. Most of the information was provided by the mothers of cases and controls. In addition, fathers of 45 cases and 60 controls were also present at the interview or were interviewed directly about themselves over the telephone. Based on the smoking habits presented for mothers and fathers, and compared to subjects whose parents were both nonsmokers, increased risks were found in relation to smoking by either parent (OR = 1.61, 95% CI = 0.94-2.75) and to mothers' smoking (OR = 1.33, 95% CI = 0.72-2.46). A significant increased risk of brain tumors was associated with fathers' smoking (OR = 2.19, 95% CI = 1.25-3.85). Fathers' smoking is presumed to explain the association with mothers' smoking which, when examined alone, was not associated with an increased risk (OR = 0.4, 95% CI = 0.1-1.3). Risk of brain tumors was significantly increased if fathers' smoked before pregnancy (OR = 2.0, 95% CI = 1.0-4.1) or if mothers' reported they were exposed to fathers' smoking during pregnancy (OR = 2.2, 95% CI = 1.2-3.8).

McCredie *et al.* (1994) interpreted the effect of fathers' smoking to be due to recall bias by mothers. According to the authors

> "no increasing risk was seen with increasing use of cigarettes and after stratification by source of information (father or mother), the increased risk was present in the proxy data (ORs of 5.5 and 4.2, respectively, for the 2 smoking variables just mentioned) but not in those obtained directly from the father (ORs of 1.0 and 1.1). Moreover, no increased risk was found with mother's exposure to tobacco smoke either of other household members (OR = 1.3, 95% CI = 0.6 to 2.8) or at work (OR = 0.4, 95% CI = 0.4-1.4)."

However, based on the data presented, it cannot be determined whether the increased risk associated with fathers' smoking is explained by selective recall by mothers or whether the finding of no association is due to case fathers' denial of their own smoking. The distribution of fathers' smoking by respondent (*i.e.*, mothers or fathers) or by case/control status was not presented. The authors also indicated that control women who were interviewed were of higher social class than the eligible controls who refused to participate, raising the possibility that control fathers who participated may be less likely to smoke because of the inverse association between smoking and social class.

Kuijten et al. (1990) A study conducted by Kuijten *et al.* (1990) was designed to identify risk factors for astrocytoma, the most frequently occurring central nervous system tumors in children. Eligible cases included children diagnosed with this type of brain tumor before age 15 years, between 1980-1986, in one of eight tumor registry hospitals in Pennsylvania, New Jersey, and Delaware. Controls were selected by random-digit dialing and were pair-matched to cases for age (±2 years), race, and telephone exchange. Information was available on mothers of 163 cases and controls, and fathers of 160 cases and controls. Mothers and fathers were interviewed separately by telephone, and presumably each was asked about their own smoking habits. Mothers' smoking (OR = 1.0, 95% CI = 0.6-1.7) and mothers' exposure to sidestream smoke (OR = 0.8, 95% CI = 0.5-1.3) were not associated with risk of astrocytoma (Kuijten *et al.*, 1990).

Other studies' results on brain tumors in children. Data from three (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992) of the four studies focusing on all childhood cancers showed no association between maternal smoking during pregnancy and risk of cancers of the brain/nervous system. In all three studies, the RRs were close to 1.0 irrespective of the amount smoked by mothers (1-9, 10+ cigarettes/day) (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992). Information on father's smoking was not available in these studies (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Pershagen *et al.*, 1992; see Table 7.14). In the study by John *et al.* (1991), mothers' smoking was also not associated with risk, but fathers' smoking was associated with an elevated risk (RR = 1.4, 95% CI = 0.7-2.8). The effect of fathers' smoking on brain tumor risk was more apparent in the absence of mothers' smoking (RR = 1.9, 95% CI = 0.9-4.2).

7.4.3.3 Summary In adults, the epidemiologic evidence for an association between ETS exposure and risk of brain tumor is inadequate, but the effect has not been fully researched. Although a cohort (Hirayama, 1984) and a case-control study (Ryan *et al.*, 1992) are suggestive of a positive association in adults, the results were based on small numbers (Hirayama, 1984) and may be confounded by active smoking (Ryan *et al.*, 1992). In a second case-control study (Sandler *et al.*, 1985a & b), a non-significant increase was observed with fathers' but not mothers' smoking.

In children, data from the ten available studies do not support an effect due to mothers' smoking during pregnancy or the year before pregnancy. The only suggestive finding was for mothers who continued to smoke during pregnancy compared to mothers who stopped smoking during pregnancy in one study (Gold *et al.*, 1979), but this finding was not confirmed in a larger study conducted by the same investigators (Gold *et al.*, 1993). Six of the ten studies also collected information on fathers' smoking during the index pregnancy. In four studies, there was an association between paternal smoking and risk of brain tumors (Preston-Martin *et al.*, 1982; Howe *et al.*, 1989; John *et al.*, 1991; McCredie *et al.*, 1994); results were statistically significant in two studies (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). In a third study, the effect of fathers' smoking in the absence of mothers' smoking was of borderline statistical significance (John *et al.*, 1991). The range of ORs for paternal smoking in the positive studies was 1.5 to 2.2.

The positive association between paternal smoking and childhood brain tumors reported (Preston-Martin *et al.*, 1982; John *et al.*, 1991; McCredie *et al.*, 1994) and the biologic plausibility of the hypothesis justify further research to clarify the relationship. Given that purported relationships with risk of childhood brain tumors have been reported for electromagnetic field exposures, parental occupation, and radon exposures, future studies on ETS and brain tumors would need to account for the effects of these other suspected risk factors.

7.4.4 Leukemia

There is increasing evidence that cigarette smoking may be causally related to leukemia in adults (Austin and Cole, 1986; Brownson *et al.*, 1993b). Smoking has emerged as a risk factor for leukemia in a number of prospective studies, including the first (Hammond, 1966; Garfinkel and Boffetta, 1990) and second American Cancer Society studies (Garfinkel and Boffetta 1990), the U.S. Veteran cohort study (Kahn, 1966; Rogot and Murray, 1980; Kinlen and Rogot, 1988; McLaughlin *et al.*, 1989), and the Adventist Health study (Mills *et al.*, 1990). In two other cohort studies with small numbers of leukemia deaths (<75 in each study), smoking was associated with statistically nonsignificant increased risks of leukemia (Weir and Dunn, 1970; Linet *et al.*, 1992). Smoking was not a risk factor for leukemia in the British doctors' cohort in which more than 70 percent of the deaths from marrow and reticuloendothelial malignancies were lymphomas and myelomas (Doll and Peto, 1976). Case-control studies which have compared smoking histories of leukemia patients with population controls have

7.4.4.1 Active Smoking and Leukemia

found statistically significant positive associations with tobacco use (Sandler *et al.*, 1993; Brown *et al.*, 1992; Severson, 1987; Severson *et al.*, 1990). Tobacco use was also a significant risk factor in a case-control study in which all leukemia patients diagnosed between 1984 and 1987 in the Missouri Cancer Registry were compared to other cancer patients (excluding lip, oral cavity, esophagus, lung, and bladder) (Brownson, 1989). No association with smoking was found in two U.S. hospital-based case-control studies (Kabat *et al.*, 1988; Spitz *et al.*, 1990) in which selection bias of leukemia cases was likely or in a third study restricted to chronic lymphatic leukemia (Flodin *et al.*, 1988). The association with smoking is most consistent for myeloid leukemias, particularly acute myeloid leukemia, and less consistent for chronic lymphocytic leukemia (Kinlen and Rogot, 1988; McLaughlin *et al.*, 1989; Garfinkel and Boffetta, 1990; Mills *et al.*, 1990; Brownson, 1989).

Cigarette smoke contains many compounds, some of which have been associated with increased risk of leukemia. These include benzene, nitrosamines, urethane, and radioactive compounds (Austin and Cole, 1986). In animal studies, leukemia can also be induced by transplacentally-acting carcinogens, many of which are found in tobacco smoke (Coghlin *et al.*, 1991; Sorsa and Husgafuel-Pursiarnen, 1988).

7.4.4.2 ETS and Risk of Hematopoietic Tumors in Adults

The association between ETS exposure and risk of hematopoietic tumors including leukemia was reported in one study. Among nonsmoking women with tumors of hematopoietic tissues (including Hodgkins disease, non-Hodgkins disease lymphomas, and acute leukemias), Sandler *et al.* (1985b) reported an increased risk in relation to mothers' (OR = 2.18, 95% CI = 0.69-6.92) and fathers' (OR = 2.42, 95% CI = 0.88-6.61) smoking during the childhood years of the index subjects (see Section 7.1.1 for study description). Although smoking habits of husbands were available in the same study, their effect on risk was not reported (Sandler *et al.*, 1985a).

7.4.4.3 ETS and Risk of Leukemia in Children

One of the first studies to investigate the role of parental smoking and risk of leukemia in children was conducted by Manning and Carroll (1957) (see Section 7.1.2 for a detailed description). In this hospital-based study, smoking habits of mothers of 188 children with acute leukemia were compared to those of mothers of controls. Thirty-nine percent of mothers of children with leukemia smoked 10 or more cigarettes a day at interview compared to 38 percent among mothers of children admitted for orthopedic reasons. A second study included 1,416 childhood cancers (677 were leukemia) and an equal number of population controls in the United Kingdom (Stewart *et al.*, 1958) (see Section 7.1.2 for a detailed description). There was little case-control difference in smoking habits of fathers, but there was a slight excess of case mothers who smoked. A third study (Neutel and Buck, 1971) compared rates of leukemia by smoking habits of mothers during pregnancy (see Section 7.1.2 for details). The rate of leukemia in children was higher among mothers who smoked (6.0 per 100,000 child-years) compared to mothers who did not smoke (3.4 per 100,000 child years) (RR = 1.8). However, these results were based on a small number of events (<12 cases of leukemia) among subjects with nonsmoking and smoking mothers.

Since the 1980s, one cohort study and seven case-control studies offer additional information on the possible effect of parental smoking on childhood leukemia (Table 7.15). Three of the studies included only acute lymphocytic leukemia (ALL) (Van Steensel-Moll *et al.*, 1985; Stjernfeldt *et al.*, 1986; Buckley *et al.*, 1986), one study was limited to acute myeloid leukemia (Severson *et al.*, 1993), whereas four studies included all leukemias (McKinney and Stiller, 1986; Magnani *et al.*, 1990; John *et al.*, 1991; Pershagen *et al.*, 1992). In two studies, risk estimates were presented for ALL and non-acute lymphocytic leukemia (non-ALL) separately (Magnani *et al.*, 1990; John *et al.*, 1991).

In the Swedish cohort study (Pershagen *et al.*, 1992) (see Section 7.1.2 for a detailed description), cancer incidence in some 50,000 children born between 1982 and 1987 was determined. Maternal smoking at 2 to 3 months of pregnancy was categorized as none, 1-9 cigarettes/day, and >10 cigarettes/day. There were 129 cancers of the lymphatic and hematopoietic system (84 lymphatic leukemia, 15 myeloid leukemia, 16 reticulosis, and 14 other hematopoietic and lymphatic system). There was no increased risk associated with mothers' smoking during pregnancy for lymphatic leukemia when year and county of birth, birth order of index subject, and maternal age were adjusted for in the analysis (Table 7.14). Mothers' smoking during the entire pregnancy was not available. An association would have been missed only if there was a differential number of case mothers (compared to control mothers) who smoked later in the pregnancy, and if smoking in the second and third trimesters are more likely to be associated with risk. More importantly, the follow-up period only allowed ascertainment of leukemia up to 5 years of age so that associations between risk of leukemia at older ages and maternal smoking could not be evaluated.

Of the case-control studies on childhood leukemia (Van Steensel-Moll *et al.*, 1985; Severson *et al.*, 1993) or childhood cancers which included leukemia (Stjernfeldt *et al.*, 1986a & b; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Magnani *et al.*, 1990; John *et al.*, 1991) (see Section 7.1.2), a significant association between mothers' smoking during the index pregnancy and risk of ALL was observed in two studies (Stjernfeldt *et al.*, 1986a & b; John *et al.*, 1992) (see Section 7.1.2 for study details). Compared to children of nonsmokers, subjects whose mothers smoked 10+ cigarettes/day showed about a 2-fold increased risk in one study (RR = 2.1, 95% CI = 1.3-3.3) (Stjernfeldt *et al.*, 1986a & b) and a 3-fold increased risk in another (RR = 2.9, 95% CI = 1.2-6.8) (John *et al.*, 1991) (Table 7.14). A subsequent report by Stjernfeldt *et al.* (1992) confirmed that the effect of mothers' smoking was independent of the risk associated with diagnostic X-rays. Among subjects whose mothers had not had X-ray exposure during pregnancy, the ORs for ALL were 1.3 and 2.2, respectively if mothers smoked 1-9 and 10+ cigarettes/day compared to children of nonsmokers. The corresponding ORs were 1.8 and 3.6 in the group whose mothers had had X-ray exposure. In the other positive study (John *et al.*, 1991), mothers' and fathers' smoking together was associated with about a 2-fold increased risk (OR = 2.2, 95% CI = 1.0-5.0). The OR for ALL was 2.9 (95% CI = 0.8-10.3) when only mothers smoked and 1.7 (95% CI = 0.7-3.8) when only fathers

smoked. Mothers' smoking prior to conception, during the first trimester of pregnancy, and during the entire pregnancy were all associated with increased risks of ALL, and it was not possible to determine the effect of mothers' smoking prior to versus during pregnancy. The effect of parental smoking was specific to ALL. There was no increased risk of other leukemias in relation to smoking of mothers and fathers (OR = 1.0, 95% CI = 0.2-4.2) (John *et al.*, 1991).

Five case-control studies are not supportive of an association between childhood leukemia risk and ETS exposure. One study was conducted in the Netherlands, using a complete nationwide register of histologically-confirmed childhood leukemia cases diagnosed between 1973 and 1980 (Van Steensel-Moll *et al.*, 1985). Seven hundred and thirteen children, aged less than 15 years, were diagnosed with leukemia during this time period. Using the census lists available by municipality, two controls with the same date of birth (within two months), the same sex, and who lived in the same municipality as the case at the time of diagnosis were randomly selected. The second control served as replacement if the first control did not respond. Between 1981 and 1982, parents of cases and controls were sent a questionnaire which asked about maternal events before and during pregnancy of the index subjects. A total of 625 leukemia patients and 615 controls responded, representing response rates of 90 percent, 70 percent, and 68 percent, respectively, for the parents of leukemic patients, and first and second controls. Analyses were restricted to 519 patients with ALL and 507 controls. Mothers of ALL cases and controls did not differ in their smoking habits in the year before pregnancy (age- and sex-adjusted RR = 1.0, 95% CI = 0.8-1.3) or during pregnancy (age- and sex-adjusted RR = 1.0, 95% CI = 0.7-1.3).

A second study not supportive of an association was reported by McKinney and Stiller (1986) (see Section 7.1.2 for study details). In this study, 93 of the 171 leukemias were non-ALL (McKinney *et al.*, 1987). Thus, if an association between ETS and leukemia is specific for ALL, an analysis including all leukemias combined may have diluted an ETS effect. Another study which did not find an association between ALL and parental smoking during the index pregnancy was reported by Buckley *et al.* (1986) (see Section 7.1.2). This study was published as a letter to the editor, and few details were provided.

No association between parental smoking and risk of leukemia in children was found in a hospital-based case-control study conducted in the main pediatric hospital in Turin, Italy between 1981 and 1984 (Magnani *et al.*, 1990). There were a total of 142 children with ALL, 22 with non-ALL, and 19 with non-Hodgkins lymphoma (NHL). These were compared to 307 controls who were identified by a random sampling of children hospitalized in the medical or surgical wards of the hospital. Data on parental smoking habits, parental occupation, ionizing radiation, and childhood diseases were collected using a standard questionnaire administered to a relative of the child while the child was still in the hospital. After adjusting for socioeconomic status, risk of ALL was not associated with mothers or father's smoking habits up to the birth of index subject (Table 7.15). It is difficult to

interpret results from this study because of several methodologic limitations. Factors such as residence and socioeconomic status may have affected the selection of cases and controls in this hospital-based study. In addition, there were no records of potential hospital controls that were missed because of early discharge during the first two years of this study. Finally, both incident and prevalent cases were included as eligible cases.

A fifth study, restricted to acute myeloid leukemia (AML) also did not find an association with maternal smoking. AML is the most frequently diagnosed leukemia in adults and is the subtype most consistently associated with active smoking (Austin and Cole, 1986; Brownson *et al*., 1993b). However, AML is less common in children, representing about 15 percent of leukemia in children. This case-control study was a multicentered study conducted as part of the Childrens Cancer Group studies of *in utero* and postnatal exposures. Cases were identified through the registration files of the Children's Cancer Group, a cooperative clinical trials group which included about 100 primary and affiliate institutions throughout North America. Eligible cases in this study included patients newly diagnosed with AML from January 1980 through December 1984 who were 18 years of age or younger at the time of diagnosis. A total of 187 matched case-control pairs were interviewed, representing completion rates of 71 percent among eligible cases (n = 187) and 78 percent among eligible controls (n = 262). The objective was to interview one control per case matched to cases on age, race, and telephone area code and exchange, and selected by random digit dialing.

Mothers and fathers of study subjects were interviewed separately by telephone. As part of the interview, both the mother and the father were asked about cigarette smoking status (current, past, or never) and smoking practices during: a) the month immediately preceding the index pregnancy; b) the index pregnancy; and c) nursing. Detailed information was requested regarding the trimesters in which the parent smoked and the number of cigarettes smoked per day during the pregnancy. Mothers of children with AML were less likely to be current smokers, *i.e.*, smoking cigarettes at the time of interview. However, mothers of children with AML were more likely to have ever smoked (OR = 1.32, 95% CI = 0.85-2.09) or smoked during pregnancy (OR = 1.20, 95% CI = 0.77-1.86) although these results were not statistically significant. The authors indicated that paternal smoking was also not associated with risk of AML (results on paternal smoking were not shown).

7.4.4.4 Summary In adults, the association between ETS exposure and hematopoietic tumors was addressed in only one study. That study (Sandler *et al.,* 1985b) reported increased risk in relation to mothers' and fathers' smoking during childhood. The epidemiologic evidence for parental smoking and risk of leukemia in children is conflicting. No association between ETS exposure and risk of leukemia was found in the only cohort study, and a significant positive association, specifically for ALL was observed in 2 of the 7 case-control studies. In one of the two studies which found an increased risk with mothers' smoking, fathers' smoking was available and appeared to have an independent effect on risk. The range of ORs associated with

Table 7.15
Maternal or Parental Smoking During Pregnancy and Childhood Leukemia

Cohort Studies (Age of Subjects)	**# Cases (Type of Leukemia)**	**Smoking Habits (cig/day)**	**OR (95% CI) Maternal Smoking**	**OR (95% CI) Paternal Smoking**
Pershagen *et al.*, 1992	All Leukemia	2-3 mos of pregnancy		
(Age ≤ 5)	72	No	1.0	Not available
	18	1-9	0.9 (0.6-1.6)	
	9	10+	0.7 (0.4-1.5)	
	21 (lymphatic)	Yes	0.8 (0.5-1.3)	
	6 (myeloid)	Yes	1.6 (0.6-4.8)	
Case-Control Studies (Age of Subjects)	**# Cases/ # Controls (Type)[a]**	**Smoking Habits (cig/day)**	**OR (95% CI) Maternal Smoking**	**OR (95% CI) Paternal Smoking**
Van Steensel-Moll *et al.*,1985	519/507 (ALL)	Yes, yr before Pregnancy	1.0 (0.8-1.3)	Not available
(Age ≤ 15)		Yes, during pregnancy	1.0 (0.7-1.3)	
		During pregnancy		
Stjernfeldt *et al.*, 1986	132/340	1-9	1.3 (0.7-2.6)	Not available
(Age ≤ 16)	(ALL)	10+	2.1 (1.3-3.3)	
		During pregnancy		
McKinney *et al.*, 1986	171/342	1-10	1.0 (0.6-1.7)	No association
(Age ≤ 15)	(78 ALL, 93 non-ALL)	11+	0.6 (0.4-1.0)	
		During pregnancy		
Buckley *et al.*, 1986	742/740	1-9	1.0 (0.6-1.5)	No association
(Age ≤ 15)	(ALL)	10+	0.9 (0.7-1.1)	
Magnani *et al.*, 1990	142/307	Smoking up to child's birth		
(Not specified)	(ALL)	Yes	0.7 (0.5-1.1)	0.9 (0.6-1.5)
		1-15 cig/day	0.6 (0.4-1.0)	0.9 (0.5-1.6)
		16+ cig/day	1.0 (0.4-2.7)	0.9 (0.6-1.5)
	22/307 (non-ALL)	Yes	2.0 (0.8-4.8)	0.9 (0.3-2.1)

Table 7.15 (Continued)

Cohort Studies (Age of Subjects)	# Cases (Type of Leukemia)[a]	Smoking Habits (cig/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
			During 3 trimesters	During pregnancy
John *et al.*, 1991	73/196	1-10	2.0 (0.7-5.9)	2.6 (0.9-7.9)
(Age ≤ 14)	(ALL)	11-20	2.9 (1.2-6.8)	1.6 (0.7-3.7)
		21+		1.6 (0.7-4.0)
			Parent smoking in absence of other parent	
			2.9 (0.8-10.3)	1.7 (0.7-3.8)
	(non-ALL)		During 3 trimesters	During pregnancy
		Yes	0.6 (0.1-3.0)	0.8 (0.2-2.3)
Severson *et al.*, 1993	187/187		During pregnancy	
(Age ≤ 18)	(acute myeloid leukemia)	Yes	1.2 (0.8-1.9)	No association

[a] *ALL = Acute lymphocytic leukemias, non-ALL = non acute lymphocytic leukemias.*

mothers' smoking at least 10 cigarettes per day during pregnancy was 2.1 to 2.9 and 1.6 for fathers' smoking at least 10 cigarettes per day. With respect to the relationship of ETS exposure and childhood leukemia, there is no satisfactory explanation for the inconsistent results between the case-control studies not supportive of an association (Van Steensel-Moll *et al.*, 1985; McKinney and Stiller, 1986; Buckley *et al.*, 1986; Magnani *et al.*, 1990; Severson *et al.*, 1993) and those supportive of an association (Stjernfeldt *et al.*, 1986a & b; John *et al.*, 1991).

There are several difficulties in trying to reconcile these different findings. First, most of the studies did not present sufficient information to allow comparison of the prevalence of maternal and paternal smoking in the studies. Second, it is not known whether the age distributions of leukemia or ALL were similar in the studies showing an association and those showing no association. It is conceivable that the effect of ETS on risk of leukemia may vary by age. Risk factors for leukemia diagnosed in children aged 3-4 are likely to differ from those in children diagnosed with leukemia in their teens. Thus, the relative roles of intrauterine ETS exposure, prenatal esposure, and postnatal exposure to ETS may differ depending on the age at onset of leukemia. Third, the source and types of subjects used as controls may be particularly important. Controls selected from general practitioner lists and hospital admissions for minor conditions may be biased with respect to tobacco-smoke exposure since maternal smoking has been associated with various conditions, including nonmalignant lung dis-

eases. Fourth, the role of potential confounders including the effect of socioeconomic status may be especially important. In some studies, adjustment for paternal education level reduced the risks in relation to ETS exposure (John *et al.*, 1991), suggesting that perhaps both paternal and maternal education level should be adjusted for in the analysis.

Despite the fact there are eight studies on ETS exposure and parental smoking, and that most of these studies had relatively large sample sizes, a conclusion regarding the association cannot be reached for the reasons mentioned above. Future studies would need to distinguish between ALL and non-ALL, and to examine the risk pattern by age of diagnosis of leukemia (*e.g.*, ≤5, 6-10, ≥11 years of age). In addition, the studies should be designed to minimize selection bias of cases and controls (*i.e.*, by making sure that factors such as residence, medical coverage, and socioeconomic status do not influence selection into study), to minimize information bias (*i.e.*, by obtaining necessary information on maternal and paternal smoking during, and after the index pregnancy), and to be able to adjust for potential confounders in the analysis.

7.4.5 Lymphomas and Non-Hodgkin's Lymphomas

The effect of ETS exposure and risk of lymphomas and non-Hodgkin's lymphomas (NHL) was examined in six studies of childhood cancers (Table 7.16). In one case-control study with 169 cases of NHL (Buckley *et al.*, 1986), there was no association between maternal smoking during pregnancy and risk (Table 7.15), whereas increased risks were reported in two small studies (less than 20 cases of NHL in each) (Stjernfeldt *et al.*, 1986a & b; Magnani *et al.*, 1990). Two studies offered information on risk of lymphomas and exposure to ETS (McKinney and Stiller, 1986; John *et al.*, 1991). McKinney and Stiller, (1986) found a 90 percent increase in risk of lymphomas in subjects whose mothers' smoked 1-10 cigarettes/day during pregnancy, but there was no increased risk for subjects whose mothers who smoked more. John *et al.* (1991) reported an increased risk of lymphoma in relation to fathers' smoking during the index pregnancy (RR = 1.9, 95% CI = 0.7-4.8) and mothers' smoking during all three trimesters of pregnancy (RR = 1.9, 95% CI = 1.0-7.6). There were, however, too few cases in this study (n = 26) to investigate the association by amount smoked by mothers or fathers. In the cohort analysis by Pershagen *et al.* (1992), maternal smoking was associated with an increased risk for cancers of the hematopoietic and lymphatic system (excluding leukemia). Children whose mothers smoked at 2-3 months of pregnancy showed an elevated risk for reticulosis (RR = 1.7, 95% CI = 0.6-5.0, based on 16 cases) and tumors of other hematopoietic and lymphatic systems (RR = 2.0, 95% CI = 0.7-5.5, based on 14 cases). For this group of cancers combined, the RR was 2.4 (95% CI = 1.0-5.5) for subjects whose mothers' smoked less than 10 cigarettes/day, but an increased risk was not observed for subjects whose mothers smoked more.

In summary, the data on ETS exposure and risk of lymphomas and NHL are inadequate. Although small increased risks have been reported in some studies, the results are difficult to interpret given that they were based on small numbers, with wide confidence limits, and the dose-response trends were largely not smooth.

7.4.6 Other Rare Childhood Cancers

A few epidemiologic studies have examined the potential impact of maternal smoking and ETS exposure on rare childhood cancers. These studies are discussed below.

7.4.6.1 Neuroblastoma

Neuroblastoma is an embryonal tumor of the sympathetic nervous system diagnosed primarily in infancy. Extrinsic factors that influence the risk of neuroblastoma are likely to act while the child is *in utero*, or perhaps upon parental germ cells prior to conception. Thus, the focus of etiologic investigations is on parental exposures during and prior to the prenatal period.

Kramer *et al.* (1987) conducted a case-control study of neuroblastoma focusing on both family medical history and parental medical and drug exposures prior to birth of the index child. Histologically confirmed cases, identified by the Greater Delaware Valley Pediatric Tumor Registry between 1970 and 1979, were included. One population control per case was selected by random-digit dialing. Controls were matched to cases by date of birth (±3 years), race, and cases' telephone number (area code and first five digits). Of the 139 eligible cases (74.8 percent), 104 were successfully interviewed. These cases were compared to 101 of 177 controls who were interviewed (57.1 percent). A small increased risk was observed for mother's smoking during pregnancy (OR = 1.26, 90% CI = 0.76-2.09) and at any time prior to conception of the index child (OR = 1.26, $p = 0.20$). Father's smoking during the 2 years prior to birth of the index child conferred a similar increase in risk (OR = 1.30, 90% CI = 0.83-2.05). The RR for father's smoking was stronger (OR = 1.60, 90% CI = 0.94-2.74) when his smoking habits any time prior to the index child's birth was considered.

7.4.6.2 Wilms' Tumor of the Kidney

Smoking is an established risk factor for cancers of the kidney and renal pelvis in adults (IARC, 1986). Induction of Wilms' tumors in rodents by transplacental N-ethylnitrosourea has been described (Hard, 1985), suggesting that nitrosamines, including tobacco-specific nitrosamines, may have an etiologic role in these tumors.

The role of ETS exposure and risk of Wilms' tumor of the kidney has been evaluated in four studies. One study was designed specifically to identify risk factors for Wilms' tumors (Bunin *et al.*, 1987), whereas in three other studies Wilms' tumors were one of the childhood cancers presented in the analysis (Stjernfeldt *et al.*, 1986; McKinney and Stiller, 1986; Buckley *et al.*, 1986).

Bunin *et al.* (1987) conducted a hospital-based case-control study of Wilms' tumor to examine the role of gestational risk factors. Histologically confirmed Wilms' tumor diagnosed among whites aged 15 years or younger between 1970 and 1983 were included. Controls were selected by random-digit dialing and were pair-matched to cases on year of birth (±3 years), race, and telephone area code and exchange. Of the 124 eligible cases, 88 were included and were compared to 88 of the 159 controls identified (participation rates were 71 percent and 55 percent, respectively). The authors reported that there is no association between maternal smoking during pregnancy and risk of Wilms' tumor (data were not presented).

There is no evidence for a role of maternal smoking and risk of Wilms' tumor in the study conducted by McKinney and Stiller (1986). Based on 32 cases of Wilms tumors, the RRs were 0.86 (95% CI = 0.3-2.6) and 1.17 (95% CI = 0.4-3.5), respectively, for subjects whose mothers smoked 1-10, and 11+ cigarettes during pregnancy compared to subjects whose mothers were nonsmokers. However, in two studies, there was some suggestion of a small increased risk in relation to maternal smoking. Buckley *et al.* (1986) (n = 61 kidney cancers) reported RRs of 1.58 (95% CI = 0.60-4.18) and 0.93 (95% CI = 0.47-1.83), respectively, for subjects whose mothers smoked 1-9 and 10+ cigarettes per day during pregnancy compared to children of nonsmokers. In the other study, the corresponding RRs were 0.70 (95% CI = 0.1-5.6) and 2.53 (95% CI = 0.9-7.2) in an analysis which included only 16 cases of kidney cancer (Stjernfeldt *et al.*, 1986a & b).

7.4.6.3 Germ Cell Tumors Germ cell tumors include teratomas, yolk sac tumors, and germinoma. In 1980-1982, the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) interviewed the parents of 555 children with newly diagnosed cancer and the parents of 1,100 control children chosen from hospital admissions and general practitioner lists (see 7.1.2, case-control studies). Two controls were individually matched to each case interviewed. Characteristics of mothers and their exposures during the index pregnancy were compared for 41 children with germ cell tumors and 82 controls (McKinney and Stiller, 1986). Mothers of cases and controls did not differ in their smoking habits during 1 year prior to or 1 month prior to the index pregnancy (44 percent of case mothers smoked compared to 42 percent of control mothers). Smoking patterns of fathers were also comparable (56 percent of case fathers compared to 57 percent of control fathers smoked).

7.4.6.4 Bone and Soft-Tissue Sarcomas Bone and soft tissue sarcomas account for about 10 percent of childhood cancers (Li, 1982). The main types of bone tumors are osteosarcoma and Ewing's tumor, and the main type of soft-tissue sarcoma is rhabdomyosarcoma (RMS).

Grufferman *et al.* (1982) conducted a case-control study of childhood RMS by including the families of 33 cases and 99 controls. All incident cases of childhood RMS diagnosed in North Carolina residents during 1967-1976 were considered eligible (37 were eligible). For each of the cases interviewed, 3 controls of the same age (±2 months), sex, and race were randomly selected from North Carolina birth certificates. Of the 99 controls first selected, 70 were successfully interviewed. Risk of RMS was not related to mothers' smoking at any time (RR = 0.8, 95% CI = 0.3-2.0), or mothers' smoking during the pregnancy of the index subject (RR = 1.0, 95% CI = 0.4-2.4). On the other hand, fathers' smoking was a statistically significant risk factor (RR = 3.9, 95% CI = 1.5-9.6). The point estimate of the risk in relation to fathers' smoking diminished when the analysis accounted for family income and fathers' education and occupation (RR = 2.8, p = 0.07).

As part of the IRESCC study (see 7.1.2, Case-control studies), characteristics of mothers and their prenatal exposures were compared for 43 cases with soft tissue tumors, 30 cases with bone sarcomas, and their 146

Table 7.16
Association Between Exposure to Passive Smoking and Risk of Non-Hodgkins Lymphoma and Lymphoma in Children

Studies	Exposure to Passive Smoking	Relative Risk	95% CI
Stjernfeldt *et al.*, 1986	Non-Hodgkins Lymphoma (*n* = 16)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-9	1.9	(0.3-6.7)
	10+	2.1	(0.7-6.4)
	Hodgkins Lymphoma (*n* = 15)		
	0 (cig/day)	1.0	
	1-9	1.1	(0.2-4.9)
	10+	0.3	(0.1-2.2)
Buckley *et al.*, 1986	Non-Hodgkins Lymphoma (*n* = 169)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-9	0.8	(0.3-1.8)
	10+	1.0	(0.7-1.4)
Magnani *et al.*, 1990	Non-Hodgkins Lymphoma (*n* = 19)		
	Mother's smoking up to child's birth	1.7	(0.7-4.5)
	Father's smoking up to child's birth	6.7	(1.0-43.4)
McKinney and Stiller, 1986	Lymphomas (*n* = 74)		
	Mother's smoking during pregnancy		
	0 (cig/day)	1.0	
	1-10	1.9	(0.9-4.0)
	11+	1.0	(0.5-2.1)
John *et al.*, 1991	Lymphoma (*n* = 26)		
	Mother's smoking		
	-Three months prior to conception	1.9	(0.7-5.2)
	-First trimester of pregnancy	2.5	(0.9-7.0)
	-All three trimesters of pregnancy	2.7	(1.0-7.6)
	Father's smoking during pregnancy	1.9	(0.7-4.8)
Pershagen *et al.*, 1992	Hematopoietic and Lymphatic excluding leukemia (*n* = 30)		
	Mother's smoking at 2-3 months of pregnancy		
	0 (cig/day)	1.0	
	1-9	2.4	(1.0-5.5)
	10+	1.1	(0.3-3.6)

matched controls (McKinney and Stiller, 1986; Hartley *et al.*, 1988). Compared to children whose mothers were nonsmokers, children whose mothers smoked 1-10, and 11+ cigarettes/day during pregnancy showed RRs of 1.37 (95% CI = 0.53-3.55) and 1.47 (95% CI = 0.56-3.84) respectively for soft tissue sarcomas. The corresponding RRs were 1.48 (95% CI = 0.46-4.74) and 2.16 (95% CI = 0.68, 6.85) for bone tumors (McKinney and Stiller, 1986). In a more detailed report on risk factors for these two tumor sites, Hartley *et al.* (1988) described that "mothers' and fathers' smoking history before and during the index pregnancy did not show any case excess" and did not elaborate on the findings.

No association between paternal and maternal smoking habits and risk of RMS and non-RMS-soft tissue sarcomas (STS) was reported by Magnani *et al.* (1989). In this hospital-based case-control study conducted in 1983-1984 in Torino and Padova, Italy, there were a total of 36 RMS, 16 non-RMS-STS, and 326 controls. The RRs for fathers' smoking 0, 1-15, and 16+ cigarettes/day up to the index child's birth were 1.0, 0.7 (95% CI = 0.3-2.0), and 0.8 (95% CI = 0.4-1.8), respectively. The corresponding RRs for mothers' smoking were 1.0 (95% CI = 0.4-2.3), and undefined (0 cases and 17 controls) (Magnani *et al.*, 1989).

The role of ETS in the etiology of soft tissue sarcomas is unclear, particularly in the case of RMS. Although the association between RMS and fathers' smoking reported by Grufferman *et al.* (1982) is intriguing, it has not been confirmed. These authors proposed that there may be a direct carcinogenic effect introduced either in a prezygotic manner or by passive inhalation of cigarette smoke by the patients. Evans *et al.* (1981) found morphologic sperm abnormalities in cigarette smokers, in support of a direct mutagenic effect of fathers' cigarette smoking.

7.4.6.5 Summary The epidemiologic evidence on ETS exposure and other rare childhood cancer is inadequate. Given that these are rare events, most of the studies are limited by small sample sizes, and any effect of ETS exposure is not likely to be statistically significant. Thus, it is important to evaluate these studies in terms of the collective evidence, the direction of the risk estimates from individual studies, and possible biases (*i.e.*, confounding by social class, or other antenatal exposures) in explaining the findings.

7.5 CHAPTER SUMMARY AND CONCLUSIONS In studies on all cancers (combined), there is limited evidence (two cohort and one case-control study) that exposure to spousal smoking may increase overall risk of cancer (including lung) in nonsmoking women. However, when cancers of the lung were excluded from the analysis, risk elevations for other cancers were not significant.

With respect to lung cancer, three large U.S. population-based studies and a smaller hospital-based case-control study have been published since the most recent comprehensive review (U.S. EPA, 1992); the three population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized. Results from these studies and the smaller case-con-

trol study are compatible with the causal association between ETS exposure and risk of lung cancer in nonsmokers already reported by the U.S. EPA (1992), Surgeon General (U.S. DHHS, 1986) and NRC (1986).

Although there have been only three studies on ETS exposure and nasal sinus cancers, all three studies showed a consistent association between exposure and risk, presenting strong evidence that exposure to ETS increases the risk of nasal sinus cancers in nonsmoking adults. Future studies need to characterize the magnitude of risk between nasal sinus cancer and ETS exposure and the dose-response relationship. The epidemiological and biochemical evidence suggests that exposure to ETS may increase the risk of cervical cancer in nonsmokers. On the other hand, although the biochemical data suggest that ETS is a plausible carcinogen for bladder cancer in nonsmokers, the limited epidemiologic data are not supportive of an association. There is insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and adult cancers of the bladder, breast, stomach, or brain at this time.

In children, the evidence is unclear as to whether paternal smoking increases the risk for all childhood cancers, and specifically acute lymphoblastic leukemia and brain tumors, the two leading cancer sites in children (Li, 1982). The uncertainty about the association between ETS exposure and increased risks in these two tumor sites is due largely to the conflicting results reported and the limitations of the studies finding no association. On the other hand, the association between ETS exposure and other childhood tumors is difficult to study because of the limited number of subjects with the specific cancers in most studies.

Despite the uncertainty in epidemiological data on childhood cancers and ETS exposure, an ETS effect on risk of childhood cancer is a concern due to both transplacental and passive smoke exposure. Studies to date were not designed to distinguish between transplacental exposure (*i.e.*, mother's smoking during pregnancy), prenatal ETS exposure (*i.e.*, father's smoking during pregnancy), and postnatal ETS exposure (*i.e.*, mother's and father's smoking after birth and any other relevant sources of ETS exposure). In fact, most studies only had information on mother's smoking during pregnancy, or mother and father's smoking during pregnancy. However, even if the data were available, it would be a challenge to separate the long-term effects of *in utero* exposure to maternal smoking, and the effects of prenatal and postnatal ETS exposure on the risk of cancer in children. This is because maternal and paternal smoking behavior during pregnancy and after delivery are closely linked. In any case, a transplacental effect or an ETS effect is biologically plausible. The demonstration of a 4-fold higher mean level of carcinogen-hemoglobin adducts in fetuses of smoking mothers as compared to fetuses of nonsmoking mothers, and the approximately 60 percent higher hemoglobin adduct levels in nonsmoking mothers with high levels of ETS exposure compared to those with low exposure, suggest that *in utero* exposure may be more concentrated (Coghlin *et al.*, 1991; Hammond *et al.*, 1993) (see Section 7.1.2; Table 7.2).

The concentrated transplacental exposure, in conjunction with passive smoke exposure prenatally and postnatally, may predispose the child to increased risk of various cancers.

To summarize, ETS exposure is causally associated with cancers of the lung and nasal sinus; the evidence is suggestive of a causal association between ETS exposure and cervical cancer. The relationship between ETS exposure and leukemia, childhood brain cancer, and breast cancer is less clear, and although some studies are indicative of a causal association, the overall evidence is inadequate for forming firm conclusions. Finally, there is currently insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and cancers of the bladder, stomach, hematopoietic system, and lymphatic system.

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