2. Studies of Cancer in Humans

2.1 Lung cancer

The section summarizes the results of the relevant cohort studies and case–control studies of the association between lung cancer and exposure to secondhand smoke. They are ordered by source of exposure, i.e. secondhand smoke from partners at home, at the workplace, during childhood and from other sources. For each type of study, the results are presented first without differentiation according to the levels of exposure and then the exposure–response relationship is described.

The most commonly used measure of exposure to secondhand smoke has been from the spouse. This is because it is well defined and has been validated using cotinine studies of never-smokers who do or do not live with smokers. Spousal exposure is also a marker of exposure to tobacco smoke in general because people who live with smokers tend to mix with smokers outside the home. Other measures of exposure, at the workplace or during childhood, are not so well validated. It is more difficult to quantify exposure at the workplace than spousal exposure; the extent of exposure may vary considerably between different working environments (exposure from the spouse is clearly defined and fairly consistent); people are more likely to change jobs than to remarry or divorce and, in studies based on people who have died from lung cancer, it may be more difficult for the next of kin or other respondent to know whether or not the subject had been exposed to secondhand smoke at work. Exposure during childhood has not been validated and, in studies of exposure to secondhand smoke, the relative risk for lung cancer associated with exposure during childhood should be stratified according to spousal exposure. Few studies have done this, and, even when they have, the number of lung cancer cases has been too small to enable robust conclusions to be drawn.

2.1.1 *Cohort studies*

There have been eight cohort studies of nonsmokers who were followed for several years to determine the risk for lung cancer (these are described in Table 2.1). Six of these studies (Garfinkel, 1981; Hirayama, 1984; Butler, 1988; Cardenas *et al.*, 1997; Jee *et al*., 1999; Nishino *et al*., 2001) reported the risk of lung cancer associated with exposure to secondhand smoke from the spouse. All six studies found that the risk for nonsmoking women with partners who smoked was higher than that for those whose partner did not

Table 2.1. Cohort studies of secondhand smoke and lung cancer

Reference (country, years of study)	Cohort sample	Cohort eligibility; follow-up	Source of exposure	Incidence/death; covariates adjusted for; comments
Garfinkel (1981) (USA, 1960–72)	176 739 married nonsmoking women	ACS Study: friends, neighbours and relatives of American Cancer Society volunteers; deaths reported by volunteers; death certificates obtained from state health departments; 93% follow-up Veterans Study: questionnaire mailed to veterans holding a US Government life insurance; 85% response; death certificates supplied to the Veterans' Administration or through field work at health departments	Active smoking by current spouse	Deaths 1) Crude death rates; 2) analysis with women matched by age, race, highest educational status of husband or wife, residence and occupational exposure of husband
Hirayama (1984) (Japan, 1965–81)	91 540 married nonsmoking women	95% of the census population in the study area in 29 health centre districts; follow-up consisted of special annual census and special death registry system.	Active smoking by current spouse	Deaths SMRs
Butler (1988) (USA, 1974–82)	Spouse pairs: 9378 subjects; AHSMOG cohort: 6467 subjects (66% overlap)	Non-Hispanic white Adventists; spouse pairs with a non-smoking wife; AHSMOG cohort enrolled for air pollution study; deaths ascertained by linkage to California death certificate file, national death index and notification of death by church clerks; cases ascertained with hospital history forms and review of hospital and tumour registry records; 99% histologically confirmed	Spouse pair cohort: active smoking by current spouse; AHSMOG cohort: exposure at work	Cases/deaths Adjusted for age
DeWaard *et al.* (1995) (the Netherlands, 1977–91)	23 cases and 191 controls	Nested case–control study among women enrolled in breast cancer screening projects (DOM project, enrolment 1975–77, aged 50–64 years and Lutine Study, enrolment 1982–83, aged 40–49 years)	Exposure assessed by measurement of urinary cotinine levels in declared nonsmokers	Cases/deaths Cotinine excretion adjusted for creatinine resulted in higher odds ratios.

Table 2.1 (contd)

Reference (country, years of study)	Cohort sample	Cohort eligibility; follow-up	Source of exposure	Incidence/death; covariates adjusted for; comments
Cardenas *et al.* (1997) (USA, 1982–89)	288 776 (96 542 men, 192 234 women) nonsmoking subjects	Friends, neighbours and relatives of American Cancer Society volunteers in all 50 States; aged > 30 years; death monitored by volunteers and through national death index; cause of death classified according to ICD-9.	Active smoking by current spouse; self-reported exposure at home, at work or in other areas	Deaths Adjusted for age, race, education, blue-collar employment, asbestos exposure, consumption of vegetables, citrus fruits and fat, history of chronic lung disease
Jee *et al.* (1999) (Republic of Korea, 1992–97)	157 436 married nonsmoking women	Both spouses had to have completed the Korean Medical Insurance Corporation medical examination; aged > 40 years; cases ascertained from diagnosis on discharge summary	Active smoking by current husband	Cases Univariate analysis; multivariate analysis adjusted for age of husband and wife, socioeconomic status, residence, husband's vegetable consumption and occupation
Speizer *et al.* (1999) (USA, 1976–92)	121 700 women, US registered nurses in 1976; unknown subcohort of nonsmokers	Female nurses aged 30–55 years, Nurses' Health Study; deaths ascertained by family members, postal service or through national death index; cases confirmed by pathology reports	Information on exposure to second-hand smoke during childhood and adulthood ascertained in 1982	Cases Adjusted for age
Nishino *et al.* (2001) (Japan, 1984–92)	31 345 (13 992 men, 17 353 women) non-smokers	Residents of six primary school sectors in a city and the whole area of two towns in north-eastern Honshu, aged > 40 years; cases ascertained by linkage to the prefectural cancer registry; cancer sites coded according to ICD-9	Any smoker in the household	Cases 1) Crude relative risk; 2) stratification by smoking status of husband and other household members; 3) multivariate relative risk adjusted for age, study area, alcohol intake, green and yellow vegetable intake, fruit intake, meat intake and past history of lung disease

SMR, standardized mortality ratio

smoke (see Table 2.2). In both cohort studies that reported on the effect in nonsmoking men whose wives smoked, the relative risk was increased (Hirayama 1984; Cardenas *et al.*, 1997). The two other cohort studies, which were based on general exposure to secondhand smoke (deWaard *et al*., 1995; Speizer *et al*., 1999), obtained similar results.

Table 2.2. Epidemiological studies[a] of the risk for lung cancer in lifelong non-smokers whose spouses smoked relative to the risk in those whose spouses did not smoke[b]

Reference (country)	No. of cases of lung cancer	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[c]
Women			
Case–control studies (n = 40)			
Chan & Fung (1982) (Hong Kong, SAR)	84	0.8 [0.4–1.3]	NR[d]
Correa *et al*. (1983) (USA)	22	2.1 [0.8–5.3]	NR
Trichopoulos *et al*. (1983) (Greece)	62	2.1 [1.2–3.8]	NR
Buffler *et al*. (1984) (USA)	41	0.8 [0.3–1.9]	0.8 (0.3–1.8)
Kabat & Wynder (1984) (USA)	24	0.8 [0.3–2.5]	NR
Lam (1985) (Hong Kong, SAR)	60	2.0 [1.1–3.7][e]	NR
Garfinkel *et al*. (1985) (USA)	134	1.2 [0.8–1.9]	1.2 (0.9–1.6)
Wu *et al*. (1985) (USA)	29	NR	1.2 (0.5–3.3)
Akiba *et al*. (1986) (Japan)	94	1.5 [0.9–2.6]	1.5 [0.8–2.8][f]
Lee *et al*. (1986) (United Kingdom)	32	1.0 [0.4–2.6]	1.0 (0.4–2.7)
Brownson *et al*. (1987) (USA)[g]	19	1.5 (0.4–6.0)	
Gao *et al*. (1987) (China)	246	1.2 (0.8–1.7)	1.3 (1.0–1.8)
Humble *et al*. (1987) (USA)	20	2.3 [0.8–6.8]	2.2 (0.7–6.6)
Koo *et al*. (1987) (Hong Kong, SAR)	86	1.6 [0.9–2.7]	1.6 (0.9–3.1)
Lam *et al*. (1987) (Hong Kong, SAR)	199	1.7 [1.2–2.4]	NR
Pershagen *et al*. (1987) (Sweden)	70	1.0 [0.6–1.7]	1.2 (0.7–2.1)
Geng *et al*. (1988) (China)	54	2.2 [1.1–4.3]	NR
Inoue & Hirayama (1988) (Japan)	22	2.6 (0.7–8.8)[h]	NR
Shimizu *et al*. (1988) (Japan)	90	1.1 [0.6–1.8]	1.1 (NR)
Choi *et al.* (1989) (Republic of Korea)	75	1.6 (0.9–2.9)	1.6 (NR)
Kalandidi *et al*. (1990) (Greece)	90	1.6 [0.9–2.9]	2.1 (1.1–4.1)
Sobue (1990) (Japan)	144	1.1 [0.7–1.5]	1.1 (0.8–1.6)
Wu-Williams *et al*. (1990) (China)	417	0.8 [0.6–1.0]	0.7 (0.6–0.9)
Liu & Chapman (1991)[i] (China)	54	0.7 [0.3–1.7]	0.8 (0.3–2.0)
Brownson *et al*. (1992) (USA)	431	1.0 [0.8–1.2]	1.0 (0.8–1.2)
Stockwell *et al*. (1992) (USA)	210	NR	1.6 (0.8–3.0)
Du *et al*. (1993) (China)	75	1.2 (0.7–2.1)	NR
Liu *et al*. (1993) (China)	38	1.7 (0.7–3.8)	NR
Fontham *et al*. (1994) (USA)	651	1.3 (1.0–1.5)	1.3 (1.0–1.6)
Kabat *et al*. (1995) (USA)	67	1.1 [0.6–2.0]	1.1 (0.6–1.9)
Sun *et al*. (1996) (China)	230	NR	1.2 (0.8–1.7)

Table 2.2 (contd)

Reference (country)	No. of cases of lung cancer	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[c]
Wang *et al*. (1996) (China)	135	1.1 [0.7–1.8]	NR
Boffetta *et al*. (1998) (Europe)	508	1.0 [0.8–1.3]	1.1 (0.9–1.4)
Shen *et al*. (1998) (China)	70	[1.5 (0.7–3.3)]	1.6 (0.7–3.9)
Zaridze *et al*. (1998) (Russia)	189	1.6 [1.1–2.3]	1.5 (1.1–2.2)
Rapiti *et al*. (1999) (India)	41	1.0 [0.4–2.4]	1.2 (0.5–2.9)
Zhong *et al*. (1999) (China)	407	1.2 [0.8–1.6]	1.1 (0.8–1.5)
Kreuzer *et al*. (2000)[j] (Germany)	100	0.9 [0.6–1.4]	0.8 (0.5–1.3)
Lee *et al*. (2000)[k] (Taiwan, China)	268	1.7 [1.3–2.4]	1.8 (1.3–2.5)
Johnson *et al*. (2001) (Canada)	71	NR	1.2 (0.6–4.0)
Cohort studies (n = 6)			
Garfinkel (1981) (USA)	153	NR	1.2 [0.9–1.4]
Hirayama (1984) (Japan)	200	NR	1.5 [1.0–2.1][l]
Butler (1988) (USA)	8	NR	2.0 (0.5–8.6)
Cardenas *et al*. (1997) (USA)	150	NR	1.2 (0.8–1.6)
Jee *et al*. (1999) (Republic of Korea)	63	NR	1.9 (1.0–3.5)
Nishino *et al*. (2001) (Japan)	24	NR	1.9 (0.8–4.4)
Men			
Case–control studies (n = 9)			
Correa *et al*. (1983) (USA)	8	2.0 [0.2–11.8][m]	NR
Buffler *et al*. (1984) (USA)	11	0.5 (0.1–2.2)[m]	0.5 (0.2–1.7)
Kabat & Wynder (1984) (USA)	12	1.0 [0.2–6.7][m]	NR
Akiba *et al*. (1986) (Japan)	19	2.1 (0.5–8.6)	1.8 (0.5–7.0)[f]
Lee *et al*. (1986) (United Kingdom)	15	1.3 (0.3–5.4)[m]	1.3 (0.4–4.4)
Choi *et al.* (1989) (Republic of Korea)	13	2.7 (0.5–15.2)[m]	2.7 (NR)
Kabat *et al*. (1995) (USA)	39	1.6 [0.7–3.9]	1.6 (0.7–3.8)
Boffetta *et al*. (1998) (Europe)	141	1.3 [0.8–2.2]	NR
Kreuzer *et al.* (2000)[j] (Germany)	23	0.4 (0.1–3.0)	NR
Cohort studies (n = 2)			
Hirayama (1984) (Japan)	64	NR	2.3 [1.1–4.8]
Cardenas *et al*. (1997) (USA	97	NR	1.1 (0.6–1.8)

CI, confidence interval

[a] Only the most recent publication is used for studies that have been updated from previously published reports. Also, studies based on subjects who are included in a larger series are not listed here.

[b] In addition, there are four studies that gave results for men and women combined: Hole *et al*. (1989) (7 cases), relative risk, 2.1 (95% CI, 0.5–12.8); Janerich *et al*. (1990) (188 cases), relative risk, 0.9 (95% CI, 0.6–1.6) for analysis based on subjects interviewed directly and 0.4 (0.2–1.0) for analysis based on interviews with surrogate respondents; Schwartz *et al*. (1996) (257 cases), relative risk, 1.1 (95% CI, 0.8–1.6); Boffetta *et al*. (1999a) (69 cases), relative risk 1.22 (95% CI, 0.7–2.1).

[c] Adjusted for at least age (other factors included dietary habits, education and social class)

Table 2.2 (contd)

[d] Not reported or estimatable from the reported results
[e] Results for adenocarcinoma only
[f] The original report presented 90% confidence intervals that were converted to 95% confidence intervals for this table.
[g] The raw data came from the US Environmental Protection Agency (1992).
[h] Results reported in the US Environmental Protection Agency report (1992), which also noted that the results reported in this article (odds ratio, 2.3) were erroneous
[i] One of the 202 controls was a smoker, but this would have a negligible effect on the result, so this study was included.
[j] Results from analysis excluding cases and controls already included in the study by Boffetta *et al*. (1998) [personal communication M. Kreuzer]
[k] Crude results are for comparisons between women married to smokers and those married to non-smokers. The adjusted result was obtained by pooling the odds ratio corresponding to women married to smokers who smoked in their presence with the odds ratio corresponding to women married to smokers who did not smoke in their presence.
[l] Authors reported a 90% confidence interval that was adjusted to a 95% confidence interval for this table. It should also be noted that this result was for a comparison of women whose husbands smoked 1–19 cigarettes/day with women whose husbands were nonsmokers, and did not include the highest exposure group (≥ 20 cigarettes/day).
[m] Fisher's exact 95% confidence intervals were estimated.

Exposure–response relationships

The analysis of exposure–response relationships provides critical evidence for or against a causal relationship between exposure to secondhand smoke and the development of lung cancer.

In the study by Garfinkel (1981), the relative risk did not increase with increasing exposure levels.

In the study by Hirayama (1984), the relative risks for women were 1.4, 1.4, 1.6 and 1.9 when their husbands were ex-smokers, and when they smoked 1–14, 15–19 or ≥ 20 cigarettes/day, respectively (p value for trend test, 0.002). Similarly the relative risk for nonsmoking men increased with exposure level: it was 2.1 when the wives smoked 1–19 cigarettes/day and 2.3 when they smoked ≥ 20 cigarettes/day (p value for trend test, 0.02).

The study by Cardenas *et al.* (1997) also found a significant exposure–response relationship. When the husbands smoked 1–19, 20–39 and ≥ 40 cigarettes/day, the relative risks for women exposed to secondhand smoke were 1.1, 1.2 and 1.9 respectively (p value for trend test, 0.03). There was no evidence of an association between risk and the length of time the couples had been married. A similar analysis for nonsmoking men exposed to secondhand smoke would not be robust because the number of cases was too small. The particular strengths of this study were the near complete data on cause of death (97%), direct questioning of both partners about their smoking habits, and the taking into account of numerous potential confounders such as previous lung disease, occupational exposure to asbestos, dietary habits and education.

Taken together, the three large cohort studies demonstrate an increased incidence of deaths from lung cancer associated with exposure to secondhand smoke from the spouse. The increase in deaths from lung cancer in the study by Hirayama (1984) is significant, and this study and that by Cardenas *et al.* (1997) also reported a significant exposure–response relationship.

2.1.2 *Case–control studies*

Many case–control studies have been undertaken in several countries (mostly China and the USA) (described in Table 2.3). In these studies lung cancer cases were ascertained and matched with controls (usually for age and other factors). The controls were selected from either the general population or the hospital in which the patients with lung cancer were diagnosed. Details of the smoking habits of the partners of both cases and controls were obtained either by interview or questionnaire. In some instances the next of kin provided the relevant information. These studies were based on various measures of exposure to secondhand smoke, including exposure from the partner, at the workplace, during childhood or exposure from other sources. The following section describes only large, relevant studies in which all cases and controls were interviewed in person and no information from the next of kin was used to reconstruct exposure.

(*a*) *Description of studies*

The study of Lam *et al.* (1987) included 199 cases and 335 controls from Hong Kong, Special Administrative Region of China. The study is characterized by good data on exposure (from various sources) to secondhand smoke, valid classification of the smoking habits of the husband and a consideration of potential confounders (including education, place of birth, duration of residence and marital status).

The study from China by Gao *et al*. (1987) included 246 cases and 375 controls. The cases were identified using a system built upon the Shanghai Cancer Registry. The analyses were controlled for age and education.

The study of Wu-Williams *et al.* (1990), also from China, included 417 cases and 602 controls. A limitation of this study is that it was not able to control for important indoor sources of exposure to potential lung carcinogens such as those produced during burning of coal and frying in oil.

The study of Brownson *et al.* (1992) in the USA included 431 cases and 1166 controls. It is characterized by good documentation of data on exposure in the home and the workplace, and took into account potential confounders (age, sex and socioeconomic status).

In the study of Fontham *et al*. (1994) in the USA, 651 cases and 1253 controls were interviewed. Possible misclassification of smokers and potential confounding by age, occupational exposure to known carcinogens, eating habits, familial history of lung cancer and education were taken into account. The smoking status was verified by means of cotinine determination to minimize the misclassification of smokers as nonsmokers.

Table 2.3. Main study design characteristics of case–control studies on exposure to secondhand smoke and lung cancer

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Chan & Fung (1982) (Hong Kong, SAR, 1976–77)	Women: 84 cases, 139 controls	Histologically confirmed cases of bronchial cancer were identified in five hospitals in Hong Kong. Controls were identified from patients in the orthopaedic ward at the same hospitals and were selected from the 'same general age group' as the cases.	None	Patients were interviewed using a questionnaire that included a question on exposure to passive smoke at home.
Correa *et al*. (1983) (USA, not reported)	Men: 8 cases, 178 controls Women: 22 cases, 133 controls	Cases of primary lung cancer identified from admission and pathology records at 29 hospitals. Patients with bronchioalveolar cancer were excluded. Controls were randomly selected from patients attending the same hospital and matched for race, sex and age. Patients with smoking-related diseases were excluded from the controls.	None	Study subjects were interviewed with a questionnaire including questions on history of exposure from smoking spouses and parental smoking.
Trichopoulos *et al*. (1983) (Greece, 1978–82)	Men and women: 77 cases, 225 controls	Cases of lung cancer other than adenocarcinoma of the terminal bronchi were identified from three hospitals in Athens. Controls were drawn from an orthopaedic hospital in the same area as the cases. The cases and controls had 'similar demographic and socioeconomic profiles'.	None	Physicians interviewed subjects concerning smoking habits of their spouses.
Buffler *et al*. (1984) (USA, 1976–80)	Men: 11 cases, 90 controls Women: 41 cases, 196 controls	Patients aged 30–79 years with histologically confirmed lung cancer were identified from hospital and state records in six counties in Texas. Population-based and deceased controls were selected from state and federal records that were matched to cases on age, race, sex, region of residence and vital status.	Age, race, sex, region of residence and vital status	Questionnaires were administered to study subjects or next of kin, which included questions on household members who smoked regularly.
Kabat & Wynder (1984) (USA, 1971–80)	Men: 25 cases, 25 controls Women: 53 cases, 53 controls	Cases of primary cancer of the lung were selected from hospitals. One control was matched to each case on age, sex, race, hospital and date of interview. Controls were selected from other hospitalized patients who had diseases that were not tobacco related.	None	Study subjects were interviewed in hospital using a standardized questionnaire that included questions on spousal and workplace exposure.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Lam (1985) (Hong Kong, SAR, 1981–84)	Women: 60 cases, 144 controls	Cases of primary lung cancer were identified from a hospital in Hong Kong. Controls were selected from patients in the orthopaedic wards of the same hospital and were reported to be comparable in age and social class to the cases. Sufficient numbers of cases were available to permit a meaningful analysis only for adenocarcinoma.	Although age and social class appear to have been matched for, they were not controlled for in the analysis.	Exposure assessment used interviews of study subjects or next of kin, which included questions on exposure to secondhand smoke from parents, spouse or other family members.
Garfinkel *et al*. (1985) (USA, 1971–81)	Women: 134 cases, 402 controls	Cases and controls were identified from three hospitals in New Jersey and one in Ohio. Controls were colon and rectum cancers matched to the cases on age and hospital. Both cases and controls were histologically confirmed.	Age and hospital in all analyses. Logistic regression also controlled for socioeconomic status and year of diagnosis	Study subjects or next of kin were interviewed using a questionnaire designed to elicit information on exposure to secondhand smoke from the spouse or other household member(s).
Wu *et al*. (1985) (USA, 1981–82)	Women: 29 patients with adenocarcinomas and 62 controls; 2 with squamous-cell carcinomas and 30 controls[a]	Cases diagnosed by microscopy were identified from a population-based tumour registry in Los Angeles County. Cases were white residents, under 76 years of age who had no prior history of cancer (except melanoma). Neighbourhood controls met the same criteria and were matched to cases on date of birth.	Age. Active smoking was included in analyses that were not restricted to nonsmokers.	A structured telephone questionnaire was used to elicit information on exposure to secondhand smoke from spouse or other household members, and during childhood from household members.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Akiba *et al*. (1986) (Japan, 1971–80)	Women: 94 cases, 270 controls Men: 19 cases, 241 controls	Cases and controls were identified from a cohort of atomic bomb survivors in Hiroshima and Nagasaki. Cases were identified from tumour, mortality and other medical registries. Controls were matched to cases by birth, sex, city of residence, vital status and whether they participated in an annual medical programme. For deceased cases, the corresponding controls were required to have died from a disease other than cancer or chronic respiratory diseases, and were matched to cases on year of death.	Age, sex, city, and year of death	Subjects or next of kin were interviewed using a structured questionnaire to elicit information on exposure to secondhand smoke from a spouse or parent.
Lee *et al*. (1986) (United Kingdom, 1979–82)	Women: 32 cases, 66 controls Men: 15 cases, 30 controls	Cases and controls were nonsmokers identified from several hospitals in England. Controls were patients who did not have lung cancer, chronic bronchitis, ischaemic heart disease or stroke. Two controls for each case were selected and matched on sex, age, marital status, and as far as possible, hospital.	Age, sex, hospital and marital status	The patients and their spouses were interviewed to obtain a history of spousal smoking.
Schwartz (1996) (USA, 1984–87)	Men and women: 401 cases, 398 controls	Cases between the ages of 40 and 84 years were identified in Detroit from an Occupational Cancer Incidence Surveillance Study (OCISS) in conjunction with the Metropolitan Detroit Cancer Surveillance System. Population-based controls were randomly selected from the controls who took part in the OCISS study. Controls were frequency-matched to cases on age, sex, race and county of residence.	Age, sex and race	Telephone interviews were conducted with cases (17%) or controls (78%) or their proxies. The questionnaire included information on exposure to secondhand smoke at work or at home.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Brownson *et al*. (1987) (USA, 1979–82)	Women: 19 cases, 47 controls Men: 4 cases, 19 controls	Cases of adenocarcinoma and controls were identified from the Colorado Central Cancer Registry. All cases were confirmed by microscopy. Controls were patients with colon and bone marrow cancer and were group-matched to cases on age and sex. Cases and controls were required to have resided for a minimum of 6 months in the Denver metropolitan area prior to diagnosis.	Age, sex and socioeconomic status	Cases and controls or next of kin were interviewed and information collected on the smoking status of the spouse and the number of hours per day exposed to secondhand smoke.
Gao *et al*. (1987) (China, 1984–86)	Women: 246 cases, 375 controls	Cases of lung cancer were identified among female residents of Shanghai aged 35–69 from a system built upon the Shanghai Cancer Registry. Female controls were randomly selected from the Shanghai area and approximately frequency-matched on age.	Age and education	Cases and controls were interviewed to obtain information on exposure in childhood and adulthood.
Geng *et al*. (1988) (China, not stated)	Women: 54 cases, 93 controls	Cases were identified among females who had lived for more than 10 years in Tianjin, China. Controls were matched to the cases on sex, race, age and marital status. The precise source of the cases or controls is not stated.	None[b]	The methods used to collect information on exposure to secondhand smoke are not described.
Humble *et al*. (1987) (USA, 1980–82)	Men: 8 cases, 130 controls Women: 20 cases, 162 controls	Cases were identified from the New Mexican Tumor Registry. An initial series was selected between 1980 and 1982 that included all individuals less than 50 years of age, Hispanics aged over 50 years, and a random sample of male (40%) and female (50%) non-Hispanics over 50 years.	Ethnicity and age	Interviews of study subjects (48% cases) or their next of kin (52% cases) were conducted to collect information on spousal smoking habits.
Koo *et al*. (1987) (Hong Kong, SAR, 1981–83)	Women: 86 cases, 136 controls	Cases were identified as part of a larger study on female lung cancer in Hong Kong from the wards and outpatient departments of eight hospitals. An equal number of 'healthy' controls were selected and matched to cases on age, district and socioeconomic status (housing type).	Age, district and housing type, formal schooling and number of live births	Cases and controls were interviewed to elicit information on exposure to secondhand smoke from spouses and other relatives at home.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Lam *et al*. (1987) (Hong Kong SAR, 1983–86)	Women: 199 cases, 35 controls	Pathologically confirmed cases of lung cancer were identified from eight hospitals. Controls were matched to the cases on age and drawn from the same neighbourhood as the corresponding case.	None	Study subjects were interviewed using a questionnaire that included questions concerning the husband's smoking habits.
Pershagen *et al*. (1987) (Sweden, 1963–80)	Women: 70 cases[c]	Cases and controls were selected from two cohort studies in Sweden. The first was a sample of men and women aged 15–65 years in the 1960 National Census who were mailed a questionnaire on smoking habits in 1963. The second was from a study of Swedish twins born between 1886 and 1925. Lung cancer cases were identified until 1980 by links with the Swedish Cancer Registry and the National Register on Causes of Death. Two control series were selected at random from the cohort. One was based on matching controls to cases based on year of birth, and the other on vital status at the end of follow-up as well as year of birth.	Age and vital status	A questionnaire was mailed in 1984 to each study subject, or if they were dead, to their next of kin (excluding the husband). The questionnaire included questions on exposure to secondhand smoke from husbands and parents.
Inoue & Hirayama (1988) (Japan, 1972–83)	Women: 22 cases[d], 62 controls	Cases and controls are from Kamakure and Miura, Japan. The methods used to identify the cases and controls were not clearly stated. Controls were individuals with cerebrovascular disease who were matched to the cases on age, year of death and district.	Age, year of death and district	Interviews were conducted using 'standard questionnaires'.
Shimizu *et al*. (1988) (Japan, 1982–85)	Women: 90 cases, 163 controls	Cases of primary lung cancer were identified from 4 hospitals in Nagoya, Japan. Controls were patients from adjacent wards with diseases other than lung cancer who were matched to the cases on age and date of admission.	Age, hospital and date of admission	Participants answered a questionnaire on the first or second day of admission that included questions on exposure to secondhand smoke from the spouse and other family members, and at the workplace.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Choi *et al.* (1989) (Republic of Korea, 1985–88)	Women: 75 cases, 144 controls	375 patients with lung cancer admitted to Korean Cancer Centre Hospital with histopathologically confirmed diagnosis. Two controls were selected per case matched by age (± 5 years), gender, admission date and area (urban/rural); patients with smoking-related diseases were excluded.	Unmatched analysis of subgroup of non-smoking study subjects	A questionnaire was administered face-to-face including questions on smoking.
Janerich *et al*. (1990) (USA, 1982–85)	Men and women: 191 cases, 191 controls	Cases were identified from 125 diagnostic or treatment facilities covering 23 counties in New York State, and from the New York State cancer registry. Cases were between 20 and 80 years of age, and had to have been resident of one of the 23 counties. Controls were identified from records of the New York Department of Motor Vehicles, and matched to the cases on age, county of residence and smoking history (i.e. nonsmokers).	Age and county of residence	Face-to-face interviews were conducted with cases or controls or their next of kin. When a next-of-kin interview was required, the next of kin of the matching controls were also interviewed. The questionnaire included questions on exposure to smoke from the spouse, at the workplace and during childhood.
Kalandidi *et al*. (1990) (Greece, 1987–89)	Women: 90 cases, 120 controls	Cases with a 'definite' diagnosis of lung cancer were identified from 7 hospitals in the greater Athens area. Controls were women hospitalized in the orthopaedic department of the same or a nearby hospital, and were randomly selected from those who entered within a week of a corresponding case. Controls had to be 35 years or older.	Age, years of schooling, interviewer and total energy consumption	A questionnaire was administered face-to-face to the cases and controls that included questions on exposure to secondhand smoke from the spouse, other household members and at the workplace.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Sobue (1990) (Japan, 1986–88)	Women: 144 cases, 731 controls	Cases of lung cancer and controls aged 40–79 years were identified from eight hospitals in Osaka, Japan. Controls were individuals with diseases other than lung cancer.	Age and education	A self-administered questionnaire was given to cases and controls at the time of admission which included questions on exposure to secondhand smoke.
Wu-Williams *et al*. (1990) (China, 1985–87)	Women: 417 cases, 602 controls	Patients under the age of 70 years with primary lung cancers were identified in the cancer registries of Shenyang and Harbin, China and of major hospitals serving these areas. Controls were randomly selected from the populations of Shenyang and Harbin, and were frequency-matched to the cases by age.	Age, education and centre	Cases and controls were interviewed using a questionnaire that included questions concerning exposure to secondhand smoke from the spouse and other co-habitants, and at the workplace.
Liu *et al*. (1991) (China, 1985–86)	Men and women: 4 cases, 19 controls	Cases of lung cancer were identified from hospitals and clinics in Xuanwei. Controls were matched to the cases on age, sex and village of residence.	Age, sex, village of residence and cooking history	Cases and controls were personally interviewed using a questionnaire that included a question on exposure to second-hand smoke at home (primarily from the spouse)
Brownson *et al*. (1992) (USA, 1986–91)	Women: 431 cases, 1166 controls	Cases of primary lung cancer among white females were identified from the Missouri cancer registry; 76% of the cases were histologically verified. Controls were selected for women under 65 years from the state driver's license files, and for women 65 years or over from the Health Care Finance Administration's roster of Medicare recipients. Controls were frequency-matched to cases on age.	Age, previous lung disease and dietary β-carotene and fat	Telephone interviews were conducted that included questions concerning exposure to secondhand smoke during childhood and adulthood.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Stockwell *et al*. (1992) (USA, 1987–91)	Women: 210 cases, 301 controls	Cases of histologically confirmed primary lung cancer were identified from hospital tumour registries, and a state-wide cancer registry in 28 counties in central Florida. Population-based controls were selected using random digit dialling.	Age, race and education	Interviews of patients or next of kin were conducted in person, by telephone or occasionally by post. The questionnaire included questions on exposure to secondhand smoke at home, at work or in social settings.
Du *et al*. (1993) (China, 1985–86)	**1985 analysis** Men and women: 120 cases, 120 controls with non-respiratory disease, 120 controls with non-respiratory cancer **1986 analysis** Women: 75 cases, 128 non-cancer patients as controls plus 126 controls with tumours other than of the lung	Cases in this study were apparently identified from deaths reported to the local police stations in Guanghzo. Two separate analyses are presented (1) for nonsmokers in 1985 and (2) for female nonsmokers in 1986. Two control groups were selected for each analysis, but it is not clear how these controls were selected. The control groups for the first analysis consisted of (1) non-respiratory system diseases and (2) non-respiratory cancers. The control groups for the second analysis consisted of (1) non-tumour disease and (2) tumours other than of the lung. In the first analysis, controls were matched to cases on sex and age, and were matched on residence in both analyses.	First analysis sex, age and residence Second analysis did not adjust for covariates.	A questionnaire was used by trained personnel to obtain information from family members; it included questions on spousal smoking habits.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Liu *et al*. (1993) (China, 1983–84)	Women: 38 cases, 69 controls	Cases of primary lung cancer were identified from eight major hospitals covering most of Guangzhou. Controls were selected from inpatients at six of these hospitals and patients with chronic obstructive lung diseases, pulmonary tuberculosis, cancers and coronary heart disease were excluded. Controls were matched to cases on age, sex, residential district and date of diagnosis or admission to hospital.	Age, sex, residential area, calendar time, education and occupation	Interviews were carried out in the homes of the subjects using a questionnaire that included questions on spousal smoking habits.
Fontham *et al*. (1994) (USA, 1986–90)	Women: 651 cases, 1253 controls	Cases of primary lung cancer confirmed by microscopy were identified between 1986 and 1988 among residents of Atlanta, and Houston; and between 1989 and 1990 among residents of New Orleans, Los Angeles and San Francisco. Population-based controls were chosen using random digit dialling and random sampling from the Health Care Financing Administration's files. Controls were frequency-matched to cases on race, study centre and age. Cases and controls were required to be between 20 and 79 years of age, to speak English, Spanish or Chinese, and to have no prior history of cancer.	Age, race, study centre, education, family history of cancer, occupational and dietary factors	In-person interviews were conducted with cases and controls or with next of kin. The questionnaire included questions on exposure to secondhand smoke during adulthood (from spouse and at work), and during childhood (from parents or other household members). Urine cotinine measurements were made and used to eliminate individuals who may have been smokers.
Kabat *et al*. (1995) (USA, 1983–90)	Women: 69 cases, 187 controls Men: 100 cases, 117 controls	Histologically confirmed cases were identified in hospitals in New York City, Chicago, Detroit and Philadelphia. Controls were patients admitted to the same hospitals with diseases thought to be unrelated to tobacco smoke. Cases were matched to controls on age, sex, race, hospital and date of interview.	Age, sex, race, education and type of hospital (cancer centre versus other)	In-person interviews were conducted that included questions on exposure to secondhand smoke in childhood and adulthood (at home and in the workplace)

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
de Waard *et al*. (1995) (the Netherlands, 1989, 1991, 1992)	Women: 23 cases, 305 controls	Cases and controls were identified from two cohorts of women screened for breast cancer in Utrecht. The first cohort included women aged 50–64 years who were screened in 1975 and 1977, and re-examined 1 year later. The second cohort included women aged 40–49 years who were screened between 1982 and 1983. Lung cancer cases were identified from mortality and cancer incidence registries. Cancer cases and controls were identified for the first cohort in 1989, 1991 and 1992, whereas cases and controls for the second cohort were identified only in 1992. Four controls were selected for each case identified in 1989 and 1991, and two controls per case in 1992 from the cohort files. Controls were matched to cases on 'about the same age and day of urine collection' for the 1989 cases, and it is unclear whether this matching criterion was also applied to cases and controls from the other years.	Possibly age and calendar time, but it is not clear if these were matched for in all cases or adjusted for in the analyses.	Urinary cotinine concentrations measured in samples collected during the screenings. Non-smokers were defined as subjects with creatinine adjusted cotinine levels of < 9.2 ng/mg creatinine
Sun *et al*. (1996) (China, not reported)	Women: 230 cases, 230 controls	This was a population based case–control study in Harbin. Only an abstract was available, and the source of the cases and controls was not described in it.	Age and education	In-person interviews of cases and controls included questions on exposure to secondhand smoke during childhood, adolescence and adulthood.
Wang *et al*. (1996) (China, 1992–94)	Women: 135 cases, 135 controls	Cases of primary lung cancer who were between 35 and 69 years of age were identified in 18 hospitals in Shenyang. Controls were randomly selected from the urban population in Shenyang, and matched to cases on age.	Cases and controls were matched for age, but it is unclear whether an unmatched analysis was performed.	Cases and controls were interviewed face-to-face using a questionnaire that included questions on exposure to secondhand smoke in childhood and adulthood.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Boffetta *et al*. (1998) (Europe, 1988–94)	Men: 141 cases, 531 controls Women: 508 cases, 1011 controls	Cases and controls were ≤ 74 years of age and had smoked < 400 cigarettes in their lifetimes. Cases were identified from 12 centres in seven European countries and 96.5% were confirmed by microscopy. Controls were hospital-based in some centres and community-based in others. Hospital-based controls were chosen to exclude those with other diseases related to smoking. Community-based controls were drawn from population registries. Controls were matched to cases on age and sex using individual matching in some centres and frequency matching in others. Questionnaire response rates ranged from 53 to > 95% except for 3 centres who had response rates < 50% among controls.	Sex, age and centre	Questionnaire on exposure to secondhand smoke from spouse, during childhood, in the workplace and from other sources was developed based on a previous study of urine cotinine levels and exposure to secondhand smoke including smoke from cigarillos, cigars and pipes as well as cigarettes.
Jöckel *et al*. (1998b) (Germany, 1988–93)	Men and women: 71 cases, 236 controls	Cases and controls were also a part of the study by Boffetta *et al.* (1998). Nonsmokers were identified from a larger case–control study from Bremen, Frankfurt and the surrounding areas. Controls were population based and matched to the cases on sex, age and region.	Sex, age, region, exposure to asbestos, social class, and intake of vegetables and fruits	Compatible with questionnaire used in study by Boffetta 1998. Individuals who had never smoked regularly for more than 6 months were classified as 'never-smokers', and were combined with workers exposed to low levels of secondhand smoke (< 75th percentile) to form the referent group.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Shen *et al*. (1998) (China, 1993)	Women: 70 cases, 70 controls	Cases of primary lung cancer (adenocarcinoma) living ≥ 20 years in Nanjing; healthy controls came from the same neighbourhood, 1:1 matched by sex and age (± 5 years); response rate was 100%.	Chronic lung disease, cooking conditions, family history of lung cancer	Standardized questionnaire administered by trained staff covered exposure to secondhand smoke for the 20 years preceding diagnosis: no. of cigarettes smoked/day, no. of years of exposure to secondhand smoke.
Zaridze *et al*. (1998) (Russia, not reported)	Women: 189 cases, 358 controls	Histologically confirmed cases of primary lung cancer were identified in two cancer treatment hospitals in Moscow. Controls were female oncology patients from the same hospitals who did not have lung or upper respiratory cancers. Cases and controls were required to be nonsmokers who lived in Moscow.	Age and education	In-person interviews were conducted within 2–3 days of hospital admission; they included questions on exposure to secondhand smoke in adulthood and childhood.
Boffetta *et al*. (1999a) (Europe, 1988–94)	Women: 208 cases, 361 controls	Same as Boffetta *et al*. (1998) except that results are stratified by type of exposure to secondhand smoke (cigarettes or cigars, cigarillos and pipes)	Age and centre	Same as Boffetta *et al*. (1998)
Boffetta *et al*. (1999b) (Europe, 1994–96)	Men: 4 cases, 41 controls Women: 66 cases, 137 controls	Histologically confirmed lung adenocarcinomas were identified from 9 centres in 7 countries from a larger study designed to assess the role of biomarkers of susceptibility in lung cancer among nonsmokers. Controls were selected from nonsmokers in the source populations or in hospital patients. Controls were frequency-matched to cases on age and gender.	Age, gender, and centre. Some models also included urban residence, education and occupational exposure.	Exposure to secondhand smoke was assessed using the same questionnaire as in Boffetta *et al*. (1998).

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Rapiti *et al*. (1999) (India, 1991–92)	Men: 17 cases, 56 controls Women: 41 cases, 67 controls	Histologically or cytologically confirmed cases of primary lung cancer were identified in a hospital in Chandigarh, Northern India. Two controls were selected for each case. One control was a patient at the same hospital who was not hospitalized for more than a month and did not have a disease related to active or passive smoking, alcohol or diet. The other control was a visitor of the patient. No matching of cases and controls was performed.	Sex, age, religion and residence	Interviews of subjects were conducted that included questions on exposure to secondhand smoke from the spouse, at the workplace and during childhood.
Zhong *et al*. (1999) (China, 1992–94)	Women: 504 cases, 601 controls	Cases of primary lung cancer aged 35–69 years were identified from the Shanghai cancer registry. Controls were randomly selected from a Shanghai residential registry and frequency-matched to the age distribution of female lung cancer patients in Shanghai in 1987–89.	Age, income, vitamin C intake, kitchen smokiness, family history of lung cancer, and potentially high risk occupations, and respondent status	Personal interviews with study subjects or their next of kin (2.3% for controls, and 20.2% for cases). The interview included questions on exposure to secondhand smoke from the spouse, at the workplace and during childhood.
Brennan *et al*. (2000) (Europe, 1994–96)	Subset of cases and controls from centres included in Boffetta *et al*. (1998) for whom dietary information was available	Same as Boffetta *et al*. (1998), but analyses were restricted to centres that had information on subjects' consumption of fruit, lettuce, tomato, carrot, cheese, carotenoids, β-carotene or retinol. Analyses were stratified by high and low consumption of these dietary variables, and high and low exposure to secondhand smoke.	Age, gender and centre	Same as Boffetta *et al*. (1998). High exposure to secondhand smoke was defined as being in the upper quartile from combined spousal and workplace exposures.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Kreuzer *et al*. (2000) (Germany, 1990–96)	Men and women: 292 cases, 1338 controls	An extension of the German part of the European multicentre study (Boffetta *et al*., 1998). The cases and controls were a subset of nonsmokers from a larger study of radon exposure in Germany. Cases were identified from 15 hospitals in the study area and were restricted to those who were < 75 years of age; resident in the study area; had lived for > 25 years in Germany; interviewed within 3 months of diagnosis, and not too ill. Controls satisfying the first three criteria listed above were identified from mandatory registries or by modified random digit dialling and were frequency-matched to the cases on sex, age and region. The response rate in the cases was 76%, but that of the controls was only 41%.	Age, region, gender; some models included occupational exposure, exposure to radon, diet, family history of cancer, previous non-malignant respiratory disease and social class.	Same as Boffetta *et al*. (1998)
Lee *et al*. (2000) (China (Province of Taiwan), 1992–98)	Women: 268 cases, 445 controls	Histologically verified cases were identified from Kaohsiung Medical University Hospital in Taiwan. Controls were patients with conditions unrelated to tobacco smoking who were selected within 3 weeks of the case admission from the same hospital, and matched on age.	Age, date of hospital admission, residential area, education, occupation, tuber-culosis, cooking fuels and presence of a fume extractor	Interviews were conducted using a structured questionnaire designed to elicit information on exposure to secondhand smoke.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Wang *et al*. (2000) (China, 1994–98)	Men: 33 cases, 1214 controls Women: 200 cases, 407 controls	Cases of lung cancer who were aged 30–75 years and residents of Pingliang or Qingyang prefectures were identified from hospitals and clinics in these and neighbouring regions. Controls were randomly selected from 1990 census lists for the 2 prefectures and frequency matched to cases on age, sex and prefecture.	Age, sex and prefecture	In person interviews were conducted with cases and controls or with their next of kin when necessary. The questionnaire included questions on exposure to secondhand smoke during adulthood, childhood and in the workplace.
Johnson *et al*. (2001) (Canada, 1994–97)	Women: 71 cases, 761 controls	Cases of histologically confirmed primary lung cancer were identified from a national cancer surveillance system that covers 8 of Canada's 10 provinces. In five provinces controls were identified from health insurance plans, in one from property assessment databases, and in two using random digit dialling. Controls were frequency-matched to the expected distribution of cancer cases by age and province.	Age, province, education and fruit and vegetable consumption	Mailed questionnaires were completed by cases and controls except in one province where next of kin completed them. The questionnaires included questions on exposure to secondhand smoke at work, at home and during childhood.
Kreuzer *et al*. (2001) (Germany, 1990–96)	Men: 58 cases, 803 controls	Same as Kreuzer *et al*. (2000) except that analyses were restricted to men.	Same as Kreuzer *et al*. (2000)	Same as Boffetta *et al*. (1998). Results only presented for low and high exposure to secondhand smoke where high was defined as having greater than the 75th percentile of cumulative duration of exposure weighted by a subjective index of intensity.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Kreuzer *et al*. (2002) (Germany, 1990–96)	Women: 234 cases, 535 controls	Same as Kreuzer *et al*. (2000) except that analyses were restricted to women	Same as Kreuzer *et al*. (2000)	Same as Boffetta *et al*. (1998). Results only presented for high and medium exposure to secondhand smoke versus low or non-exposed. High was defined as having greater than the 90th percentile of cumulative duration of exposure, and low was defined as having less than the 75th percentile.

[a] This study presented results separately for patients with adenocarcinoma and for patients with squamous-cell carcinoma. However, the numbers for the squamous-cell carcinomas were too few to present meaningful results for secondhand smoke in nonsmokers.
[b] Although this study did match cases to controls on several potential confounders, an unmatched analysis was published.
[c] The study had a total of 184 controls in each of the control groups. However, it is unclear how many controls were used in the analysis of exposure to secondhand smoke because several cases (and presumably their matched controls) were dropped from these analyses.
[d] Information on spousal smoking habits was available for only some of the cases and controls. The actual number of cases and controls included in the analysis was not reported, but was smaller than the given numbers.

The study from China by Sun *et al*. (1996) included 230 cases and 230 controls. The study controlled for age and education, but not for burning of coal and frying in oil.

The study of Lee *et al*. (2000) from China (Province of Taiwan) included 268 cases and 445 controls and was an extension of the study of Ko *et al*. (1997). Detailed information on exposure to secondhand smoke was collected, and nonsmoking status was verified by household members. Potential confounding by age, education, occupation, cooking fuels and other factors was allowed for.

The participants in a European multicentre study included 650 cases and 1542 controls from 12 centres in seven countries. Potential confounders such as occupational exposure, socioeconomic status and intake of fruits and vegetables were taken into account. The main publication was by Boffetta *et al.* (1998), but additional analyses were made of effects of secondhand smoke from cigars, cigarillos and pipes (Boffetta *et al*., 1999b) and of exposure to secondhand smoke and diet (Brennan *et al.*, 2000). In addition, the data from some centres on specific aspects have been published separately and in some cases with additional data (Germany: Jöckel *et al.*, 1998a,b; Kreuzer *et al.*, 2000, 2001, 2002; Sweden: Nyberg *et al.*, 1998).

The study of Zaridze *et al*. (1998) from Russia included 189 cases and 358 controls. Information on exposure to secondhand smoke in the family and from colleagues at work was obtained, and potential confounders (age and education) were considered.

(*b*) *Exposure to secondhand smoke from the partner*

Table 2.2 shows the relative risk for lung cancer associated with exposure to secondhand smoke from the spouse. Taking the crude relative risks, or the adjusted estimates when the crude ones are not available (in any event, the crude and adjusted estimates are similar) 25 of the 40 case–control studies of nonsmoking women showed an increased risk; the results of seven of the 25 studies were statistically significant (Trichopolous *et al.*, 1983; Lam, 1985; Lam *et al.*, 1987; Geng *et al.*, 1988; Fontham *et al.*, 1994; Zaridze *et al.*, 1998; Lee *et al.*, 2000). In studies of nonsmoking men, five of the nine studies showed an increased risk, although none were statistically significant.

Exposure–response relationships

Several studies reported the risk of lung cancer associated with increasing levels of exposure, in particular, the number of cigarettes smoked by the spouse per day, the number of years of living with a smoker and pack–years; these studies are listed in Table 2.4. Because most of these studies were relatively small, they would not have had sufficient statistical power to find an exposure–response relationship. Eight studies found a statistically significant trend (p value < 0.05) between lung cancer risk and the number of cigarettes smoked by the spouse (Trichopolous *et al.*, 1983; Hirayama, 1984; Garfinkel *et al.*, 1985; Lam *et al.*, 1987; Geng *et al.*, 1988; Inoue & Hirayama, 1988; Liu *et al.*, 1993; Cardenas *et al.*, 1997) and one other found an almost statistically significant trend (Akiba *et al.*, 1986; $p = 0.06$). Six studies found a statistically significant trend (p value < 0.05) for lung cancer risk and the number of years of marriage to a smoker (Gao *et al.*,

Table 2.4. Relative risk of lung cancer in lifelong nonsmoking women comparing those with the highest exposure to secondhand smoke from a smoking partner to women with nonsmoking partners (the relative risks are ranked in ascending order for each type of exposure)

Reference	Exposure level	Relative risk[a] (95% CI)	
	No. of cigarettes smoked per day by the spouse		
Garfinkel (1981)	≥ 20	1.1	(0.8–1.6)
Kabat *et al.* (1995)	> 10	1.1	(0.5–2.3)
Humble *et al.* (1987)	≥ 21	1.2	(0.3–5.2)
Koo *et al.* (1987)	≥ 21	1.2	(0.5–3.0)
Boffetta *et al.* (1998)	> 18.1	1.3	(0.8–2.2)
Wang *et al*. (1996)	≥ 20	1.4	(0.8–2.6)
Zhong *et al*. (1999)	> 20	1.4	(0.7–2.6)
Jee *et al*. (1999)	≥ 20	1.5	(0.7–3.3)
Du *et al.* (1993)	> 20	1.6[b]	(0.8–3.2)
Kalandidi *et al.* (1990)	≥ 41	1.6	(0.5–4.6)
Hirayama (1984)[c,d]	≥ 20	1.7	(1.1–2.7)
Cardenas *et al.* (1997)	≥ 40	1.9	(1.0–3.6)
Trichopoulos *et al.* (1983)	≥ 31	1.9	(0.7–5.0)
Akiba *et al.* (1986)[d]	≥ 30	2.1	(1.7–2.6)
Garfinkel *et al.* (1985)	≥ 20	2.1	(1.1–4.0)
Lam *et al.* (1987)	≥ 21	2.1	(1.1–4.0)
Geng *et al.* (1988)	≥ 20	2.8	(1.9–4.1)
Liu *et al.* (1993)	≥ 20	2.9	(1.2–7.3)
Pershagen *et al.* (1987)	≥ 16[e]	3.2	(1.0–9.5)
Inoue & Hirayama (1988)	≥ 20	3.4	(1.2–9.7)
	No. of years of marriage to a smoker		
Buffler *et al*. (1984)	≥ 33	0.9	(0.4–2.3)
Sun *et al*. (1996)	≥ 35	0.9	(0.5–1.7)
Boffetta *et al.* (1998)	≥ 43	1.0	(0.7–1.7)
Cardenas *et al.* (1997)	≥ 30	1.1	(0.6–2.1)
Wang *et al*. (1996)	≥ 41	1.1	(0.4–3.1)
Zhong *et al*. (1999)	≥ 36	1.1	(0.7–1.8)
Du *et al.* (1993)	≥ 30	1.2	(0.6–2.3)
Fontham *et al.* (1994)	≥ 31	1.2	(0.9–1.7)
Akiba *et al.* (1986)[d]	≥ 40	1.3	(0.6–2.8)
Zaridze *et al.* (1998)	> 15	1.4	(1.0–2.1)
Gao *et al.* (1987)	≥ 40	1.7	(1.0–2.9)
Kalandidi *et al.* (1990)	≥ 40	1.9	(0.8–4.3)
Wu *et al.* (1985)	≥ 31[f]	2.0	NA[g]
Humble *et al.* (1987)	≥ 27	2.1	(0.7–6.9)

Table 2.4 (contd)

Reference	Exposure level	Relative risk[a] (95% CI)	
Choi *et al.* (1989)	≥ 41	2.3	(1.0–5.6)
Stockwell *et al.* (1992)	≥ 40	2.4	(1.1–5.3)
Jee *et al*. (1999)	≥ 30	3.1	(1.4–6.6)
Geng *et al.* (1988)	≥ 40	3.3	(2.1–5.2)
	No. of pack–years of exposure[h]		
Rapiti *et al*. (1999)	> 128	0.4	(0.1–1.8)
Kreuzer *et al*. (2000)[i]	> 23	0.8	(0.2–3.1)
Brownson *et al.* (1992)	≥ 40	1.3	(1.0–1.7)
Boffetta *et al.* (1998)	≥ 23	1.5	(1.0–2.4)
Cardenas *et al.* (1997)	≥ 36	1.5	(0.8–2.6)
Fontham *et al.* (1994)	≥ 80	1.8	(1.0–3.3)
Lee *et al*. (2000)	> 40	3.3	(1.7–6.2)
Correa *et al.* (1983)	≥ 41	3.5	[1.2–10.2][j]

[a] Rate ratios for cohort studies (Garfinkel (1981), Hirayama (1984), Cardenas (1997) & Jee (1999)); odds ratios for case–control studies (all the other studies); adjusted relative risk, where not available crude relative risk

[b] Results are from an analysis using non-tumour controls. The paper also presents results using controls with tumours of sites other than lung (odds ratio, 1.4; 95% CI, 0.7–2.5).

[c] The results are from Table 2 of Hirayama (1984), which were adjusted by the wife's age.

[d] The report presented 90% CIs; 95% CIs were estimated for this table.

[e] For ≥ 30 years of marriage

[f] Years of exposure for adults (from partner and at workplace)

[g] Not available or estimatable from data presented in the paper

[h] Pack–years = number of packs of cigarettes smoked daily by the partner × years of smoking

[i] Some of the cases and controls reported on in Kreuzer *et al*. (2000) were part of another study included in this table (Boffetta *et al*., 1998). The results given here for the study by Kreuzer are based on those cases and controls that were not part of the study by Boffetta (personal communication M. Kreuzer).

[j] Confidence intervals in brackets were not given in the original report and were estimated for this table using an approximate method.

1987; Geng *et al.*, 1988; Stockwell *et al.*, 1992; Fontham *et al.*, 1994; Cardenas *et al.*, 1997; Jee *et al.*, 1999) and the results of two others were almost significant (Kalandidi *et al.*, 1990; Zaridze *et al.*, 1998; p value = 0.07 in both).

Table 2.4 shows the increase in risk in nonsmoking women who have the highest level of exposure according to each measure. All 20 of the studies that reported on the number of cigarettes smoked showed an increased risk in the highest exposure group, and seven of the studies reported a doubling of risk or more. Similarly, of the 18 studies that looked

at the number of years of marriage to a smoker, all but three showed an increased risk in the highest exposure group; six reported a relative risk of at least 2.0.

In summary, there is evidence of an exposure–response relationship, thus providing further support for a causal relationship between the development of lung cancer and exposure to secondhand smoke from partners.

(*c*) *Exposure to secondhand smoke at the workplace*

In total, 23 studies have been published on exposure to secondhand smoke at the workplace (Table 2.5). The results from these studies are mixed with some showing a positive association and others not. Only one study reported a statistically significant association between exposure to secondhand smoke at the workplace and risk for lung cancer (Reynolds *et al*., 1996). Many of the studies assessed only recent workplace exposure to secondhand smoke; this is likely to result in a serious misclassification of exposure because past exposure is more likely to be etiologically relevant.

Exposure–response relationships

Two studies found no statistically significant exposure–response relationship (Kalandidi *et al.*, 1990; Kabat *et al.*, 1995).

In the study by Reynolds *et al*. (1996) in the USA, the risk for lung cancer in women who were exposed to secondhand smoke at work was significantly increased to 1.6 (95% CI, 1.2–2.0). For women who had been exposed to secondhand smoke for 1–15, 16–30 or > 30 years, the relative risk for developing lung cancer increased significantly ($p < 0.001$) with the length of the exposure period: 1.5 (95% CI, 1.1–1.9), 1.6 (95% CI, 1.1–2.2) and 2.1 (95% CI, 1.4–3.2), respectively.

In the European multicentre study (Boffetta *et al.* 1998), the relative risk for lung cancer after exposure to secondhand smoke at work was 1.2 (95% CI, 0.9–1.5). No exposure–response relationship was seen when the data were analysed according to duration of exposure but a significant trend was observed after analysis of weighted exposure, which is most likely a better index of exposure than duration. A significant relative risk of 2.1 (95% CI, 1.3–3.2) was observed in the group with the highest weighted exposure.

Two studies from Germany which are included in part in Boffetta *et al.* (1998) also showed an increased risk in the highest exposure group of 1.9 (95% CI, 1.1–3.6) and 2.5 (women only, 95% CI, 1.1–5.7) (Jöckel *et al*., 1998b; Kreuzer *et al*., 2000).

The study of Rapiti *et al*. (1999) reported increasing relative risks with increasing duration of exposure, but the trend did not reach statistical significance.

In the study of Zhong *et al*. (1999), women ever exposed to secondhand smoke at work showed an odds ratio of 1.7 (95% CI, 1.3–2.3). There was a statistically significant ($p < 0.001$) increase in risk associated with the number of hours of exposure per day at work with odds ratios of 1.0 (95% CI, 0.6–1.7), 1.6 (95% CI, 1.0–2.5) and 2.9 (95% CI, 1.8–4.7) for 1–2, 3–4 and > 4 h per day. When the number of co-workers who smoked was considered there was again a statistically significant trend ($p < 0.001$) with odds ratios of 1.0 (95% CI, 0.6–1.6), 1.7 (95% CI, 1.1–2.8) and 3.0 (95% CI, 1.8–4.9) for 1–2,

Table 2.5. The relative risk for lung cancer in nonsmokers exposed to secondhand smoke at the workplace compared with nonsmokers who were not

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk for lung cancer (95% CI) if exposed at the workplace	
			Crude analysis	Adjusted analysis
Kabat *et al*. (1984)	Men	25	3.3 [1.0–10.6]	NR
	Women	53	0.7 [0.3–1.5]	NR
Koo *et al*. (1984)	Women	88	1.2 [0.5–3.0]	NR
Garfinkel *et al*. (1985)	Women	76	NR	0.9 (0.7–1.2)[a]
Wu *et al*. (1985)	Women	29	NR	1.3 (0.5–3.3)[b]
Lee *et al*. (1986)	Men	10	1.6 [0.4–6.6]	NR
	Women	15	0.6 [0.2–2.3]	NR
Butler (1988)	Men	6	NR	1.0 [0.2–5.4]
	Women	7	NR	0.98 [0.2–5.4]
Shimizu *et al*. (1988)	Women	90	1.2 [0.6–2.6][c]	NR
Kalandidi *et al*. (1990)	Women	89	1.4 [0.8–2.5]	NR
Wu-Williams *et al*. (1990)	Women	415	1.2 [1.0–1.6]	1.2 (0.9–1.6)
Kabat *et al*. (1995)	Men	41	NR	1.0 (0.5–2.1)
	Women	58	NR	1.2 (0.6–2.1)
Reynolds *et al.* (1996)	Women	528	1.4 [1.1–1.7]	1.6 (1.2–2.0)
Schwartz *et al*. (1996)	Men + women	257	NR	1.5 (1.0–2.2)
Sun *et al*. (1996)	Women	230	NR	1.4 (0.9–2.0)
Wang *et al*. (1996)	Women	135	0.9 (0.5–1.8)	NR
Boffetta *et al*. (1998)	Men + women	650	1.1 [0.9–1.3]	1.2 (0.9–1.5)
	Men	141	1.2 [0.8–1.8]	NR
	Women	509	1.3 [1.0–1.6]	1.2 (0.9–1.5)
Zaridze *et al*. (1998)	Women	189	1.0 [0.7–1.6]	0.9 (0.6–1.4)
Boffetta *et al.* (1999a)	Men + women	70	1.2 (0.7–2.1)	1.0 (0.5–1.8)
Rapiti *et al*. (1999)	Men + women	58	NR	1.1 (0.3–4.1)[d]
Zhong *et al*. (1999)	Women	504	1.4 [1.0–1.8]	1.7 (1.3–2.3)
Kreuzer *et al*. (2000)[e]	Men + women	123	0.7 [0.5–1.0]	1.1 (0.7–1.7)
	Men	23	0.5 [0.2–1.3]	NR
	Women	100	1.1 [0.7–1.7]	1.4 (0.8–2.2)
Lee *et al*. (2000)	Women	268	1.2 [0.7–1.9]	0.9 [0.5–1.7]
Wang *et al*. (2000)	Men + women	233	NR	1.6 (0.7–3.3)
Johnson *et al*. (2001)	Women	71	1.2 [0.7–2.0]	NR

NR, not reported

[a] Results shown are for exposure over the preceding 25 years

[b] Results are for adenocarcinoma. There were too few cases in this study to permit an analysis for squamous-cell carcinoma or other histological types.

[c] The 95% CI was not reported. It was estimated using the average standard error taken from Kalandidi *et al*. (1990) and Nyberg *et al*. (1998), because all three studies included similar numbers of cases of lung cancer.

[d] The reported result was 1.1 (95% CI, 0.9–1.6); the authors reported the correct estimates in Wells *et al*. (1998).

[e] Some of the cases and controls in the study by Kreuzer *et al*. (2000) were also part of another study included in this table (Boffetta *et al*., 1998). The results given here are based on those cases and controls that were not part of the study by Boffetta *et al.* [personal communication M. Kreuzer].

3–4 and > 4 co-workers who smoked, whereas there was no increase in relative risk with increasing numbers of years of exposure to secondhand smoke. Risk estimates were not affected when analyses were restricted to personal interviews excluding proxy interviews.

In summary, the studies in which exposure–response relationships were analysed generally revealed an increase in the relative risk for lung cancer associated with exposure to secondhand smoke at work and statistically significant increases in relative risk in those groups with the highest level of exposure. The associations are stronger in studies with better assessment of exposure and other aspects of study design.

(*d*) *Exposure during childhood*

The studies on exposure to secondhand smoke during childhood are summarized in Table 2.6. The results of these studies have been somewhat contradictory. Out of 23 studies, only three studies of exposure from the mother reported a significantly increased relative risk (Brownson *et al*., 1992; Sun *et al*., 1996; Rapiti *et al*., 1999) and two studies reported a significant increase in relative risk related to exposure from the father or either parent (Sun *et al*., 1996; Rapiti *et al*., 1999). One study found a significant inverse association with exposure from the father or either parent (Boffetta *et al*., 1998).

Exposure–response relationships

The study of Wang *et al*. (2000) observed a significant trend ($p < 0.01$) with increasing pack–years of childhood exposure to secondhand smoke with odds ratios for men and women combined of 1.0, 1.4 (95% CI, 1.0–2.1), 1.8 (95% CI, 1.0–3.3) and 3.0 (95% CI, 1.0–8.9) for < 1, 1–9, 10–19 and ≥ 20 pack–years. In contrast, the study of Boffetta *et al*. (1998) suggested a negative trend for cumulative exposure, which was statitistically significant for all subjects combined ($p = 0.02$).

In summary, there is no clear indication that lung cancer risk in later life is associated with exposure to secondhand smoke in childhood. However, an important problem in interpreting these studies is the very poor quality of the assessment of exposure that occurred 50 or more years in the past.

(*e*) *Exposure from other sources*

Few studies have addressed exposure to secondhand smoke from other sources. Kreuzer *et al*. (2000) reported a significantly increased relative risk of 2.6 (95% CI, 1.3–5.4) for exposure in vehicles in the highest category of weighted duration of exposure.

Other studies have either not addressed these other sources of exposure or have considered them only as part of a cumulative exposure from all sources.

In summary, insufficient data are available to evaluate the risk from exposure to secondhand smoke from other sources.

Table 2.6. The relative risk[a] for lung cancer in nonsmokers exposed to second-hand smoke during childhood compared with that in nonsmokers who were not

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk (95% CI) for lung cancer according to exposure during childhood		
			Mother	Father	Either parent
Garfinkel *et al*. (1985)	Women	134	NR	NR	0.9 (0.7–1.1)
Wu *et al*. (1985)	Women	29	NR	NR	0.6 (0.2–1.7)
Koo *et al*. (1987)	Women	88	NR	NR	0.6 [0.2–1.8]
Pershagen *et al*. (1987)	Women	47	NR	NR	1.0 (0.4–2.3)
Shimizu *et al*. (1988)	Women	90	4.0 [1.0–15.7][b]	1.1 [0.6–2.0][b]	NR
Svensson *et al*. (1989)	Women	34	3.1 [0.7–14.0]	0.9 [0.4–1.9]	NR
Janerich *et al*. (1990)	Men + women	191	NR	NR	1.3 [0.9–2.0]
Sobue (1990)	Women	144	1.4 [0.8–2.5]	0.8 [0.5–1.2]	NR
Wu-Williams *et al*. (1990)	Women	417	0.9 (0.7–1.1)	1.1 (0.8–1.4)	NR
Brownson *et al*. (1992)	Women	431	NR	NR	0.6 [0.5–0.8]
Stockwell *et al*. (1992)	Women	210	1.6 (0.6–4.3)	1.2 (0.6–2.3)	NR
Fontham *et al*. (1994)	Women	651	0.9 (0.7–1.2)	0.9 (0.7–1.0)	NR
Kabat *et al*. (1995)	Men	40	NR	NR	0.9 (0.4–1.9)
	Women	69	NR	NR	1.6 (0.95–2.8)
Sun *et al*. (1996)	Women	230	2.1 (1.3–3.3)	2.4 (1.6–3.5)	2.3 (1.6–3.4)
Wang *et al*. (1996)	Women	135	NR	NR	0.9 (0.6–1.5)
Zaridze *et al*. (1998)	Women	189	NR	1.0 [0.7–1.4]	NR
Boffetta *et al*. (1998)	Men + women	641	0.9 (0.6–1.5)	0.8 (0.6–0.9)	0.8 [0.6–0.9]
	Men	140	NR	NR	0.7 [0.5–1.1]
	Women	501	NR	NR	0.7 [0.6–0.9]

Table 2.6 (contd)

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk (95% CI) for lung cancer according to exposure during childhood		
			Mother	Father	Either parent
Boffetta *et al.* (1999a)	Men + women	67	0.3 (0.1–1.1)	0.6 (0.3–1.0)	0.5 (0.3–0.9)
Rapiti *et al.* (1999)	Men + women	58	5.7 [1.3–25.6]	4.5 [2.3–8.8]	3.6 [1.8–6.9]
	Men	17	–[c]	0.2 [0.0–1.7]	0.2 [0.0–1.5]
	Women	41	7.7 [1.6–37.2]	12.6 [4.9–32.7]	8.7 [3.6–21.2]
Zhong *et al.* (1999)	Women	504	NR	NR	1.0 [0.8–1.3]
Kreuzer *et al.* (2000)[d]	Men + women	123	NR	NR	1.0 [0.7–1.5]
	Men	23	NR	NR	0.97 [0.4–2.3]
	Women	100	NR	NR	0.9 [0.5–1.4]
Lee *et al.* (2000)[e]	Women	268	1.5 [0.6–3.9]	1.2 [0.9–1.6]	NR
Wang *et al.* (2000)	Men + women	228	NR	NR	1.4 [1.0–2.0]
	Men	32	NR	NR	1.7 [0.8–3.9]
	Women	196	NR	NR	1.3 [0.9–1.9]
Johnson *et al.* (2001)	Women	71	NR	NR	1.3 [0.8–2.2]

NR, not reported

[a] The crude results are given in the table and where these were not available, the adjusted ones are given.

[b] Only the p value was reported ($p < 0.05$ mother; $p > 0.05$ father); the standard error used to estimate the 95% CI was taken to be the same as in Nyberg *et al*. (1998) because both studies have a similar number of cases.

[c] There were no exposed cases and controls, and thus the odds ratio is undefined.

[d] Results from an analysis that excluded cases and controls that were included in Boffetta *et al*. (1998)

[e] The adjusted results are for children whose parents smoked in their presence whereas the crude results are for having a parent who was a smoker which is consistent with the definition used in the other studies.

(*f*) *Bias and confounding*

There are two sources of bias (misclassification bias and bias resulting from exposure to secondhand smoke in the reference group) and several potential confounders (e.g. dietary confounding) that can result in the relative risk being overestimated or underestimated in the studies of the association between lung cancer and exposure to secondhand smoke described above.

(i) *Misclassification bias*

Misclassification bias occurs when some of the subjects recorded as never-smokers who are included in the studies are in fact current or former smokers who have misreported their smoking status. Their true smoking status makes these subjects more likely to develop lung cancer and because smokers tend to live with smokers, this bias will overestimate the true risk for lung cancer from exposure to secondhand smoke from the spouse. There has been much discussion in the literature on this bias, and it is the main factor proposed as partly or fully explaining the increased risk for lung cancer observed in epidemiological studies. The bias has four determinants:

- *The prevalence of smoking in a particular population*. This can be obtained directly from some of the studies or from national statistics.
- *The aggregation ratio (the extent to which a smoker is more likely to live with another smoker rather than a nonsmoker)*. It is generally accepted to be between 2 and 4 (Wald *et al*., 1986; US Environmental Protection Agency, 1992; Lee, 1992; Hackshaw *et al*., 1997).
- *The relative risk for lung cancer in current and former smokers misclassified as never-smokers*. Some meta-analyses have assumed that the risk for lung cancer in misclassified smokers is the same as that in all reported smokers (US Environmental Protection Agency, 1992; Lee, 1992, 1998). However, misclassified current smokers tend to be light smokers and misclassified former smokers have usually given up smoking many years before the study, so the risk in both groups will be less than the average risk in all current or former smokers. The overall relative risk for lung cancer in misclassified ever smokers has been estimated to be about 3 (Hackshaw *et al*., 1997).
- *The percentage of current and former smokers misclassified as never-smokers*. The percentage of misclassified current smokers can be estimated by comparing self-reported smoking status with serum, urine or salivary cotinine levels; current smokers who report themselves to be never-smokers would tend to have high concentrations (for example, a urinary cotinine concentration > 50 ng/mg creatinine). Wells *et al*. (1998) combined the results of 13 studies, seven of which were used in the US Environmental Protection Agency (1992) report, and concluded that the rates of misclassification of smokers are low; 1.6% of Caucasian women who were current smokers reported themselves as never-smokers. The estimate was higher, though still low, for women from a minority background (4.9%). Similar conclusions had been drawn from a review of six studies on cotinine and nicotine (two of which were included in the review by Wells *et al*., 1998) in which it was estimated that 3.1% of ever smokers were current smokers who reported themselves as never-smokers (Hackshaw *et al*., 1997). Two of the case–control studies on secondhand smoke and risk of lung cancer in female never-smokers (Table 2.2) measured urinary cotinine in the subjects and compared this with their reported smoking status. The percentage of reported never-smoking women with urinary cotinine concentrations > 50 ng/mg creatinine was 3.5% in the study by

Riboli *et al*. (1995) (included in Boffetta *et al.*, 1998 in Table 2.2) and 3.1% of patients with lung cancer and 5.0% of controls in the study by Fontham *et al*. (1994).

(ii) *Bias resulting from exposure to secondhand smoke in the reference group*

Studies of the risk for lung cancer and exposure to secondhand smoke have defined the reference group as never-smoking women with husbands who are nonsmokers. However, these women, although not exposed at home, may be exposed to secondhand smoke outside the home. This bias will tend to underestimate the true relative risk.

(iii) *Dietary confounding*

Several potential confounders have been proposed that may partly or fully explain the increased risk of lung cancer associated with exposure to secondhand smoke from the spouse. None of these potential confounders have been established as having a causal link with lung cancer. For example, dietary confounding (perhaps the main potential confounder) may arise because (i) nonsmokers who live with smokers tend to have similar diets, (ii) the diets of smokers tend to be poorer than those of nonsmokers (i.e. lower consumption of fruits and vegetables) and (iii) people who consume less fruits and vegetables may be more likely to develop lung cancer. Several of the observational studies listed in Table 2.2 had attempted to adjust for consumption of fruits and vegetables or other dietary factors (Dalager *et al.*, 1986 [used data from Correa *et al.* (1983) and Buffler *et al.* (1984) in Table 2.2]; Hirayama, 1989 [used data from Hirayama (1984)]; Kalandidi *et al.*, 1990; Alavanja *et al*., 1993 [used data from Brownson *et al.* (1992)]; Fontham *et al*., 1994; Mayne *et al.*, 1994 [used data from Janerich *et al.* (1990)]; Cardenas *et al.*, 1997; Boffetta *et al.*, 1998; Zhong *et al.*, 1999; Brennan *et al*., 2000; Johnson *et al.*, 2001); they showed that the effect of dietary confounding was negligible.

2.1.3 *Meta-analyses of observational studies of exposure to secondhand smoke and lung cancer in adults*

(*a*) *Introduction*

Since the publication of the first epidemiological studies that reported directly on the association between exposure to secondhand smoke and the risk of lung cancer in nonsmokers (Garfinkel, 1981; Hirayama, 1981), there have been several other cohort studies and case–control studies. Most of these studies were based on a relatively small number of lung cancer cases and did not, therefore, have enough power to show a statistically significant association on their own. Meta-analyses have therefore been performed with the aim of pooling the available data and thus providing a more precise estimate of the risk. A meta-analysis is a formal statistical technique used to combine the estimates of relative risk across studies into a single estimate. Originally developed for clinical trials, it has also been applied to observational studies (see Peto, 1992, for a brief

discussion of some aspects of meta-analyses of case–control and cohort studies on cancer). In spite of some concerns over the application of meta-analysis to studies of secondhand smoke and lung cancer, it is an appropriate approach for interpreting the published data collectively.

(*b*) *Published meta-analyses*

This section presents the results of selected published reports.

(i) *Exposure to secondhand smoke from the spouse*

Table 2.7 shows the main results of published meta-analyses on the risk for lung cancer in never-smokers associated with exposure to secondhand smoke from the spouse, including an indication of whether any adjustment was made for bias and confounding. All the pooled estimates show an increased risk (relative risks of 1.1–1.6), despite using different combinations of studies and methodology.

Some meta-analyses adjusted for the misclassification of ever-smokers as never-smokers (which will tend to overestimate risk). For example, in the analysis by Hackshaw *et al.* (1997) the relative risk was reduced from 1.24 to 1.18 after allowing for misclassification bias in 37 studies of nonsmoking women. In the analysis by Lee *et al.* (2001), which was based on 47 studies and used a different methodology, after allowing for misclassification bias the relative risk was reduced from 1.23 to 1.17. The effect is small.

Few meta-analyses have adjusted for background exposure to secondhand smoke from sources other than the spouse in the reference group (which will tend to underestimate risk). Hackshaw *et al.* (1997) reported that the effect of such an adjustment was to increase the observed relative risk from 1.24 to 1.42.

Few reviews have attempted to adjust for diet as a potential confounder. Hackshaw *et al*. (1997) used pooled data from nine studies of the risk of lung cancer associated with fruit and vegetable consumption in nonsmokers and pooled data from three studies on the difference in diet between nonsmokers who did and did not live with a smoker; the relative risk for lung cancer due to exposure to secondhand smoke from the spouse was reduced from 1.24 (as observed) to 1.21 after adjusting for fruit and vegetable consumption. A similarly small effect was reported by Lee *et al.* (2001), after adjusting for consumption of dietary fat and education as well as consumption of fruits and vegetables, and using different methodology and a larger set of studies (for the risk of lung cancer associated with each confounder: 17 studies on consumption of fruits and vegetables, seven on dietary fat and 12 on education; for the difference between nonsmokers who do and do not live with a smoker: nine studies on consumption of fruits and vegetables, seven on dietary fat and nine on education). The relative risk for lung cancer when the husband smoked 10 cigarettes/day was reduced from 1.10 (observed) to 1.09, after allowing for these three confounders (Lee *et al.*, 2001). In both analyses the effect of allowing for confounding was small.

Table 2.7. Summary results of selected published meta-analyses of the risk for lung cancer in never-smokers exposed to secondhand smoke from the spouse

Reference	No. of studies	Sex of subjects	Pooled relative risk (95% CI)	Pooled estimate adjusted for			Adjusted pooled relative risk
				Misclassification bias	Exposure to secondhand smoke other than from the spouse	Dietary confounding	
National Research Council (1986)	13	Men and women	1.34 (1.18–1.53)	Yes	Yes	No	1.42
	13	Women	1.32 (1.16–1.53)	No	No	No	
Wald *et al*. (1986)	13	Men and women	1.35 (1.19–1.54)	Yes	Yes	No	1.53
Fleiss & Gross (1991)	9 (USA only)	Women	1.12 (0.95–1.30)	No	No	No	
Lee (1992)	28	Men and women	1.20 (1.09–1.31)	No	No	No	
	28	Women	1.18 (1.07–1.30)	No	No	No	
	11	Men	1.39 (0.97–1.99)	No	No	No	
Tweedie & Mengersen (1992)	26	Women	1.17 (1.06–1.28)	Yes	Yes	No	1.08
US Environmental Protection Agency (1992)	11 (USA only)	Women	1.19 (1.04–1.35)	Yes	Yes	No	1.59
Hackshaw (1998)	37	Women	1.24 (1.13–1.36)	Yes	Yes	Yes	1.26
	9	Men	1.34 (0.97–1.84)	No	No	No	
Zhong *et al*. (2000)	40	Women	1.20 (1.12–1.29)	No	No	No	
Lee *et al.* (2001)	47	Women	1.23 (1.12–1.36)	Yes	No	No	1.17
Boffetta *et al*. (2002)	45	Women	1.25 (1.14–1.38)	No	No	No	
	9	Men	1.25 (0.95–1.65)				

Generally, the overestimation due to misclassification bias and potential confounding seems to be balanced by the underestimation due to exposure to secondhand smoke in the reference group (Hackshaw *et al.*, 1997).

(ii) *Exposure at the workplace*

Interest in the risk of lung cancer associated with exposure to secondhand smoke at work has increased over the years and several meta-analyses have been published. These are listed in Table 2.8; some report no association, for example, Lee (1992) and Levois and Layard (1994), whereas others do report an association (Biggerstaff *et al.*, 1994; Wells, 1998; Zhong *et al*., 2000). However, the results of some of the studies may be unreliable because they used levels of exposure reported by next of kin (who may not know the true exposure status of the case or control), and because some studies evaluated only recent exposure to secondhand smoke in the workplace. Wells *et al*. (1998) excluded studies that documented only recent exposure and also studies that (i) included more than 50% surrogate responses for cases, (ii) had only minimal exposure, (iii) included exposure to other respiratory carcinogens, (iv) included subjects who had smoked, and (v) did not report appropriate data to allow the confidence intervals to be checked. Based on these criteria, Wells *et al*. (1998) identified the following studies for inclusion in their meta-analysis: Wu *et al*. (1985), Shimizu *et al*. (1988), Kalandidi *et al*. (1990), Kabat *et al*. (1995) and Reynolds *et al*. (1996); the pooled risk estimate was 1.4 (1.2–1.7). Overall, there seems to be an increased risk of lung cancer in subjects exposed to secondhand smoke at the workplace.

Table 2.8. Summary of results from published meta-analyses of exposure to secondhand smoke and lung cancer in never-smokers exposed at the workplace

Reference	No. of studies included	Sex	Pooled relative risk (95% CI)
Lee (1992)	9	Men and women	0.98 (0.84–1.08)
Biggerstaff *et al*. (1994)	8	Women	1.12 (0.93–1.34)
Levois & Layard (1994)	14	Men and women	1.01 (0.92–1.11)
Chappell & Gratt (1996)	8	Men and women	0.99 (0.91–1.08)
Wells *et al*. (1998)	5[a]	Men and women	1.39 (1.15–1.68)
Zhong *et al*. (2000)	14	Men and women	1.16 (1.05–1.28)

[a] Restricted to studies that were based on self-reported exposure

(iii) *Exposure during childhood*

There have been few meta-analyses on the risk of lung cancer in adulthood following exposure to secondhand smoke during childhood; the results of three of these meta-analyses are given in Table 2.9. None suggested an association, although no stratification

Table 2.9. Results from published meta-analyses of exposure to secondhand smoke and lung cancer in adult never-smokers exposed during childhood

Reference	No. of studies included	Sex	Pooled relative risk (95% CI)
Lee *et al*. (1992)	10	Men and women	0.98 (0.86–1.12)
Boffetta *et al*. (2000)	11	Men and women	
		Men and women	0.91 (0.80–1.05)
		From father	0.83 (0.72–0.95)
		From mother	0.99 (0.78–1.26)
Zhong *et al*. (2000)	18	Men and women	0.91 (0.83–1.00)

according to gender or exposure from the mother or father was carried out. Overall, published meta-analyses have found no evidence for an increased risk for lung cancer associated with childhood exposure to secondhand smoke.

(iv) *Statistical methods and other considerations*

Pooling relative risks

Different methods of combining relative risk estimates from individual studies have generally tended to give similar results. For example, in 37 studies of the risk for lung cancer of never-smoking women exposed or unexposed to secondhand smoke from the spouse, the relative risks (95% CI) using the fixed or random effects model were 1.21 (1.12–1.30) and 1.24 (1.13–1.36), respectively (Hackshaw *et al*., 1997) (the random effects model allows for heterogeneity between the risk estimates).

More complex approaches, such as Bayesian analysis, also do not yield materially different results. The difference between the pooled estimates obtained using a Bayesian model and those obtained using a simpler random effects model was small. Tweedie *et al.* (1996) pooled 40 studies of male or female never-smokers exposed to secondhand smoke from the spouse, the pooled relative risk for lung cancer was 1.20 (95% CI, 1.07–1.34) using the random effects model and 1.22 (95% CI, 1.08–1.37) using a Bayesian model (Tweedie *et al*., 1996).

Pooling results relating to exposure–response relationships

Several studies on the effects of exposure to secondhand smoke in never-smokers have reported the relative risk for lung cancer according to the number of cigarettes smoked by the spouse or the number of years that the nonsmoker has lived with a spouse who smokes. A few researchers, using various combinations of studies and methodology, have attempted to pool the results of epidemiological studies of exposure–response in never-smoking women. For an increase of 10 cigarettes per day smoked by the husband, the excess relative risk for lung cancer compared with never-smoking husbands was esti-

mated to be 23% (95% CI, 14–32) by Hackshaw *et al*. (1997), 17% (95% CI, 12–22) by Brown (1999) and 10% (95% CI, 5–15) by Lee *et al.* (2000). The excess relative risk that resulted from living for 10 years with a husband who smokes compared with one who does not was estimated to be 11% (95% CI, 4–17) by Hackshaw *et al*. (1997) and 7% (95% CI, 4–11) by Lee *et al.* (2000). The estimates are reasonably consistent between different reports and all found a statistically significant increase in risk associated with increasing exposure.

Heterogeneity between the estimates of relative risk

Performing a meta-analysis when there are statistically significant differences between the estimates of relative risk may yield an incorrect pooled estimate. If heterogeneity exists, an attempt should be made to explain it. If it can be explained by a single factor (or factors), then estimates should be stratified according to that factor. The authors of several reviews of the association between exposure to secondhand smoke and lung cancer have allowed for the existence of heterogeneity between geographical regions or found evidence of it and therefore stratified the relative risk estimates according to region (for example, US Environmental Protection Agency, 1992; Lee, 1998). Lee (1998) assessed heterogeneity related to several factors including geographical region, study publication date, study type and study size and concluded that there were statistically significant differences between the relative risk estimates by almost all factors. However, this was shown to be due to a single large discrepant study that unduly influenced the assessment of heterogeneity; this may be a problem especially when there are relatively few studies in the meta-analysis. In the meta-analysis by Hackshaw *et al*. (1997), the test for heterogeneity based on 37 studies on nonsmoking women was almost significant (p = 0.10), although when one study was excluded the p value became 0.46. The discrepant study, from China, was large (417 cases of lung cancer) and reported an almost statistically significant *reduction* in the risk of lung cancer associated with exposure to secondhand smoke from the spouse (relative risk, 0.8; 95% CI, 0.6–1.0), making its results inconsistent with those of the other studies. When this study was excluded, no evidence of heterogeneity was found for several factors (Hackshaw *et al*., 1997; Hackshaw, 1998; Zhong *et al*., 2000).

Publication bias

In meta-analyses of studies of the relationship between secondhand smoke and lung cancer there is a possibility of publication bias if studies with positive results (those that show an increased risk of lung cancer) are more likely to be published than studies with negative ones (those that show a decreased risk or no difference in risk). The pooled estimate of risk would then be biased upwards. Simple methods to ascertain whether much publication bias exists suggest that there is little evidence of this, for example funnel plots (Lubin, 1999) or estimating the number of negative unpublished studies that would be required to explain the increased risk observed from epidemiological studies — about 300 (Hackshaw *et al*., 1997; Lee, 1998); it is implausible that there would be so many

unpublished negative studies. Copas and Shi (2000) used a complex method to adjust the observed relative risk for lung cancer (reported in Hackshaw *et al*., 1997) for publication bias; the pooled estimate was reduced from 1.24 to 1.15, but Copas and Shi assumed that 40% of all studies are unpublished. Even with such an extreme assumption, the adjusted estimate is consistent with the reported relative risk adjusted for bias and confounding (1.26; 95% CI, 1.06–1.47). The problem with assessing publication bias is that it is difficult to determine empirically how many studies are unpublished (Bero *et al*., 1994).

(*c*) *Updated meta-analyses*

Several individual studies on secondhand smoke and the risk of lung cancer in nonsmokers have been published since one of the last detailed meta-analyses on the subject (Hackshaw *et al*., 1997). This section presents updated meta-analyses using currently available results. The selection of studies to be included is as described by Hackshaw *et al*. (1997), and the method of pooling the relative risk estimates is that described by Dersimonian and Laird (1986), which allows for any heterogeneity between the estimates. Some case–control studies reported only crude estimates of relative risk, some reported only adjusted estimates (adjusted for various factors such as age and diet) and others reported both crude and adjusted estimates. Consideration therefore needed to be given to which should be used in the meta-analyses. Pooled estimates were obtained based on the crude relative risks and, where these were not available, the adjusted relative risks. This reduces the effect of those studies that adjusted for factors that are not established confounders. The pooled estimate was also obtained based on the adjusted relative risks, and where these were not available, the crude relative risks to show that the two approaches yielded similar results.

Table 2.10 shows the results of the updated meta-analyses according to type of exposure to secondhand smoke and gender of the subject (for the estimates from the individual studies, see Tables 2.2, 2.5 and 2.6).

(i) *Exposure from the spouse*

Among nonsmoking women who lived with a spouse who smoked, the risk of lung cancer was increased by 24% (relative risk, 1.24; 95% CI, 1.14–1.3; Table 2.10). This estimate was based on the crude estimates of relative risk found in the studies and, where these were not available, the adjusted estimates. Use of the adjusted estimates and, where these were not available, the crude estimates yielded a similar relative risk of 1.27 (95% CI, 1.15–1.41). The studies came from several countries, and the test for heterogeneity between the relative risk estimates across all 46 studies just misses statistical significance (p value = 0.08). However, if the discrepant study from China by Wu-Williams *et al*. (1990) that reported an almost statistically significant decrease in risk due to exposure to secondhand smoke is excluded, the pooled relative risk is not materially changed (1.25; 95% CI, 1.17–1.33), but the test for heterogeneity yields a p value of 0.34. Among nonsmoking men who lived with a smoker, the risk of lung cancer was increased by 37%. The risk estimates for both nonsmoking men and women are statistically significant.

Table 2.10. Summary of the updated meta-analyses of the relative risk for lung cancer in never-smokers exposed to specified sources of secondhand smoke

Source of exposure	No. of studies (total no. of lung cancer cases)	Sex of subject	Pooled relative risk (95% CI)[a]	*p* value	Evidence of significant heterogeneity between the studies
Spouse	46 (6257)	Women	1.24 (1.14–1.34)	< 0.001	No, $p = 0.08$[b]
	11 (442)	Men	1.37 (1.02–1.83)	0.03	No, $p = 0.80$
Workplace	19 (3588)	Women	1.19 (1.09–1.30)	< 0.001	No, $p = 0.87$
	6 (246)	Men	1.12 (0.80–1.56)	0.51	No, $p = 0.38$
	7 (1582)	Women and men combined	1.03 (0.86–1.23)	0.74	No, $p = 0.10$
Childhood					
Mother	9 (2085)	Women	1.50 (1.04–2.14)	0.03	Yes, $p = 0.004$
Father	10 (2274)		1.25 (0.94–1.68)	0.13	Yes, $p < 0.001$
Either parent	14 (2576)		1.11 (0.87–1.42)	0.41	Yes, $p < 0.001$
Either parent	5 (252)	Men	0.86 (0.62–1.20)	0.38	No, $p = 0.35$
Either parent	6 (1306)	Women and men combined	1.14 (0.77–1.70)	0.51	Yes, $p < 0.001$

[a] Based on the crude relative risks from the individual reports and where these were not available, the adjusted estimates

[b] When the study by Wu-Williams *et al*. (1990) from China is excluded (it reported an almost statistically significant decrease in risk for lung cancer associated with exposure to secondhand smoke), the pooled relative risk is similar 1.25 (1.17–1.33), but the test for heterogeneity yields a *p* value of 0.34.

(ii) *Exposure at the workplace*

The increase in risk for lung cancer in nonsmoking women is about 20% (relative risk, 1.19; 95% CI, 1.09–1.30; Table 2.10). If the pooled estimate was based on the adjusted relative risks reported in the studies and, where these were not available, the crude estimates, the result was similar (relative risk, 1.21; 95% CI, 1.09–1.35). There was also an increase in risk in men (12%) though this result was not statistically significant (probably because of the smaller number of studies and fewer cases of lung cancer in the meta-analysis). There was no evidence of heterogeneity between the individual risk estimates.

(iii) *Exposure during childhood*

There is a statistically significant increase in risk among women exposed to secondhand smoke from the mother during childhood (50% increase in risk, but the confidence interval is wide, 4–114%). There is a lower, and non-significant increase in risk for exposure to secondhand smoke from the father (25%). However, there is significant heterogeneity between the estimates of relative risk. The results on exposure during childhood are less clear than those on exposure from the spouse or at the workplace.

Overall, the evidence from the meta-analyses is clear; adult nonsmokers exposed to secondhand smoke have a higher risk for lung cancer. Although the precise quantitative estimate of risk may vary between different measures of exposure, it is consistently raised. The data on exposure to secondhand smoke from the spouse also show that risk increases with increasing exposure. The evidence for an association between lung cancer and childhood exposure to secondhand smoke is less consistent than that for exposure in adulthood.

2.2 Breast cancer

Five prospective cohort studies (Hirayama, 1984; Jee *et al*., 1999; Wartenberg *et al*., 2000; Nishino *et al*., 2001; Egan *et al*., 2002) and 12 reports of 10 case–control studies (Sandler *et al*., 1985a,b; Smith *et al*., 1994; Morabia *et al*., 1996; Millikan *et al*., 1998; Lash & Aschengrau, 1999; Delfino *et al*., 2000; Johnson *et al*., 2000; Marcus *et al*., 2000; Morabia *et al*., 2000; Chang-Claude *et al.*, 2002; Kropp & Chang-Claude, 2002) have examined the role of secondhand smoke in breast cancer. The cohort studies are summarized in Table 2.11 and the reports from the case–control studies are summarized in Table 2.12.

2.2.1 *Cohort studies*

The first cohort study that suggested a possible association of exposure to secondhand smoke with breast cancer was reported by Hirayama in 1984. Specific details of how risk estimates for breast cancer were calculated were provided by Wells (1991). A total of 115 deaths from breast cancer were identified after 15 years of follow-up (1966–81) of over

Table 2.11. Cohort studies of breast cancer and involuntary exposure to tobacco smoke

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Hirayama (1984)	Japan	115 breast cancer deaths among 91 540 nonsmoking married women	In-person interview (baseline)	15 years of follow-up. Completeness not reported	*Husband ever smoked* 1.26 (0.8–2.0)	
Jee *et al.* (1999)	Republic of Korea	138 breast cancer cases among 157 436 non-smoking married women	Self-administered questionnaire: husband's active smoking in 1992 and 1994; wife's involuntary smoking in 1993	3.5 years of follow-up of breast cancer cases. Completeness not reported	*Husband's smoking status* Former smoker Current smoker Current smoker for > 30 years	 1.2 (0.8–1.8) 1.3 (0.9–1.8) 1.7 (1.0–2.8)
Wartenberg *et al*. (2000)	USA	669 breast cancer deaths among 146 488 never-smoking single-marriage women	Postal questionnaire to both husband and wife	12 years of follow-up. 98% completeness	*Husband's smoking status* Former smoker Current smoker (baseline) *Years husband smoked* 1–10 11–20 21–30 ≥ 31 *p* trend = 0.9	 1.0 (0.8–1.2) 1.0 (0.8–1.2) 0.9 (0.6–1.3) 0.7 (0.5–1.0) 1.0 (0.7–1.3) 1.1 (0.8–1.3)

Table 2.11 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)
Nishino *et al*. (2001)	Japan	67 incident cases of breast cancer among 9675 never-smoking women aged ≥ 40	Self-administered questionnaires	9 years of follow-up. Completeness not reported	*Husband smoked* 0.6 (0.3–1.1) *Other household member smoked* 0.8 (0.4–1.5)
Egan *et al*. (2002)	USA	1359 breast cancer cases among 35 193 never-smoking women	Postal questionnaire	14 years of follow-up of invasive breast cancer. 96% completeness	*Parental smoking* Mother only 1.0 (0.7–1.4) Father only 1.1 (1.0–1.3) Both parents 0.9 (0.8–1.1) *Current exposure to secondhand smoke* Occasional 1.2 (1.0–1.4) Regular at home or at work 1.0 (0.8–1.2) Regular at home and at work 0.9 (0.7–1.2)

Table 2.12. Case–control studies of breast cancer and involuntary exposure to tobacco smoke

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Sandler *et al*. (1985a)	USA	29 nonsmoking incident cases; 223 nonsmoking controls	Postal question-naire	22 months; cases diagnosed in women aged 15–59 years. 70% case response rate; 57% control response rate	Maternal smoking Paternal smoking	0.9 0.9
Sandler *et al*. (1985b)	USA	32 nonsmoking incident cases; 247 nonsmoking controls	Postal question-naire	22 months; cases diagnosed in women aged 15–59 years. 70% case response rate; 75% response rate for telephone controls; 60% response rate for friend controls	Husband's smoking	2.0 (0.9–4.3)
Smith *et al*. (1994)	United Kingdom	94 nonsmoking incident cases; 99 nonsmoking controls	In-person inter-view with postal questionnaire on exposure to secondhand smoke	3 years; cases diagnosed in women aged < 36 years. 72% case response rate; 89% control response rate. Data on exposure to secondhand smoke available on 65% of matched pairs	*Childhood exposure in cigarette–years* 1–200 > 200 *Adult exposure* *From partner in cigarette–years* ≥ 1 *From other household smokers (years)* 1–5 ≥ 6 *At work (years)* 1–5 ≥ 6 *Period of exposure* Child only Adult only Both	 1.2 (0.5–2.9) 1.1 (0.5–2.7) 1.6 (0.8–3.1) 1.5 (0.7–3.2) 1.1 (0.5–2.8) 1.7 (0.7–3.8) 1.4 (0.6–3.1) 1.3 (0.2–10.8) 3.1 (0.7–13.3) 2.6 (0.7–9.4)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Morabia *et al*. (1996)	Switzerland	126 never-smoking incident cases; 620 never-smoking controls	In-person interview	22 months for cases diagnosed in women < 75 years of age. 71% case response rate; 70% control response rate	Ever exposed to second-hand smoke	3.2 (1.7–5.9)
					(Hours/day) × year	
					1–50	3.1 (1.5–6.2)
					> 50	3.2 (1.6–6.3)
					Ever exposed to second-hand smoke from spouse	3.1 (1.6–6.1)
					From spouse (hours/day) × year	
					1–50	3.1 (1.3–7.5)
					> 50	3.2 (1.5–6.5)
Millikan *et al*. (1998)	USA	248 never-smoking incident cases; 253 never-smoking controls	In-person interview plus 30-mL blood sample	3.5 years for cases diagnosed in women 20–74 years of age. 77% case response rate; 68% control response rate; 98% of study subjects provided blood samples	*Exposed to secondhand smoke after age 18 years*	
					All-nonsmokers	1.3 (0.9–1.9)
					Premenopausal	1.5 (0.8–2.8)
					NAT1*10	1.7 (0.7–4.3)
					NAT1non*10	1.3 (0.5–3.2)
					NAT2rapid	2.3 (0.9–6.2)
					NAT2slow	1.2 (0.5–2.8)
					Postmenopausal	1.2 (0.7–2.2)
					NAT1*10	1.2 (0.6–2.6)
					NAT1non*10	1.3 (0.5–3.6)
					NAT2rapid	0.8 (0.4–1.8)
					NATslow	1.9 (0.7–5.2)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Lash & Aschengrau (1999)	USA	120 never-smoking cases, 406 never-smoking controls	Proxy interview; 33% of cases and 45% of controls	3 years for cases diagnosed in women. 79% case response rate; 75% control response rate	Passive smoking	2.0 (1.1–3.7)
					By years of exposure to secondhand smoke	
					≤ 20	3.2 (1.5–7.1)
					> 20	2.1 (1.0–4.1)
Delfino *et al*. (2000)	USA	64 never-smoking cases; 149 never-smoking controls (benign breast disease)	Self-administered questionnaire	Cases diagnosed in women 40 years of age and above (duration not reported). 82% case response rate; 85% control response rate	Any exposure to second-hand smoke	1.3 (0.7–2.5)
					High versus low exposure to secondhand smoke	1.5 (0.8–2.9)
					Premenopausal cases	2.7 (0.9–8.0)
					Postmenopausal cases	1.0 (0.5–2.3)
Johnson *et al*. (2000)	Canada	378 premenopausal and 700 post-menopausal never-smoking cases; 369 pre- and 845 post-menopausal never-smoking controls	Postal question-naire	≥ 3 years for cases diagnosed in women 20–74 years of age. 72% case response rate; 64% control response rate	*Premenopausal*	
					Any exposure to second-hand smoke	2.3 (1.2–4.6)
					Childhood exposure only	1.6 (0.6–4.4)
					Adult exposure only	2.6 (1.1–6.0)
					Exposure during childhood and adulthood	2.6 (1.2–5.5)
					Postmenopausal	
					Any exposure to second-hand smoke	1.2 (0.8–1.8)
					Childhood exposure only	0.9 (0.4–2.0)
					Adult exposure only	1.1 (0.6–1.8)
					Exposure during childhood and adulthood	1.3 (0.8–2.0)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Marcus *et al*. (2000)	USA	445 never-smoking cases; 423 never-smoking controls	In-person interview	3.5 years for cases diagnosed in women 20–74 years of age. 77% case response rate; 68% control response rate	Never-smokers exposed to secondhand smoke before age 18 years	0.8 (0.6–1.1)
Morabia *et al*. (2000)	Switzerland	84 never-smoking cases; 99 never-smoking controls	In-person interview and buccal swab	1 year for incident cases diagnosed in women < 75 years of age. 71% case response rate; 70% control response rate in original study; 83% response rate in substudy	Any exposure to secondhand smoke *NAT2 acetylation genotype* Slow Fast	3.1 (1.5–6.0) 1.9 (0.7–4.6) 5.9 (2.0–17.4)
Chang-Claude *et al.* (2002)	Germany	174 never-smoking cases; 365 never-smoking controls	Self-administered questionnaire and for passive smoking questions by telephone interview	4 years for cases; passive smoking response rates: ~46% of total eligible and 48% of eligible controls	*Ever exposed by NAT2 acetylator status* Rapid Slow	 2.0 (1.0–4.1) 1.2 (0.7–2.0)
Kropp & Chang-Claude (2002)	Germany	197 never-smoking cases; 459 never-smoking controls	Self-administered questionnaire and for passive smoking questions by telephone interview	4 years for cases; passive smoking response rates: ~46% of total eligible and 48% of eligible controls	*Exposure to secondhand smoke* As a child only As an adult only Both *Lifetime in (hours/day) × years* 1–50 ≥ 51 $p = 0.009$	 1.1 (0.6–2.3) 1.9 (1.2–3.0) 1.6 (1.0–2.6) 1.4 (0.9–2.3) 1.8 (1.2–2.9)

91 000 married nonsmoking Japanese women. Women whose husbands had ever smoked had a small non-significantly increased risk of breast cancer (relative risk, 1.26; 95% CI, 0.8–2.0*)*. [The Working Group noted this was a first prospective report with a number of limitations. For example, it reported mortality rather than incidence; there was limited assessment of risk specific to breast cancer (spouse only); there was no adjustment for potential confounders; exposure was assessed at only one time-point.]

In a study in the Republic of Korea, Jee *et al*. (1999) also found small non-significantly increased risks of breast cancer associated with husbands' smoking status: for former smokers the relative risk was 1.2 (95% CI, 0.8–1.8) and for current smokers the relative risk was 1.3 (95% CI, 0.9–1.8). Relative risks were adjusted for age of husbands and wives, socioeconomic status, residence, vegetable consumption and occupation of the husband. These findings were based on 138 incident and prevalent breast cancer cases in 3.5 years of follow-up (July 1994–December 1997) of a cohort of 157 436 nonsmoking Korean women. A higher risk, of borderline significance, was observed for women married to current smokers who had smoked for more than 30 years (relative risk, 1.7; 95% CI, 1.0–2.8). [The Working Group noted that this study had several limitations, i.e. prevalent cases were not excluded; limited adjustment was made for potential confounders, and the adjustment did not include reproductive or hormonal factors; assessment of exposure included only secondhand smoke from the spouse.]

Wartenberg *et al*. (2000) reported findings from the large American Cancer Society Cancer Prevention Study II cohort based on 12 years of follow-up (1982–94) of never-smoking women who had been married once. A total of 669 deaths from breast cancer were included and risk estimates were adjusted for year of age at baseline, race, number of years of education, history of breast cancer in mother or sister, personal history of breast cysts, age at first live birth, age at menopause, number of spontaneous abortions, use of oral contraceptives, use of estrogen replacement therapy, body mass index, alcohol intake, fat consumption, vegetable consumption, occupation and occupation of spouse. No increased risks were found for women married to current smokers (relative risk, 1.0; 95% CI, 0.8–1.2) or former smokers (relative risk, 1.0; 95% CI, 0.8–1.2) when compared with never-smokers married to nonsmoking husbands. No association was found by type of tobacco. No trend in risk was observed by years, packs per day or pack–years of spousal smoking. No significant associations were noted between breast cancer and all exposures at home (relative risk, 1.1; 95% CI, 0.9–1.3), at work (relative risk, 0.8; 95% CI; 0.6–1.0), or in other places (relative risk, 0.9; 95% CI, 0.7–1.2). When reported exposures from all sources were combined and examined according to daily hours of exposure using no exposure from any source as referent (0 hour), no trend was observed. [The Working Group considered that the strengths of this study included the large number of cases, the excellent follow-up, the thorough statistical adjustment for potential confounders and that the spouse directly reported his own tobacco use. The limitations include the use of mortality rather than incidence as the outcome and that the assessment of spousal smoking was made at only one time-point.]

A smaller cohort study that included 9675 Japanese female never-smokers over the age of 40 years accrued 67 incident cases over a 9-year follow-up period (1984–92) (Nishino *et al*., 2001). Relative risks were adjusted for age, study area, alcohol consumption, intake of green and yellow vegetables, intake of fruit, age at first birth, number of live births, age at menarche and body mass index. The age-adjusted relative risk for breast cancer was 0.6 (95% CI, 0.3–1.0) among women whose husbands smoked when compared to that in women married to nonsmokers. The age-adjusted risk associated with living in a household with other smokers was also below unity (relative risk, 0.4; 95% CI, 0.2–0.8) when compared with women living in households where there were no smokers. Further adjustment of these relative risks for the potential confounders listed above did not appreciably change the risk estimates, but the relative risks were no longer statistically significant after full adjustment: exposure from spouse, 0.6 (95% CI, 0.3–1.1), and other household members, 0.8 (95% CI, 0.4–1.5*)*. [The Working Group considered that the strengths of this study include adjustment for some reproductive or hormonal and dietary factors; its limitations include the very small sample size, lack of information on marital status at baseline and inclusion of unmarried women at high risk of breast cancer as unexposed which may have reduced point estimates of relative risk.]

The Nurses' Health Study in the USA has provided the largest number of prospectively accrued breast cancer cases in never-smoking women (Egan *et al*., 2002). After 14 years of follow-up (1982–96), 1359 cases of invasive breast cancer were diagnosed among 35 193 never-smokers. Exposure to secondhand smoke was assessed as exposure during childhood as well as during adult life at home, at work and in other settings. Relative risks were adjusted for many variables including age, parity, age at first birth, menopausal status, age at menopause, change in weight (i.e. weight at age 18 years compared to the most recent reported weight), age at menarche, history of benign breast disease, family history of breast cancer, post-menopausal hormone treatment, alcohol intake and carotenoid intake. No statistically significant associations were found for exposure between breast cancer and exposure to secondhand smoke in adult life or in childhood, and most relative risks were near unity. No trends were apparent either for number of years lived with a smoker as an adult (p for trend = 0.87) or for a categorized index of adult exposures (p for trend = 0.97). Women who reported the highest levels of exposure to secondhand smoke during adulthood had a rate of breast cancer similar to that of women who reported no current exposure to secondhand smoke (relative risk, 1.0; 95% CI, 0.8–1.3). The findings were similar for pre- and postmenopausal women. [The Working Group noted that this study's main strength is that it is the largest and most methodologically rigorous prospective study to date. Other strengths were that exposure assessments were updated over time, incident cases rather than mortality were studied and comprehensive adjustment was made for potential confounders.]

2.2.2 *Case–control studies*

The first two reports (Sandler *et al*., 1985a,b) on involuntary smoking and breast cancer were based on a case–control study conducted in North Carolina, USA. Cases were selected from a single hospital tumour registry and included patients diagnosed between 1 July 1979 and 31 March 1981, who were between the ages of 15 and 59 years at the time of diagnosis. Approximately 60% of the controls were friends or acquaintances identified by cases and the remaining 40% were selected by systematic telephone sampling. The two control groups were combined after separate analyses of the two groups indicated similar results. The risk for breast cancer in nonsmoking women was not associated with exposure to secondhand smoke during childhood from either mother (relative risk, 0.9) or father (relative risk, 0.9) (Sandler *et al*., 1985a). Exposure to secondhand smoke in nonsmoking women based on husband's smoking was associated with a two-fold, nonsignificant increase in risk (relative risk, 2.0; 95% CI, 0.9–4.3) (Sandler *et al*., 1985b). Risk estimates of childhood exposure were adjusted for age and education, and risk estimates of exposure during adulthood were adjusted for age, race and education. Both reports included only a few lifetime nonsmokers with breast cancer (29 and 32 cases, respectively). [The Working Group noted that the limitations of this study include small sample size, lack of adjustment for reproductive factors and the potentially inappropriate control group (i.e. friends and neighbours of cases supplemented with controls selected by random digit dialling.]

Smith *et al*. (1994) investigated the relationship between exposure to secondhand smoke and risk for breast cancer in a sample of nonsmokers including 94 incident cases and 99 controls drawn from a larger study of breast cancer diagnosed in young women below the age of 36 years between 1982 and 1985. This study was conducted in the United Kingdom and information on exposure to secondhand smoke was collected by postal questionnaire in a sample of participants from the main study. Controls were selected randomly from the list of the case's general practitioner and matched to the case on age. Risk estimates were adjusted for age, residence, age at menarche, family history of breast cancer, history of biopsy for benign breast disease, oral contraceptive use and history of breastfeeding. Although most of the risk estimates exceeded unity as shown in Table 2.12, none were statistically significant and there was no evidence of a positive trend in risk associated with increasing exposure. When total lifetime exposure as measured in cigarette–years was considered, elevations in risk were found for all levels above zero (referent). However, the trend was not statistically significant. No effect of active smoking was found in this study. [The Working Group considered this study to have limited generalizability (cases < 36 years of age) and noted that no exposure–response relationship was observed despite comparatively high point estimates of risk.]

A population-based case–control study conducted in Switzerland by Morabia *et al*. (1996) was designed specifically to evaluate the role of exposure to secondhand smoke in risk of breast cancer. It included 126 cases and 620 controls who were lifetime never-smokers. Never-smokers were defined as having smoked fewer than 100 cigarettes in a

lifetime. Eligible cases were women less than 75 years of age who had been diagnosed with invasive breast cancer between 1 January 1992 and 31 October 1993. Population controls were selected from the official registers of residents of Geneva and were 30–74 years of age. This study included a detailed assessment of exposure to secondhand smoke and risk estimates were adjusted for the following potential confounders: age, education, body mass index, age at menarche, age at first live birth, oral contraceptive use, breast cancer in mother or sister, history of breast biopsy, alcohol intake and saturated fat intake. The referent unexposed group in this study included women who were never regularly exposed (< 1 (h/day) × years) to either active or passive smoking (28/244 cases and 241/1032 controls). Estimates of relative risk associated with any exposure to secondhand smoke, duration of exposure to secondhand smoke, exposure to spousal secondhand smoke only and duration of spousal smoking were all approximately three and were statistically significant; however, risk estimates stratified by duration (1–50 or > 50 (h/day) × years) were virtually identical and there was no suggestion of an exposure–response relationship. [The Working Group considered that the strengths of the study were its comprehensive assessment of exposure, being population-based and the large number of potential confounders included in the analysis. Concerns included the following: magnitude of the association between cancer and passive smoking is the same as that for active smoking in same study, no exposure–response relationship was found for secondhand smoke and the very restrictive reference category used may have biased the results.]

Morabia *et al*. (2000) next conducted a sub-study from the above-mentioned case–control study. It was designed to evaluate the role of *N*-acetyltransferase 2 (NAT2) in the relationship between breast cancer and active and passive smoking. Cases believed to be alive and living in Geneva in 1996–97 were re-contacted, as were a subset of controls, and asked to provide a buccal swab for DNA extraction and NAT2 genotyping for subsequent classification as slow or fast acetylators. This sub-study included 84 cases who were never-smokers and 99 controls who were never-smokers. As in the parent study, a three-fold increase in risk of breast cancer was associated with any reported exposure to secondhand smoke (relative risk, 3.1; 95% CI, 1.5–6.0). The association between exposure to secondhand smoke and breast cancer appeared to be modified by acetylation status; breast cancer risk was higher in persons with the fast acetylation genotype (relative risk, 5.9; 95% CI, 2.0–17.4) than in slow acetylators (relative risk, 1.9; 95% CI, 0.7–4.6). [The Working Group's comments on the parent study also applied to this sub-study.]

Millikan *et al*. (1998) conducted a population-based case–control study in North Carolina, USA, that also examined the effect of *N*-acetylation genotypes (NAT1 and NAT2), exposure to secondhand smoke and breast cancer risk. Cases included women between 20 and 74 years of age who were diagnosed with invasive primary breast cancer between May 1993 and December 1996. Controls less than 65 years of age were selected from files of the North Carolina Division of Motor Vehicles and those from 65 to 74 years of age from the United States Health Care Financing Administration (HCFA) files. All African–American cases and a sample of white cases were selected. This report was based

on cases and controls who provided a blood sample. Cases and controls were broadly frequency-matched on race (African–American and white) and age (age less than 50 years and 50 years and above). Relative risk estimates were adjusted for age, race, age at menarche, age at first full-term pregnancy, parity, family history of breast cancer, breast biopsies showing benign tumours and alcohol consumption. Statistically non-significant increases in risk were associated with exposure to secondhand smoke after the age of 18 years in never-smokers (relative risk, 1.3; 95% CI, 0.9–1.9). The point estimates for premenopausal (relative risk, 1.5; 95% CI, 0.8–2.8) and postmenopausal women (relative risk, 1.2; 95% CI, 0.7–2.2) were not substantially different. Stratification by menopausal status and NAT1 and NAT2 genotypes resulted in statistically non-significant relative risks for all subgroups. The point estimates for exposure to secondhand smoke after the age of 18 years were highest for pre-menopausal never-smoking women for NAT1*10 (relative risk, 1.7; 95% CI, 0.7–4.3) and NAT2rapid (relative risk, 2.3; 95% CI, 0.9–6.2).

Marcus *et al*. (2000) included additional cases from this North Carolina study without the requirement for a blood sample and addressed the issue of exposure to secondhand smoke before the age of 18 years. Exposure to secondhand smoke at home during childhood showed no statistically significant association with risk of breast cancer in this study (relative risk, 0.8; 95% CI, 0.6–1.1). [The Working Group considered that the strengths of this study included the large number of never-smoking cases and controls; the multiethnic study population (although no ethnicity-specific risk estimates for exposure to secondhand smoke were reported and that the study investigated possible high-risk subgroups.]

Lash and Aschengrau (1999) reported the findings of a case–control study conducted in five towns in Massachusetts, USA. The incident cases of breast cancer were diagnosed from 1983–1986. Population controls from these towns for living cases under 65 years of age were selected using random-digit dialling and for women 65 years and older from the US Health Care Financing Administration (HCFA) files. Because deceased cases were also eligible for this study, deceased controls were selected from Massachusetts Department of Vital Statistics and Research. A total of 120 cases and 406 controls were never-smokers. About one-third of the interviews relating to cases and 45% of the interviews relating to controls were with proxy respondents. Age, parity, history of breast cancer other than index diagnosis, family history of breast cancer, history of benign breast disease, and history of radiation therapy were adjusted for in the analyses. A twofold increase in risk (relative risk, 2.0; 95% CI, 1.1–3.7) was associated with any exposure to secondhand smoke; however, increasing duration was not associated with increasing risk. The relative risk estimates for exposure to secondhand smoke and for active smoking also determined in this study were similar. [The Working Group noted that the limitations of the study were that the original study was not designed to evaluate exposure to secondhand smoke; it was unclear whether controls from the parent study which included three types of cancer cases were matched to breast cancer cases in this substudy, and that this substudy included a large number of proxy respondents.]

Findings from a small clinic-based case–control study, conducted in Orange County, California, USA, were reported by Delfino *et al*. (2000). Three breast cancer centres were

included in the study. Subjects diagnosed with a suspicious breast mass detected either clinically or radiographically who were over the age of 39 years were considered to be eligible. Information on exposure was obtained from a self-administered questionnaire completed prior to biopsy in order to minimize recall bias and interviewer bias. Among women who were never-smokers, 64 were subsequently found to have malignant tumours and comprised the case series, and 149 never-smokers with benign breast disease were classified as controls. Risk estimates for exposure to secondhand smoke in the home were adjusted for age, menopausal status, age at menarche, age at first full-term pregnancy, total months of pregnancy, lactation history, education, race/ethnicity, body mass index and family history of breast cancer. NAT2 genotype was also determined, but was not associated with risk for breast cancer in this study. No statistically significant association was found between exposure to secondhand smoke and breast cancer risk in these never-smokers (relative risk, 1.3; 95% CI, 0.7–2.5) for any exposure to secondhand smoke in the home. [The Working Group considered that the strengths of this study included the fact that exposure data were collected prior to determination of case–control status. Its limitations were that it was a small study and that information on exposure to secondhand smoke was limited to exposure in the household.]

A large Canadian study (Johnson *et al*., 2000) identified population-based incident cases of breast cancer aged 25–74 years at diagnosis from the National Enhanced Cancer Surveillance System beginning in April 1994 in some provinces (later in others) and continuing until July 1997. The study included 378 premenopausal and 700 postmenopausal never-smoking cases and 369 pre- and 845 postmenopausal population-based never-smoking controls. Exposure to secondhand smoke in the household during childhood and adult life as well as in the workplace were assessed. Relative risk estimates were adjusted for age, province, education, body mass index, alcohol use, physical activity, age at menarche, age at the end of first pregnancy lasting 5 months or longer, number of live births, months of breastfeeding and height. There was no evidence of an association between breast cancer and exposure to secondhand smoke during childhood or adulthood in postmenopausal women (relative risk estimates ranged from 0.9 to 1.3, none were statistically significant). However, premenopausal women had significantly elevated risks for breast cancer associated with any exposure to secondhand smoke (relative risk, 2.3; 95% CI, 1.2–4.6), exposure to secondhand smoke during adulthood (relative risk, 2.6; 95% CI, 1.1–6.0), and exposure to secondhand smoke during both childhood and adulthood (relative risk, 2.6; 95% CI, 1.2–5.5). There was evidence of a strong dose–response relationship in premenopausal women associated with duration of residential and occupational exposure (p for trend = 0.0007). [The Working Group noted that the risk associated with passive smoking was similar in magnitude to that in former active smokers (relative risk, 2.6) and was higher than that for current active smokers (relative risk, 1.9) in the same study. The limitations of the study were that information was missing on a large number of cases and controls who were excluded from this study and information on exposure to secondhand smoke was available for only 59% of never-smokers.]

Two recent reports from a case–control study of breast cancer in German women aged 50 years and younger have used as the referent for assessing the risks of both active and involuntary smoking those women who have experienced no active and no passive exposure to tobacco smoke (lifetime non-exposed: < 1 (h/day) × year) (Kropp & Chang-Claude, 2002; Chang-Claude *et al.*, 2002). The study included 706 cases (response rate, 70.1%) and 1381 controls (response rate, 61.2%). Data were initially collected by self-administered questionnaires for active smoking, and later, living cases and controls were re-contacted for information on involuntary exposure to tobacco smoke. Of the original participants, approximately 66% of the cases and 79% of the controls completed this part of the study. Risk estimates were adjusted for daily alcohol intake, total number of months of breastfeeding, education, first-degree family history of breast cancer, menopausal status and body mass index. For active smoking, a relative risk of 1.1 (95% CI, 0.6–2.0) was recorded, whereas never-smokers exposed to involuntary smoking had a statistically increased risk of about 60% (Kropp & Chang-Claude, 2002). In a subgroup analysis of 422 cases and 887 controls, the effect of NAT2 on the association between tobacco and breast cancer was considered (Chang-Claude *et al.*, 2002). When compared to women who had never been exposed to any tobacco smoke, no association with active smoking was seen in rapid acetylators and a modest statistically non-significant increase in risk was observed in slow acetylators. In contrast, passive smoking was associated with a statistically non-significant risk that was higher in rapid than in slow acetylators (relative risk, 2.0; 95% CI, 1.0–4.1; and 1.2; 95% CI, 0.7–2.0, respectively). [The Working Group noted that this study has included many subgroup analyses, had reported incongruent findings related to active and involuntary smoking in the same study AND had obtained passive smoking data for only about 50% of study subjects. However, the strength of this study was the inclusion of a referent group of subjects who had not been exposed to any tobacco smoke during their lifetimes by self-report.]

2.3 Childhood cancers

Many studies have evaluated the association of cancer risk in childhood with exposure to parental smoking since this issue was considered previously in the *IARC Monograph* Volume 38 (IARC, 1986). These associations will be evaluated below for all cancers combined and separately, for brain tumours, leukaemias and lymphomas, and other childhood cancers.

Few studies distinguish times of exposure to tobacco smoke from parents, i.e. whether the exposure was preconception, *in utero* or postnatal. Exposure may have occurred in all three periods even when a study reports on only one, or exposure may also be reported as ‘ever’. Involuntary smoking during each of these time periods tends to be correlated, in particular exposure to secondhand smoke from the father because father’s smoking habits are less likely to change.

2.3.1 *All sites combined*

Four cohort studies (Neutel & Buck, 1971; Golding *et al*., 1990; Pershagen *et al*., 1992; Klebanoff *et al*., 1996) and ten case–control studies (Buckley *et al*., 1986; McKinney *et al*., 1986; Stjernfeldt *et al*., 1986; Forsberg & Kallen, 1990; John *et al*., 1991; Golding *et al*., 1992; Sorahan *et al*., 1995; Ji *et al*., 1997; Sorahan *et al*., 1997a,b) (Table 2.13) have examined the role of involuntary exposure to tobacco smoke in risk for childhood cancers in general.

All four cohort studies specifically reported on the risk associated with cancer related to mothers' smoking during pregnancy. Neutel and Buck (1971) identified 97 deaths from childhood cancer in a cohort of 89 302 births from Ontario (Canada), and England and Wales followed from 7 to 10 years. Children with a mother who had smoked during pregnancy had a relative risk of 1.3 (95% CI, 0.8–2.2). No exposure–response relationship was apparent. [The Working Group noted several limitations of this study: no control for potential confounders; completeness of follow-up unknown, and limited assessment of exposure to secondhand smoke.]

Golding *et al*. (1990) followed a cohort of 16 193 births for 10 years (1970–80) and a total of 33 cancers were diagnosed. After adjustment for social class, exposure to X-rays during pregnancy, term delivery, administration of pethidine in labour and of drugs during infancy, a statistically significant increase in risk was found for children whose mothers smoked five or more cigarettes per day during the index pregnancy (relative risk, 2.5; 95% CI, 1.2–5.1). [The Working Group noted that the strength of this study was that the effect of exposure to secondhand smoke was independent of other risk factors found in this study. Its limitations were that the completeness of follow-up was unknown and that there was limited assessment of exposure to secondhand smoke.]

Pershagen *et al*. (1992), in Sweden, followed a large cohort of 497 051 births. In 5 years of follow-up, a total of 327 cancers that could be linked to data on maternal smoking were diagnosed. Relative risks were adjusted for year and county of birth, birth order and maternal age. No association was found for any maternal smoking during pregnancy (relative risk, 1.0; 95% CI, 0.8–1.3) and no exposure–response relationship was seen for number of cigarettes smoked during pregnancy (< 10 cigarettes per day, relative risk, 1.0; ≥ 10 cigarettes per day, relative risk, 0.9). No cancer at any of the sites evaluated individually was associated with maternal smoking. [The Working Group noted that the strengths of this study were that it was the largest cohort study, some statistical adjustment of risk estimates had been made and there was a high rate of follow-up. Its limitation was that there had been limited assessment of exposure to secondhand smoke.]

The most recent prospective study to evaluate the association between maternal smoking during pregnancy and childhood cancer is the US Collaborative Perinatal Project that included 54 795 children born from 1959–66 who were followed until the age of seven or eight years (Klebanoff *et al*., 1996). The hazard ratio for cancer in children whose mother smoked during pregnancy compared to those whose mother did not was 0.7 (95% CI, 0.4–1.2). Adjustment of the hazard ratio for maternal race, age, education,

Table 2.13. Childhood cancers, all sites combined, and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Cohort studies					
Neutel & Buck (1971) (Canada, United Kingdom)	72 952 births in Ontario; 16 350 births in England and Wales	Interview	7–10 years in Ontario; 7 years in England and Wales; completeness not reported	Maternal smoking during pregnancy	1.3 (0.8–2.2)
Golding *et al*. (1990) (United Kingdom)	16 193 births, 33 cases	Cancer registry, medical record	10 years diagnosis of children ≤ 10 years of age; completeness not reported	Maternal smoking ≥ 5 cigarettes/day during pregnancy	2.5 (1.2–5.1)
Pershagen *et al*. (1992) (Sweden)	497 051 births, 327 cases	Cancer registry	5 years follow-up; 327 of 422 cancers linked to births with smoking data; 99% complete follow-up	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	1.0 (0.8–1.3) 1.0 (0.8–1.4) 0.9 (0.6–1.3)
Klebanoff *et al*. (1996) (USA)	54 795 births, 51 cases		7–8 years follow-up of cancers diagnosed in children ≤ 8 years old; completeness of follow-up not reported	Maternal smoking during pregnancy *Incidence rate* Smoker Nonsmoker *Hazard ratio*	 0.9 per 1000 4 per 1000 $p < 0.15$ 0.7 (0.4–1.2)

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Case–control studies					
Buckley *et al*. (1986) (USA, Canada)	1814 cases, 720 controls	In-person interview	3 years diagnosis in children (age not reported); 100% response rate	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	 1.3 (0.9–1.9) 1.0 (0.8–1.2)
McKinney *et al*. (1986) (United Kingdom)	555 cases, 1110 controls	Not reported	Duration and response rate not reported; children < 15 years of age	Maternal smoking during pregnancy *Cigarettes/day* 1–10 ≥ 11	 1.1 (0.9–1.5) 0.8 (0.7–1.1)
Stjernfeldt *et al*. (1986) (Sweden)	305 cases, 340 controls	Physician-distributed questionnaire	3 years diagnosis of children < 17 years old; > 95% response rate	Maternal smoking during pregnancy *Cigarettes/day* 1–9 ≥ 10	 1.1 1.6, $p < 0.01$
Forsberg & Kallen (1990) (Sweden)	69 cases, 139 controls	Medical record	2 years diagnosis of children < 10 years of age; response rate not reported	Any maternal smoking	1.1 (0.6–2.0)
John *et al*. (1991) (USA)	223 cases, 196 controls	Telephone interview	7 years diagnosis of children < 15 years of age; 71% case response rate; 63% control response rate	Any maternal smoking in first trimester Paternal smoking in year prior to birth	1.3 (0.7–2.1) 1.2 (0.8–2.1)

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Golding *et al*. (1992) (United Kingdom)	195 cases, 558 controls	Medical record	20 years diagnosis of children (age not reported); response rate not reported	Maternal smoking in pregnancy	2.0 (1.3–3.2)
Sorahan *et al*. (1995) (United Kingdom)	1641 cases, 1641 controls	In-person interview	Deaths 1977–81 in children < 16 years of age; 61% case response rate; control response rate not reported	Maternal prenatal smoking *Cigarettes/day* 1–9 10–19 20–29 30–39 ≥ 40 Paternal prenatal smoking *Cigarettes/day* 1–9 10–19 20–29 30–39 ≥ 40	 1.0 (0.7–1.3) 1.2 (1.0–1.4) 1.0 (0.8–1.2) 0.9 (0.6–1.5) 1.6 (0.9–3.0) 1.2 (0.8–1.8) 1.2 (1.0–1.6) 1.3 (1.1–1.5) 1.4 (1.0–1.8) 1.5 (1.1–2.0)
Sorahan *et al*. (1997a) (United Kingdom)	1549 cases, 1549 controls	In-person interview	Deaths 1953–55 in children < 16 years of age; 88% case response rate; 94% control response rate	Maternal smoking *Cigarettes/day* 1–9 10–20 > 20	 1.0 (0.8–1.2) 1.2 (1.0–1.5) 1.2 (0.7–2.3) *p* for trend = 0.09

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Sorahan *et al*. (1997a) (contd)				Paternal smoking *Cigarettes/day* 1–9 10–20 > 20 *p* for trend < 0.001	 1.0 (0.8–1.3) 1.3 (1.1–1.6) 1.4 (1.1–1.9)
Sorahan *et al*. (1997b) (United Kingdom)	2587 cases, 2587 controls	In-person interview	Deaths 1971–76 in children < 16 years of age; 63% case response rate; control response rate not reported	Maternal smoking only Paternal smoking only Both parents smoking	1.0 (0.8–1.1) 1.3 (1.1–1.5) 1.3 (1.3–2.4)
Ji *et al*. (1997) (China)	642 cases, 642 controls	In-person interview	10 years diagnosis of children < 15 years of age; 83% case response rate; 100% control response rate	Paternal smoking *Cigarettes/day* < 10 10–14 ≥ 15 Paternal smoking (years) < 10 10–14 ≥ 15 *p* for trend = 0.007	 1.5 (1.1–2.3) 1.1 (0.8–1.6) 1.5 (1.0–2.3) 1.2 (0.7–1.8) 1.1 (0.8–1.7) 1.7 (1.2–2.5)

socioeconomic status, height and pre-pregnancy weight as well as previous pregnancies, exposure to diagnostic radiation during pregnancy, feeding of infant in hospital, sex of infant and date of delivery had only a minimal effect on the point estimates, all of which remained in the range of 0.6. [The Working Group noted that the limitations of this study were that the completeness of follow-up was unknown, but the estimates of expected incidence suggest that few cases were missed, and that assessment of exposure to secondhand smoke was limited.]

Buckley *et al*. (1986) conducted a case–control analysis using data from the US/Canada Children's Cancer Study Group. These investigators compared smoking by mothers and fathers of 1814 childhood cancer cases with that of parents of 720 controls selected at random from approximately the same geographical regions as cases. Smoking in the periods before and during pregnancy was assessed. No association was found between maternal smoking during pregnancy (< 10 cigarettes per day, relative risk, 1.3; 95% CI, 0.9–1.9; ≥ 10 cigarettes per day, relative risk, 1.0; 95% CI, 0.8–1.2) and no association with paternal smoking was found [relative risk not reported]. Adjustment for potential confounders such as year of birth, age of mother, illnesses during pregnancy and socioeconomic factors, did not alter findings. [The Working Group noted that the strength of this study was the large sample size and its limitations were that the report lacked details of the study and the control group was not well described.]

In a case–control study based on the Inter-Regional Epidemiological Study of Childhood Cancer in the United Kingdom, 555 cases of cancer in children < 15 years of age and 1110 controls matched for age and sex were compared for exposure to maternal smoking during pregnancy (McKinney *et al*., 1986). There was no evidence of an association between maternal smoking and risk for childhood cancer (1–10 cigarettes per day, relative risk, 1.1; 95% CI, 0.9–1.5; > 11 cigarettes per day, relative risk, 0.8; 95% CI, 0.7–1.1). [The Working Group noted that the strength of this study was the large sample size. The limitations were that the report provided few study details; other than matching for age and sex there was no adjustment for potential confounders, and there was limited assessment of exposure to secondhand smoke.] This dataset was recently re-evaluated (Sorahan *et al*., 2001). Microfilmed interview records of all study subjects were reviewed and information on parental cigarette smoking habits was re-abstracted. There was a statistically significant positive trend ($p = 0.02$) associated with daily paternal cigarette consumption before pregnancy for all cancers combined when cases were compared with controls selected from General Practitioners' (GPs') lists ($n = 555$), but no significant association was observed when cases were compared with hospital controls ($n = 555$). The opposite was seen for maternal smoking before pregnancy: an inverse trend ($p < 0.001$) was noted between daily cigarette consumption when cases were compared with hospital controls, but not when compared with GP controls. Risk estimates were adjusted for socioeconomic status, ethnicity, parental age at child's birth and other parent's smoking. [The Working Group noted that the two sets of controls produced very different results that are not easily explained.]

Stjernfeldt *et al*. (1986) reported the findings of a nationwide case–control study in Sweden that included 305 cases of cancer in children ≤ 16 years of age and 340 children with insulin-dependent diabetes mellitus who served as controls. Estimates of relative risk were adjusted for year of child's birth and maternal age, illness during pregnancy, occupation and place of residence. A 50% ($p < 0.01$) increase in risk for cancer was associated with in-utero exposure to maternal smoking. [The Working Group noted that the strengths of the study included the good response rate and the attempt to control for response bias by using children with diabetes mellitus as controls; its limitation was that the appropriateness of the control group was unknown.]

A case–control study from Sweden by Forsberg and Kallen (1990) found no association between childhood cancers and maternal smoking (relative risk, 1.1; 95% CI, 0.6–2.0) based on 69 cases and 139 controls for whom maternal smoking status was known. [The Working Group noted that the limitations of this study included the small sample size, uncertainty as to whether original case–control matching also applied to the substudy sample and the limited assessment of exposure.]

John *et al*. (1991) evaluated both maternal and paternal prenatal smoking histories in relation to risk for childhood cancer. The study included 223 incident cases < 15 years of age diagnosed from 1976 to 1983 in Denver, CO, USA. Controls were selected using random digit dialling and were matched to cases on age, sex and telephone exchange, and 196 controls were included in the analysis. Mothers' and fathers' smoking was highly correlated. Of the 109 children exposed to mother's smoking during the first trimester, 81% were also exposed to father's tobacco smoking while an additional 105 children were exposed to father's smoking alone. Mother's smoking during the first trimester was associated with a modest statistically nonsignificant increase in risk for childhood cancer after adjustment for father's education (relative risk, 1.3; 95% CI, 0.7–2.1). Children whose mothers did not smoke who were exposed to father's smoking also had a modest, statistically non-significant increase in risk (relative risk, 1.2; 95% CI, 0.8–2.1). [The Working Group noted that this study included a more detailed assessment of exposure to secondhand smoke than did earlier studies.]

Golding *et al*. (1992) conducted a case–control study in the United Kingdom to assess the association of childhood cancer with administration of intramuscular vitamin K and pethidine during labour. Data on mothers' smoking during pregnancy as a potential confounder were collected. A twofold increase in risk (relative risk, 2.0; 95% CI, 1.3–3.2) adjusted for year of delivery was found. [The Working Group noted that this study was not designed to investigate exposure to secondhand smoke, that only maternal smoking during pregnancy was recorded and that there was only minimal control for potential confounders.]

Three reports from the Oxford Survey of Childhood Cancer (OSCC) provided data from large case–control studies of childhood cancer deaths during different time periods: 1977–81 (Sorahan *et al*., 1995), 1953–55 (Sorahan *et al*., 1997a) and 1971–76 (Sorahan *et al*., 1997b). The first report in 1995 included 1641 cases and an equal number of controls. There was no association with prenatal maternal cigarette smoking; however,

paternal smoking was associated with a statistically significant positive trend (p for trend = 0.003). When cigarette use by one or both parents was adjusted for social class, maternal age at birth and use of alcohol, the relative risk was 1.4 (95% CI, 1.1–1.7) for father's use of cigarettes and 1.4 (95% CI, 1.1–1.7) for cigarette use by both parents, whereas cigarette use by mother was not statistically significantly associated with an increased risk (relative risk, 1.2; 95% CI, 1.0–1.6). A total of 1549 deaths from childhood cancer between 1953 and 1955 and 1549 matched healthy controls were used to further investigate the earlier findings from the OSCC (Sorahan *et al.*, 1997a). After adjustment for smoking by the spouse, social class, age of father, age of mother, birth order, and exposure to obstetric radiography, no statistically significant dose–response trend was found to be associated with maternal smoking, but maternal smoking only was associated with a 30% increased risk for childhood cancer (relative risk, 1.3; 95% CI, 1.1–1.5). At the highest level of paternal smoking (> 20 cigarettes per day), a clear trend was noted (p for trend < 0.001) with a relative risk of 1.4 (95% CI, 1.1–1.9); paternal smoking only was also associated with increased risk (relative risk, 1.7; 95% CI, 1.3–2.2). The third report (Sorahan *et al.*, 1997b) which examined deaths from 1971 to 1976 provided very similar results to those in the first two reports, i.e. no clear association with childhood cancer was evident for maternal smoking and there was a statistically significant positive trend for paternal smoking. [The Working Group noted the very large sample sizes, the consistent findings over time, the adjustment for potential confounders and the assessment of exposure from mothers and fathers with data for trends.]

A large case–control study in China by Ji *et al*. (1997) also examined paternal smoking and risk for cancer in children (< 15 years of age) of nonsmoking mothers. Relative risks were adjusted for birth weight, income, paternal age, education and alcohol drinking. For all sites combined, the relative risk for 'ever smoking' by the father was 1.3 (95% CI, 1.0–1.7). Statistically significant trends were found for duration of paternal smoking (p for trend = 0.007) and pack–years (p for trend = 0.01), but not age of starting smoking (p for trend = 0.28) or cigarettes per day (p for trend = 0.07). [The Working Group noted the large sample size, the minimization of exposure misclassification by including only children of nonsmoking mothers, the adjustment for potential confounders and the extensive exposure assessment for fathers.]

Boffetta *et al*. (2000) conducted a meta-analysis of childhood cancers associated with passive exposure to smoke based on the random effects model. The relative risk estimate for maternal smoking during pregnancy for all cancers combined included all cohort studies and eight of the ten case–control studies listed in Table 2.13 (Sorahan *et al*. 1997b; Ji *et al*. 1997; were not included). The results suggest a small increase in risk for all cancers for maternal smoking during pregnancy (relative risk, 1.1; 95% CI, 1.0–1.2), but not for specific cancer sites. Results on exposure before and after pregnancy were too sparse for any conclusion to be drawn. Studies of exposure to paternal tobacco smoke and risk for all cancers combined are fewer than those addressing maternal smoking and no relative risk was reported in this meta-analysis.

2.3.2 *Brain and central nervous system*

Table 2.14 lists one cohort study (Pershagen *et al*. 1992) and 15 case–control studies (Gold *et al*., 1979; Preston-Martin *et al*., 1982; Stjernfeldt *et al*., 1986; Howe *et al*., 1989; Kuijten *et al*., 1990; Gold *et al*., 1993; Bunin *et al*., 1994; Cordier *et al*., 1994; Filippini *et al*., 1994; McCredie *et al*., 1994; Norman *et al*., 1996; Ji *et al*., 1997; Sorahan *et al*., 1997a,b; Filippini *et al*., 2000) that have examined parental smoking and risk for brain tumours or for all tumours of the central nervous system combined.

Only the cohort study of Pershagen *et al*. (1992) (see section 2.3.1) has published a relative risk for tumours of the central nervous system. No association was found between maternal smoking in pregnancy and risk for tumours of the central nervous system.

The first case–control study to examine risk for brain tumour and maternal smoking was reported by Gold *et al*. (1979). This study was conducted in the USA and included 84 children with brain tumours and two control groups. One control group comprised 78 children with other malignancies matched on sex, race, date and age at diagnosis, and the other, 73 children selected from the state birth certificate file and matched on sex, date of birth and race. Risk associated with maternal smoking before and during pregnancy was associated with large non-statistically significant risks for childhood brain tumour that were based on a small sample size.

Preston-Martin *et al.* (1982) reported the findings from a larger case–control study in the USA designed to evaluate the risk for brain tumour associated with childhood exposure to *N*-nitroso compounds, including those from tobacco smoke. No increased risk was associated with maternal smoking, but a relative risk of 1.5 ($p = 0.03$) was found for children of mothers living with a smoker during pregnancy. The small Swedish case–control study by Stjernfeldt *et al*. (1986) (see section 2.3.1) found no increased risk for tumours of the central nervous system associated with maternal smoking in pregnancy.

An exploratory case–control study of brain tumours in Canadian children diagnosed in Ontario between 1977 and 1983 included 74 cases and 138 age- and sex-matched controls. The study found neither maternal nor paternal smoking during pregnancy to be statistically significantly associated with risk for brain tumours (Howe *et al*., 1989). Similarly, a population-based case–control study in the USA of childhood astrocytomas that included 163 case–control pairs found no increased risk associated with any smoking by either mother or father (Kuijten *et al.*, 1990).

A large population-based case–control study in the USA of childhood brain tumours examined smoking by both parents in some detail. The study included exposure assessments for the preconception period as well as the pre- and postnatal period (year of birth of child) and dose–response estimates (Gold *et al*., 1993). There was no statistically significant association between risk for brain tumours and any indicator of parental smoking. [The Working Group noted that this was a well-conducted study designed to examine parental smoking in detail, and having sufficient statistical power.]

Bunin *et al.* (1994) studied the two most common types of brain tumour, astrocytoma and primitive neuroectodermal tumour, in children less than six years of age. Controls,

Table 2.14. Tumours of the brain and central nervous system and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)
Cohort study					
Pershagen *et al*. (1992) (Sweden)	497 051 births, 81 CNS tumours	Cancer registry	Up to 5 years follow-up; 99% complete	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	 0.9 (0.5–1.6) 1.1 (0.6–2.1)
Case–control studies					
Gold *et al*. (1979) (USA)	84 brain tumours, 73 population controls, 78 cancer controls	In-person interview	10 years diagnosis of children < 20 years old; 66% case response rate; 20% population control response rate; 44% cancer control response rate	Maternal smoking during pregnancy With population controls With cancer controls	 5.0, $p < 0.22$ ∞
Preston-Martin *et al*. (1982) (USA)	209 brain tumours, 209 controls	Telephone interview	5 years diagnosis of cases < 25 years old; 66% case response rate; 78% control response rate	Maternal smoking during pregnancy Mother living with a smoker	1.1 (one-sided $p = 0.42$) 1.5 (one sided $p = 0.03$)
Stjernfeldt *et al*. (1986) (Sweden)	43 brain and CNS tumours, 332 controls	Physician-distributed questionnaire	3 years diagnosis in children < 17 years old; > 95% response rate	Maternal smoking during pregnancy *Cigarettes/day* 1–9 ≥ 10	 1.0 0.9

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Howe *et al*. (1989) (Canada)	74 brain tumours, 138 controls	In-person interview	6 years diagnosis of children < 20 years of age; 60% case response rate; 86% control response rate	*Any smoking*	Mother 1.4 (0.7–3.0)	Father 1.1 (0.6–2.1)
Kuijten *et al*. (1990) (USA)	163 astrocytomas, 163 controls	In-person interview	6 years diagnosis of children < 15 years of age; 80% case response rate; 73% control response rate	*Any smoking*	Mother 1.0 (0.6–1.7)	Father 0.8 (0.5–1.3)
Gold *et al*. (1993) (USA)	361 brain tumours, 1083 controls	In-person interview	4 years diagnosis of children < 18 years of age; 85% case response rate; 85% control response rate	*Any smoking*	Mother 0.9 (0.7–1.2)	Father 1.1 (0.8–1.4)
				During year of birth (packs/day)		
				< 1	0.8 (0.6–1.3)	0.7 (0.4–1.2)
				≥ 1	1.0 (0.7–1.4)	1.1 (0.8–1.5)
				Two years before birth (packs/day)		
				< 1	0.8 (0.5–1.1)	0.9 (0.5–1.5)
				≥ 1	1.0 (0.7–1.4)	1.2 (0.9–1.6)

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Bunin *et al*. (1994) (USA)	155 astrocytic gliomas, 166 primitive neuroectodermal tumours and 155 and 166 controls, respectively	Telephone interview	3 years diagnosis of children < 6 years of age; 65% case response rate; 83% control response rate	**Astrocytic glioma**	Mother	Father
				Ever smoked	1.1 (0.7–1.8)	1.1 (0.7–1.8)
				Smoked during pregnancy	1.0 (0.6–1.7)	1.0 (0.6–1.7)
				Primitive neuro-ectodermal tumour		
				Ever smoked	0.9 (0.6–1.5)	0.9 (0.6–1.5)
				Smoked during pregnancy	1.0 (0.6–1.7)	1.0 (0.6–1.7)
Cordier *et al*. (1994) (France)	75 brain tumours, 113 controls	In-person interview	2 years diagnosis of children < 15 years of age; 69% case response rate; 72% control response rate	Any smoking by mother	1.6 (0.7–3.5)	
Filippini *et al*. (1994) (Italy)	91 brain tumours, 321 controls	In-person interview	3 years diagnosis of children < 15 years of age; 88% case response rate; 75% control response rate	Maternal smoking during pregnancy	1.7 (0.8–3.8)	
				Maternal smoking		
				1–10 cigarettes/day	2.0 (1.0–4.0)	
				> 10 cigarettes/day	1.6 (0.5–4.8)	
				Paternal smoking before pregnancy	1.3 (0.8–2.4)	
McCredie *et al*. (1994) (Australia)	82 brain tumours, 164 controls	In-person interview	4 years diagnosis of children < 15 years of age; 85% case response rate; 60% control response rate	Questions related to sources of exposure to *N*-nitroso compounds including tobacco smoke	No association	

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Norman *et al*. (1996) (USA)	540 brain tumours, 801 controls	In-person and telephone interviews	6 years diagnosis of children < 15 years of age; 71% case response rate; 74% control response rate	Any smoking	Mother 1.0 (0.7–1.3)	Father 1.2 (0.9–1.5)
Ji *et al*. (1997) (China)	107 brain tumours, 107 controls	In-person interview	10 years diagnosis of children < 15 years of age; 83% case response rate; 100% control response rate	Paternal smoking *Cigarettes/day* 1–9 10–14 ≥ 15 *Duration of exposure (years)* < 10 10–14 ≥ 15	 1.5 (0.5–4.5) 1.6 (0.6–4.7) 2.1 (0.6–8.1) 0.8 (0.2–3.8) 1.3 (0.4–4.1) 3.4 (0.9–12.5)	
Sorahan *et al*. (1997a) (United Kingdom)	229 CNS tumours, 229 controls	In-person interview	Deaths 1953–55 in children < 16 years of age; 88% case response rate; 94% control response rate	Parental smoking	Mother 1.0 (0.8–1.4)	Father 1.2 (1.0–1.5)
Sorahan *et al*. (1997b) (United Kingdom)	410 CNS tumours, 410 controls	In-person interview	Deaths 1971–76 in children < 16 years of age; 63% case response rate; control response rate not reported	Parental smoking	Mother 1.1 (1.0–1.2)	Father 1.0 (0.9–1.1)

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)
Filippini *et al*. (2000) (Italy)	244 CNS tumours, 502 controls	Telephone interview	5 years diagnosis of children < 16 years old; 85% case response rate; 88% control response rate	*Maternal smoking* Before pregnancy Before she knew she was pregnant *Maternal exposure to secondhand smoke* During early pregnancy During late pregnancy	 1.2 (0.9–1.7) 1.5 (1.0–2.3) 1.8 (1.2–2.6) 1.7 (1.2–2.5)

CNS, central nervous system

selected by random-digit dialling, were matched to cases on race, year of birth, and telephone area code and prefix. Estimates of relative risk for astrocytoma were adjusted for income level, but primitive neuroectodermal tumour estimates were unadjusted. No association was found between either of these types of tumour and maternal active (ever and/or during pregnancy) or passive smoking (during pregnancy) or paternal smoking (ever and/or during pregnancy).

A non-statistically significant increase in risk for brain tumours (relative risk, 1.6; 95% CI, 0.7–3.5) associated with any smoking by the mother was found in a small case–control study in France (Cordier *et al*. 1994). Filippini *et al.* (1994) in Italy assessed the risk associated with active and passive smoking by mothers during pregnancy in a case–control study with 91 cases. Active smoking by the mother during pregnancy was associated with a relative risk of 1.7 (95% CI, 0.8–3.8); no dose–response relationship was observed. Relative risks were adjusted for education level. Among nonsmoking mothers, the relative risks for light and heavy exposure to secondhand smoke were 1.7 (95% CI, 0.8–3.6) and 2.2 (95% CI, 1.1–4.5; p trend = 0.02). McCredie *et al*. (1994) conducted another small, population-based case–control study of brain tumours in Australia. Two controls were matched to each case by age and sex. No association was found with exposure to tobacco smoke from another member of the household, but no risk estimates were provided. [The Working Group noted that the limitations of these studies were that they lacked statistical power; there was limited adjustment for potential confounders and limited assessment of exposure.]

The findings from a large, population-based case–control study of brain tumours in children < 15 years of age diagnosed from 1984 to 1991 provided no support for an association between brain tumour risk and maternal or paternal smoking before pregnancy or maternal smoking during pregnancy (Norman *et al*. 1996). Risk estimates were at or below unity and there was no evidence of a relationship between risk for brain tumours and amount or timing of exposure. [The Working Group noted that the strengths of this study were that it was large and included a relatively detailed assessment of exposure.]

Three studies discussed previously (Ji *et al*. 1997; Sorahan *et al*. 1997a,b) found no increased risk for brain tumours associated with father's smoking (Ji *et al*., 1997) or of tumours of the central nervous system associated with maternal or paternal smoking (Sorahan *et al*., 1997a,b; 2001).

Filippini *et al*. (2000) in northern Italy, conducted a population-based case–control study of childhood tumours of the central nervous system with cases diagnosed from 1988 to 1993. Cases from their previous study (Filippini *et al*., 1994) were excluded. Active smoking by parents before pregnancy was not associated with increased risk. Active smoking by mothers in early pregnancy was associated with a small increase in risk (relative risk, 1.5; 95% CI, 1.0–2.3). An increase in risk was also associated with passive smoking by nonsmoking mothers in early pregnancy (relative risk, 1.8; 95% CI, 1.2–2.6) and late pregnancy (relative risk, 1.7; 95% CI, 1.2–2.5).

The results of the meta-analysis by Boffetta *et al*. (2000) indicated no significant increase in risk for tumours of the central nervous system associated with maternal

smoking during pregnancy (relative risk, 1.0; 95% CI, 0.9–1.2), but exposure to paternal smoking suggested an increased risk for brain tumours (relative risk, 1.1; 95% CI, 1.1–1.4). [The Working Group noted that this meta-analysis included two studies of neuroblastoma and one study of retinoblastoma with tumours of the central nervous system.]

2.3.3 *Leukaemias and lymphomas*

The only cohort study to report specifically on lymphatic and haematopoietic cancers (Pershagen *et al.*, 1992) and 16 case–control studies with data on one or more of these types of malignancy are included in Table 2.15 (Manning & Carroll, 1957; Stewart *et al*., 1958; Van Steensel-Moll *et al*., 1985; Buckley *et al*., 1986; McKinney *et al*., 1986; Stjernfeldt *et al*., 1986; Magnani *et al*., 1990; John *et al*., 1991; Roman *et al*., 1993; Severson *et al*., 1993; Shu *et al*., 1996; Ji *et al*., 1997; Sorahan *et al*., 1997a,b; Brondum *et al*., 1999; Infante-Rivard *et al*., 2000).

A total of 129 lymphatic and haematopoietic cancers were diagnosed during 5 years of follow-up in the Swedish cohort (Pershagen *et al*., 1992). No association was observed between the development of these cancers and smoking during pregnancy or any amount of smoking by the mother.

Manning and Carroll (1957) found no difference in the proportion of mothers of children with leukaemia who smoked 10 or more cigarettes per day at the time of interview when compared to control mothers (39% versus 38%) and a somewhat lower proportion of mothers of children with lymphoma (31%) who smoked at that level. A second early study (Stewart *et al.*, 1958) reported a very small but statistically significant increase in risk for death from leukaemia among children of mothers who had ever smoked (relative risk, 1.1; $p < 0.04$). [The Working Group noted that neither study was designed specifically to study the effects of involuntary smoking; only unadjusted proportions were reported.]

Van Steensel-Moll *et al*. (1985) found no association between maternal smoking in the year before pregnancy and risk for acute lymphocytic leukaemia in a study in the Netherlands designed to assess maternal fertility problems and this risk. [The Working Group noted that the strength of this study was the large number of cases. Its limitations are the limited assessment of exposure and the questionable time period.] The case–control study in Sweden by Stjernfeldt *et al*. (1986) included 157 cases of acute lymphoblastic leukaemia, 16 cases of non-Hodgkin lymphoma and 15 cases of Hodgkin disease. A statistically significant positive trend (p trend < 0.01) was found for number of cigarettes smoked per day by the mother during pregnancy and risk for acute lymphoblastic leukaemia. No statistically significant association with smoking was observed for either non-Hodgkin lymphoma or Hodgkin disease based on a very small number of cases.

McKinney *et al*. (1986) found no association between maternal smoking during pregnancy and risk for childhood leukaemia or lymphoma. Buckley *et al.* (1986) also failed to find an association between maternal smoking during pregnancy in their large

Table 2.15. Childhood leukaemias and lymphomas and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Cohort study							
Pershagen *et al*. (1992) (Sweden)	497 051 births, 129 lymphatic and haematopoietic cancers	Cancer registry	5 years follow-up; 327 of 422 cancers linked to births with smoking data.	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	1.0 (0.7–1.5) 1.2 (0.8–1.9) 0.8 (0.4–1.5)		
Case–control studies							
Manning & Carroll (1957) (USA)	188 leukaemias, 42 lymphomas, 50 hospital controls	Interview	3 years diagnosis of children < 15 years of age	Proportion of mothers smoking ≥ 10 cigarettes/day at time of interview	Leukaemia 39%	Lymphoma 31%	Controls 38%
Stewart *et al*. (1958) (United Kingdom)	677 leukaemias, 739 other cancers, 1416 living controls	In-person interview	3 years diagnosis of children < 15 years of age	Mother ever smoked	1.1 ($p < 0.04$)		
Van Steensel-Moll *et al*. (1985) (the Netherlands)	519 ALL, 507 controls	Postal questionnaire	7 years diagnosis of children < 15 years of age; 90% case response rate; 69% control response rate	Maternal smoking during year before pregnancy	1.0 (0.8–1.3)		
Stjernfeldt *et al*. (1986) (Sweden)	157 ALL, 16 NHL, 15 HD, 340 controls	Physician-delivered questionnaire	3 years diagnosis of children < 17 years of age; 95% response rate for both cases and controls	*Maternal smoking during pregnancy* 1–9 cigarettes/day ≥ 10 cigarettes/day	ALL 1.3 2.1	NHL 2.0 2.1	HD 1.1 0.3
McKinney *et al*. (1986) (United Kingdom)	171 leukaemias, 74 lymphomas, 2 controls/case	Not reported	Response rate not reported	*Maternal smoking during pregnancy* 1–10 cigarettes/day > 10 cigarettes/day	Leukaemia 1.0 (0.6–1.7) 0.6 (0.4–1.0)	Lymphoma 1.9 (0.9–4.0) 1.0 (0.5–2.1)	
Buckley *et al*. (1986) (USA, Canada)	742 ALL, 169 NHL, 720 controls	Question-naire	3 years diagnosis of cancer in children (age not given). Response rate not reported	*Maternal smoking during pregnancy* 1–9 cigarettes/day ≥ 10 cigarettes/day	ALL 1.0 (0.6–1.0) 0.9 (0.7–1.1)	NHL 0.8 (0.3–1.8) 1.0 (0.7–1.4)	

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Magnani *et al*. (1990) (Italy)	142 ALL, 22 other leukaemias (non-ALL), 19 NHL, 307 controls	In-person interview	10 years diagnosis in cases < 15 years of age. Response rate not reported		ALL	Non-ALL	NHL
				Maternal smoking up to child's birth	0.7 (0.5–1.1)	2.0 (0.8–4.8)	1.7 (0.7–4.5)
				Paternal smoking	0.9 (0.6–1.5)	0.9 (0.3–2.1)	6.7 (1.0–43.4)
John *et al*. (1991) (USA)	73 leukaemias, 26 lymphomas, 196 controls	Telephone interview	7 years diagnosis in children < 15 years of age; 71% case response rate; 63% control response rate	*Maternal smoking*	ALL	Non-ALL	Lymphoma
				3 months before conception	2.1 (1.0–4.3)	0.8 (0.2–2.7)	1.9 (0.7–5.2)
				First trimester	2.3 (1.1–5.0)	1.1 (0.3–4.0)	2.5 (0.9–7.0)
				All 3 trimesters	2.5 (1.2–5.4)	0.6 (0.1–3.0)	2.7 (1.0–7.6)
Severson *et al*. (1993) (USA, Canada)	187 acute myeloid leukaemias, 187 controls	Telephone interview	4 years diagnosis in children < 18 years of age; 78% case response rate; 79% control response rate	*Maternal smoking*			
				During pregnancy	1.2 (0.8–1.9)		
				Current smoker	0.9 (0.6–1.4)		
				Ever smoker	1.3 (0.9–2.1)		
Roman *et al*. (1993) (United Kingdom)	54 leukaemias and NHL, 324 controls	Interview, birth certificates, occupational and medical records	17 years diagnosis in cases < 5 years of age; 76% case response rate; 95% control response rate	*Smoking during pregnancy*			
				From obstetric records	0.9 (0.3–2.5)		
				From interview	0.5 (0.2–1.2)		
Shu *et al*. (1996) (USA, Canada, Australia)	302 leukaemias, 558 controls	Telephone interview	5 years diagnosis of children ≤ 18 months of age; 79% case response rate; 75% control response rate		Mother	Father	
				Smoking during pregnancy		1.2 (0.9–1.8)	
				Cigarettes/day			
				1–10	0.7 (0.4–1.0)		
				11–20	0.6 (0.4–1.1)		
				> 20	0.6 (0.2–1.8)		
					p for trend = 0.03		
Ji *et al*. (1997) (China)	166 acute leukaemias, 87 lymphomas, 166 and 87 controls, respectively	In-person interview	10 years diagnosis of children <15 years of age; 83% case response rate; 100% control response rate	Paternal smoking before conception	Acute leukaemia	Lymphoma	
				Cigarettes/day			
				< 10	1.6 (0.7–3.9)	3.4 (0.8–14.0)	
				10–14	0.9 (0.4–1.5)	1.1 (0.3–4.8)	
				≥ 15	1.9 (0.8–4.6)	3.8 (0.9–16.5)	
					p for trend = 0.27	*p* for trend = 0.09	

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Ji *et al*. (1997) (contd)				*Pack–years*		
				≤ 5	0.9 (0.4–2.2)	2.8 (0.6–12.8)
				> 5–< 10	1.1 (0.5–2.6)	1.3 (0.3–5.5)
				≥ 10	1.9 (0.8–4.6)	5.7 (1.3–26.0)
					p for trend = 0.06	*p* for trend = 0.03
Sorahan *et al*. (1997a) (United Kingdom)	367 ALL, 115 myeloid leukaemias, 27 monocytic leukaemias, 216 other, unspecified leukaemias, 125 lymphomas, equal numbers of controls	In-person interview	2 years diagnosis of children < 16 years old; 88% case response rate; 60% control response rate	Parental smoking	Mother	Father
				Leukaemias		
				ALL	1.2 (1.0–1.5)	1.1 (0.9–1.3)
				Myeloid	1.2 (0.9–1.7)	1.0 (0.7–1.3)
				Monocytic	1.2 (0.6–2.5)	1.1 (0.6–2.0)
				Other	1.2 (0.9–1.6)	1.1 (0.9–1.4)
				Lymphomas	0.8 (0.6–1.1)	1.4 (1.0–1.8)
Sorahan *et al*. (1997b) (United Kingdom)	573 ALL, 190 myeloid leukaemias, 25 monocytic leukaemias, 47 other unspecified leukaemias, 165 lymphomas, equal numbers of controls	In-person interview	5 years diagnosis in children < 16 years of age; 57% case response rate; 52% control response rate	Parental smoking	Mother	Father
				Leukaemias		
				ALL	1.0 (0.9–1.1)	1.1 (1.0–1.2)
				Myeloid	1.0 (0.8–1.2)	1.3 (1.1–1.5)
				Monocytic	0.7 (0.4–1.2)	0.8 (0.6–1.3)
				Other	0.9 (0.7–1.2)	1.0 (0.8–1.3)
				Lymphomas	1.1 (0.9–1.2)	1.1 (0.9–1.2)
Brondum *et al*. (1999) (USA)	1842 ALL, 1987 controls, 517 AML, 612 controls	Telephone interview	3.5 years diagnosis of acute leukaemia < 5–18 years of age. Case response rates: 92% ALL, 83% AML; control response rates: 76.5% ALL controls, 79.4% AML controls		ALL	AML
				Father ever smoked	1.0 (0.9–1.2)	0.9 (0.7–1.2)
				Mother ever smoked	1.0 (0.9–1.2)	1.0 (0.7–1.2)

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Infante-Rivard *et al*. (2000)	491 ALL, 491 controls	Telephone interview	13 years diagnosis of ALL in children < 10 yrs of age. 96.3% case response rate; 83.8% control response rate	Parental smoking during childhood	Mother 1.0 (0.7–1.4)	Father 1.0 (0.7–1.4)	
				Cigarettes/day 1–20 > 20	1.0 (0.6–1.3)	1.0 (0.7–1.3)	
				Maternal smoking *Cigarettes/day*	1st trimester	2nd trimester	3rd trimester
				1–20	1.1 (0.8–1.6)	1.2 (0.8–1.6)	1.2 (0.8–1.6)
				> 20	1.0 (0.7–1.6)	1.2 (0.7–1.9)	1.2 (0.8–2.0)
	158 cases, 491 controls (case–case substudy)			*At > 20 cigarettes/day* CYP1A1*2A allele CYP1A1*2B allele CYP1A1*4 allele	Moderate risk increases Reduced risk Lower increases associated with father's smoking; mother's smoking risks higher in 3rd trimester		

ALL, acute lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; AML, acute myeloblastic leukaemia

study that included 742 cases of acute lymphocytic leukaemia and 169 cases of non-Hodgkin lymphoma.

Magnani *et al.* (1990) found no association between acute lymphocytic leukaemia, other leukaemias or non-Hodgkin lymphoma during childhood and the mother's smoking up to the time of the child's birth. The father's history of smoking was associated with a risk for non-Hodgkin lymphoma (relative risk, 6.7; 95% CI, 1.0–43.4), but not for acute lymphocytic leukaemia or other leukaemias. This Italian hospital-based case–control study included 142 cases of acute lymphocytic leukaemia, but only a small number of non-Hodgkin lymphoma (n = 19) and other types of leukaemia (n = 22). Risk estimates were adjusted for socioeconomic status only.

The case–control study in the USA reported by John *et al*. (1991) included 73 cases of leukaemia and 26 cases of lymphoma. Statistically significant increases in risk were associated with maternal smoking 3 months before conception for acute lymphocytic leukaemia; with smoking during the first trimester for acute lymphocytic leukaemia; and during all three trimesters for acute lymphocytic leukaemia (relative risk, 2.5; 95% CI, 1.2–5.4) and lymphoma (relative risk, 2.7; 95% CI, 1.0–7.6).

A US–Canadian case–control study of acute myeloid leukaemia found no association between risk for acute myeloid leukaemia and maternal smoking before, during or after pregnancy (Severson *et al*. 1993). No association was observed with smoking by the father, but this was not quantified. [The Working Group noted the reasonably detailed exposure assessment, but although relative risks were adjusted for potential confounders, the factors were not named.]

A small case–control study of leukaemia and non-Hodgkin lymphoma in the United Kingdom examined maternal smoking based on obstetric notes and by interview (Roman *et al*., 1993). Both relative risks were below unity. [The Working Group noted that very little information was provided, that no adjustment was made for confounders, and the small size of the sample.]

Shu *et al*. (1996) found that maternal smoking during pregnancy was negatively associated with risk for leukaemia (all leukaemias, acute lymphocytic leukaemia or acute myeloblastic leukaemia) in infants. Paternal smoking one month prior to pregnancy was related to an elevated risk for acute lymphocytic leukaemia (relative risk, 1.6; 95% CI, 1.0–2.4), but not acute myeloblastic leukaemia and smoking by the father during pregnancy did not lead to a statistically significant increase in risk for any type of leukaemia. [The Working Group noted that the strengths of this study included the relatively detailed exposure from mothers' and fathers' smoking, and the adjustment for some potential confounders (sex, parental age, education and alcohol consumption by the mother during pregnancy).]

The case–control study of paternal smoking and childhood cancer in China reported by Ji *et al*. (1997) included 166 cases of acute leukaemia and 87 of lymphoma. No statistically significant association with paternal smoking was found for leukaemia, although a borderline positive trend was found for the father's number of pack–years of smoking (trend, p = 0.06). The father's smoking was associated with a fourfold increase in risk for

lymphoma (relative risk, 4.0; 95% CI, 1.3–12.5) and statistically significant positive dose–response trends for lymphoma were observed for number of years smoked preconception and pack–year history, but not for number of cigarettes smoked per day.

Sorahan *et al.* (1997a) reported a modest association between risk for acute lymphocytic leukaemia and maternal smoking (relative risk, 1.2; 95% CI, 1.0–1.5), but no increased risk was found for myeloid, monocytic or other types of leukaemia or lymphoma. This study found no relationship between paternal smoking and any type of leukaemia, but the risk estimate for lymphoma was 1.4 (95% CI, 1.0–1.8). No increased risks associated with parental smoking were found when cases and controls from a later time period, 1971–76, were examined (Sorahan *et al*. 1997b).

A large case–control study in the USA of parental cigarette smoking and risk for acute leukaemia collected detailed information on exposure to smoke from the mothers and fathers of 1842 children with acute lymphocytic leukaemia and 517 with acute myeloblastic leukaemia and controls matched on age, race, and telephone area code/exchange (Brondum *et al*., 1999). There was no association between risk for acute lymphocytic leukaemia and ever smoking by the father (relative risk, 1.0; 95% CI, 0.9–1.2) or mother (relative risk, 1.0; 95% CI, 0.9–1.2); similarly, no associations were observed between acute myeloblastic leukaemia and ever smoking by the father (relative risk, 0.9; 95% CI, 0.7–1.2) or the mother (relative risk, 1.0; 95% CI, 0.7–1.2). Parental smoking during or around the time of the index pregnancy was not related to risk, nor were the number of cigarettes smoked, years of smoking or pack–years. Risk estimates were adjusted for household income, mother's race and education and father's race and education. [The Working Group noted the good statistical power and the detailed histories of both parents and also that some adjustment has been made for potential confounders.]

A case–control study in Canada of acute lymphocytic leukaemia assessed the role of parental smoking and *CYP1A1* genetic polymorphisms (Infante-Rivard *et al*., 2000). There was no statistically significant association between parents' smoking and leukaemia overall. However, a substudy that included 158 of the 491 cases suggested that the effect of parental smoking may be modified by variant alleles in the *CYP1A1*. *CYP1A1*2B* tended to decrease risks and *CYP1A1*2A* and *CYP1A1*4* increased the risks associated with smoking in the second and third trimesters. [The Working Group noted that this was the first study to look at the interaction between parental smoking, *CYP1A1* and leukaemia.]

Sorahan *et al*. (2001) (see Section 2.3.1) found a statistically non-significant positive association between risk for acute lymphocytic leukaemia and daily cigarette consumption by fathers before pregnancy and a statistically non-significant inverse association between risk for acute lymphocytic leukaemia and daily smoking by mothers before pregnancy.

The results of the meta-analysis for maternal smoking during pregnancy indicated that there were no statistically significant associations for all lymphatic and haematopoietic neoplasms (relative risk, 1.0; 95% CI, 0.9–1.2), for non-Hodgkin lymphoma or total lymphomas (relative risk, 1.1; 95% CI, 0.9–1.5) or for all leukaemias, acute leukaemia or

acute lymphocytic leukaemia (relative risk, 1.1; 95% CI, 0.8–1.3) (Boffetta *et al*., 2000). The authors found evidence of publication bias for the data available on lymphomas ($p = 0.04$). Published studies with a small number of cases reported positive associations between exposure to tobacco smoke and childhood leukaemia, whereas larger studies showed no association. This suggests that small studies that had found no association or a negative association failed to be published. The meta-analysis for paternal smoking indicated no statistically significant association with acute lymphocytic leukaemia, but a twofold increase in risk for non-Hodgkin lymphoma (relative risk, 2.1; 95% CI, 1.1–4.0).

2.3.4 *Other childhood cancers*

Several other types of childhood cancer have been studied in relation to parental smoking in epidemiological investigations.

The cohort study by Pershagen *et al*. (1992) reported no statistically significant associations between mother's smoking during pregnancy and kidney cancer (30 cases; relative risk, 0.6; 95% CI, 0.2–1.5), eye tumours (28 cases; relative risk, 1.4; 95% CI, 0.6–2.8), endocrine tumours (13 cases; relative risk, 1.9; 95% CI, 0.6–6.0) or tumours of the connective tissue and muscle (15 cases; relative risk, 1.2; 95% CI, 0.4–3.6).

Magnani *et al*. (1989) conducted a hospital-based case–control study of soft-tissue sarcomas in Italy during 1983–84. The cases included 36 children with rhabdomyosarcoma and 16 cases of other soft-tissue sarcomas who were compared with 326 controls from the same hospitals. No associations were found between soft-tissue sarcoma or rhabdomyosarcoma and either mother's or father's smoking (all point estimates of relative risks were below unity). Smoking during several time periods, before, during and after birth was then looked at separately and the results were the same as for any smoking by the parents. [The Working Group noted that this was a small study, but that the exposure assessment included different time periods.]

Two studies in the USA (Holly *et al*., 1992; Winn *et al*., 1992) examined risk factors for Ewing's sarcoma. In their population-based study, Holly *et al*. (1992) looked at 43 cases and 193 controls selected by random digit dialling and matched to cases by sex and age. This tumour was not associated with smoking by the mother during pregnancy (relative risk, 1.1; 95% CI, 0.5–2.4) or by the father (relative risk, 0.9; 95% CI, 0.4–1.9). Risk estimates were adjusted for agricultural occupation of the father, poison or overdose of medication, area of residence, year of child's birth and income. [The Working Group noted that this was a small study that had made a detailed assessment of many factors, but less for parental smoking.] Winn *et al*. (1992) reported the findings of a larger case–control study that included 208 cases throughout the USA and two control groups with equal numbers of controls (sibling controls and regional controls). When cases were compared to regional controls, no significant risk estimates were found for smoking by either parent; however, parents were more likely to have smoked during pregnancy with the child with Ewing's sarcoma than during the pregnancy with the unaffected sibling; if only the mother smoked, the relative risk was 1.5 (95% CI, 0.3–9.0); if only the father

smoked, the relative risk was 3.1 (95% CI, 0.7–14.0); if both parents smoked, the relative risk was 7.3 (95% CI, 1.3–41.6).

Two case–control studies in the USA evaluated prenatal drug consumption by the mother and risk for neuroblastoma (Kramer *et al*., 1987; Schwartzbaum, 1992). The first study was population-based and included 104 cases diagnosed from 1970 to 1979, a first group of 104 controls matched on date of birth, race and the first five digits of case's telephone number and a second group of controls comprising siblings of the index case. No significant increase in risk was associated with maternal smoking during pregnancy when cases were compared to either control group. The second study compared 101 newly diagnosed cases of neuroblastoma and 690 controls diagnosed with other types of childhood cancer at St Jude Children's Research Hospital. Cigarette smoking by the mother during pregnancy was found to increase the risk for neuroblastoma (relative risk, 1.9; 95% CI, 1.1–3.2). [The Working Group noted the questionable appropriateness of the control group in the study by Schwartzbaum and the limited exposure assessments in both studies.]

Olshan *et al*. (1993) reported findings from the National Wilms Tumour Study, a case–control study from a national collaborative clinical trial group in the USA. The study was conducted using interviews with 200 cases and 233 matched controls identified by random-digit dialling. No association was found for mother's smoking during pregnancy and risk for Wilms tumour (relative risk for smoking ten or more cigarettes per day, 0.7; 95% CI, 0.4–1.3).

2.4 Other cancers

2.4.1 *All cancer sites combined*

Hirayama (1984) reported a statistically significant association (p for trend < 0.001) between husband's smoking and cancer mortality in wives for all sites combined in the Japanese cohort (relative risk for former smoker: 1–19 cigarettes per day, 1.1; 95% CI, 1.0–1.2; relative risk for ≥ 20 cigarettes per day, 1.2; 95% CI, 1.1–1.4).

Sandler *et al*. (1985b), in their study previously described in detail (Section 2.2.2), found an increased risk of all cancers combined among nonsmokers passively exposed to cigarette smoke in adulthood (relative risk, 2.1; 95% CI, 1.4–3.0). Risk did not differ according to race (white or non-white), but was statistically significant only among women aged 30–49 years.

Miller (1990) reported the findings from a case–control study in the USA of cancer deaths among nonsmoking women in which next-of-kins were interviewed by telephone. Data on 906 nonsmoking wives were included in this report. The cases were women who had died of any type of cancer and the controls were nonsmoking wives who had died of cardiovascular, respiratory, kidney and other non-cancer diseases, excluding trauma. A nonsmoker was defined as a person who had smoked fewer than 20 packs of cigarettes during her lifetime. The percentage of deaths from cancer among non-exposed, non-

employed wives was 2.2%; for exposed, non-employed wives, 18.9%, and for employed wives, 34.3% ($p < 0.001$). [The Working Group noted that the study used a questionable comparison group and a non-standard definition of a nonsmoker.]

2.4.2 *Cervical cancer*

Three Asian cohort studies described in Section 2.1 also reported on involuntary smoking and risk for cancer of the cervix. Risk for cervical cancer associated with involuntary exposure to smoking in nonsmokers was examined in a Japanese cohort study that found no significant increase in risk associated with husbands' smoking (Hirayama, 1984). A second cohort study also considered exposure to husbands' smoking and risk for cervical cancer in nonsmoking Korean women (Jee *et al*., 1999). The relative risk based on 203 cases of cervical cancer in nonsmokers was 0.9 (95% CI, 0.6–1.3) for women married to former and 0.9 (95% CI, 0.6–1.2) for women married to current smokers when compared with women married to nonsmokers. The cohort study by Nishino *et al*. (2001) included 11 incident cases of cervical cancer. Again, no association with husband's smoking status was observed (relative risk, 1.1; 95% CI, 0.3–4.5). [The Working Group noted that these cohort studies consistently indicated no association between exposure to secondhand smoke and cervical cancer.]

The case–control study from the USA reported by Sandler *et al*. (1985b; see Section 2.2.2) found an increased risk of cervical cancer associated with spousal smoking (relative risk, 2.1; 95% CI, 1.2–3.9). A second case–control study in the USA was conducted from 1984 to 1987 in Utah where a large percentage of the population are members of the Church of Jesus Christ of the Latter-day Saints which proscribes tobacco smoking (Slattery *et al*., 1989). The cases were population-based and controls were selected by random-digit dialling and matched to cases on age and county of residence. The response rates for cases and controls were 66% and 76%, respectively. Nonsmokers involuntarily exposed for 3 hours or more per day to secondhand smoke were found to have an increased risk for cervical cancer (relative risk, 3.4; 95% CI, 1.2–9.5). Self-characterized exposure to 'a lot' of secondhand smoke was also associated with increased risk (in-home relative risk, 2.9; 95% CI, 1.1–7.9; outside the home relative risk, 1.6; 95% CI, 0.6–4.5). [The Working Group noted that a statistically non-significant increase in risk was also observed in active smokers exposed to smoking by others.]

Coker *et al*. (1992) examined the risk of exposure to secondhand smoke in a case–control study of cervical intraepithelial neoplasma (CIN) of grades II ($n = 40$) and III ($n = 63$) in the USA. No statistically significant association was found between exposure to secondhand smoke and CIN II/III in nonsmokers, after adjustment for age, race, education, number of partners, contraceptive use, history of sexually transmitted disease and history of Pap smear. Another case–control study conducted in the USA compared 582 women with abnormal Pap smears (class 2–4) with 1866 controls with normal cytology (Scholes *et al*., 1999). Nonsmokers exposed to secondhand smoke from spouses, partners or other household members were found to have a borderline increase in risk for abnormal

cervical cytology compared to nonsmokers who were not exposed to these sources of secondhand smoke (relative risk, 1.4; 95% CI, 1.0–2.0). Risk estimates were adjusted for age, age at first sexual intercourse, and number of sexual partners during lifetime.

2.4.3 *Gastrointestinal cancers*

The incidence of colorectal cancer in relation to passive exposure to smoke, which was defined as having lived with a person who smoked, was examined in a 12-year prospective cohort study in Washington County, MD, USA (Sandler *et al*., 1988). A statistically significant reduction in risk for colorectal cancer was observed for nonsmoking women who were involuntarily exposed to smoking (relative risk, 0.7; 95% CI, 0.6–1.0), but an increased risk for this cancer was found for nonsmoking men exposed to secondhand smoke in the household (relative risk, 3.0; 95% CI, 1.8–5.0).

In a Swedish population-based case–control study, Gerhardsson de Verdier *et al*. (1992) found an increased risk for colon cancer in women (relative risk, 1.8; 95% CI, 1.2–2.8) and rectal cancer in men (relative risk, 1.9; 95% CI, 1.0–3.6) in association with passive smoking after adjustment for numerous potential confounders. [The Working Group noted that it is unclear whether the analysis was restricted to never-smokers.]

A large Canadian case–control study of 1171 patients newly diagnosed with histologically confirmed stomach cancer and 2207 population controls evaluated the risk associated with active and passive smoking (Mao *et al*., 2002). Response rates of approximately 65% were obtained for both cases and controls. The analysis of passive smoking was conducted in male never-smokers (132 cases, 343 controls). Questionnaires were mailed to respondents and provided information on lifetime exposure to secondhand smoke through residential and occupational histories and also looked at source, intensity, and duration of exposure. Risk estimates for passive smoking were adjusted for 10-year age group, province of residence, education, social class, total consumption of meat and total consumption of vegetables, fruits and juices. A positive trend ($p = 0.03$) in risk for cancer of the gastric cardia was associated with lifetime exposure to secondhand smoke (sum of years of residential plus occupational exposure) in male never-smokers. At the highest level of exposure (≥ 43 years), the relative risk was 5.8 (95% CI, 1.2–27.5). No increased risks or trends were associated with risk for distal gastric cancer. Risks assessed by subsite (cardia and distal), were similar for active and passive smoking.

2.4.4 *Nasopharyngeal and nasal sinus cavity cancer*

The relationship between involuntary exposure of nonsmokers to secondhand smoke and risk for these rare cancers of the upper respiratory tract has been examined in one cohort study (Hirayama, 1984) and four case–controls studies (Fukuda & Shibata, 1990; Zheng *et al*., 1993; Cheng *et al*., 1999; Yuan *et al*., 2000). A positive association was found in most of these studies.

Hirayama (1984) found an increased risk of nasal sinus cancer in women (histology not noted) associated with increasing numbers of cigarettes smoked by husbands of non-smoking women. When compared with nonsmoking women married to nonsmokers, wives whose husbands smoked had a relative risk of 1.7 (95% CI, 0.7–4.2) for 1–14 cigarettes per day, 2.0 (95% CI, 0.6–6.3) for 15–19 cigarettes per day and 2.55 (95% CI, 1.0–6.3) for ≥ 20 cigarettes per day (p for trend = 0.03).

Fukuda and Shibata (1990) reported the results of the first Japanese case–control study based on 169 cases of squamous-cell carcinoma of the maxillary sinus and 338 controls matched on sex, age and residence in Hokkaido, Japan. Among nonsmoking women, a relative risk of 5.4 ($p < 0.05$) was associated with exposure in the household to secondhand smoke from one or more smokers. Active smoking was associated with an increased risk for squamous-cell carcinoma in men in the same study.

Zheng *et al*. (1993) used data from the 1986 US National Mortality Followback Survey to assess risk for cancer of the nasal cavity and sinuses in relation to exposure to secondhand smoke in white men. A total of 147 deaths from cancer of the nasal cavity and sinuses were compared to 449 controls who had died from one of a variety of causes (excluding any causes strongly linked to alcohol and/or tobacco use). Data were obtained from postal questionnaires completed by next-of-kins. Among nonsmokers, patients with nasal cancer were more likely to have a spouse who smoked cigarettes (relative risk, 3.0; 95% CI, 1.0–8.9) after adjustment for age and alcohol use. When the analysis of cases was restricted to those with cancer of the maxillary sinus, the risk was somewhat higher (relative risk, 4.8; 95% CI, 0.9–24.7). The risks reported for active and for involuntary smoking were of similar magnitude in this study.

Neither involuntary exposure to tobacco smoke during childhood nor exposure during adult life were positively associated with an increased risk for nasopharyngeal cancer in a study in China (Province of Taiwan) (Cheng *et al*., 1999). Although histological type was not specified, all cases were histologically confirmed. Among never-smokers, the risk estimates for cumulative exposure to passive smoking (pack–person–years) in childhood declined as exposure increased (p for trend = 0.05); a similar but non-significant inverse relationship was found for exposure during adulthood. Significant elevations in risk of nasopharyngeal cancer were observed for active smokers in this study. [The Working Group noted that the exposure assessment was relatively detailed and that the estimates of relative risk were adjusted for age, sex, education and family history of nasopharyngeal cancer.]

A large population-based case–control study conducted in Shanghai, China, included 935 cases of nasopharyngeal carcinoma and 1032 population controls randomly selected from a population-registry and frequency-matched by sex and 5-year age group (Yuan *et al*., 2000). All cases were histologically confirmed, but the cell type was not specified. The study subjects were interviewed face to face, and the response rates were 84% for cases and 99% for controls. In female never-smokers, a consistent increase in risk related to exposure to secondhand smoke during childhood was noted. If the mother smoked, the relative risk was 3.4 (95% CI, 1.4–8.1); if the father smoked, the relative risk was 3.0

(95% CI, 1.4–6.2); if another household member smoked, the relative risk was 2.7 (95% CI, 1.1–6.9), and if any household member smoked, the relative risk was 3.0 (95% CI, 1.4–6.2). Risks associated with exposure to secondhand smoke during adulthood in women were also statistically significantly increased. For male never-smokers, the associations were weaker and were not statistically significant for exposure during childhood and adulthood. Gender-specific risk estimates were adjusted for age, level of education, consumption of preserved foods, oranges and tangerines, exposure to rapeseed oil, exposure to burning coal during cooking, occupational exposure to chemical fumes, history of chronic ear and nose conditions and family history of nasopharyngeal cancer. [The Working Group noted that this was a large, well-conducted study that included a detailed exposure assessment and adjustment for numerous potential confounders.]

2.4.5 *Tumours of the brain and central nervous system*

A population-based case–control study of patients with incident primary brain tumours diagnosed from 1987 through 1990 in Adelaide, Australia, was reported by Ryan *et al.* (1992). Controls were selected from the Australian electoral rolls which cover 95% of the population. Response rates of 90% and 63% were obtained for cases and controls, respectively. The study included 110 histologically confirmed cases of glioma, 60 meningioma cases and 417 controls. An increased risk of meningioma was associated with involuntary exposure to tobacco from the spouse, particularly among women (relative risk, 2.7; 95% CI, 1.2–6.1). No statistically significant association was found between active smoking and either glioma or meningioma in this study.

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