EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND CANCERS OTHER THAN THE LUNG

Over 40 epidemiological studies have reported results relating ETS exposure in adulthood or childhood to risk of cancers other than the lung in adult nonsmokers. Some studies have concentrated on cancers at specific sites, while others have presented results for a range of sites and/or for overall cancer risk. In assessing this evidence, certain general considerations of the data have to be borne in mind:

- Study weaknesses It is notable that the only three studies which have reported results for a wide range of cancer sites are open to criticism for a number of reasons[1]. One study[2-4] had incomplete follow-up and used statistical methods of doubtful validity, another[5-7] used inappropriate controls and had a substantial difference in response rates between cases and controls, while the third[8] is not large enough to provide adequate numbers of cases for many cancer types.

- Categorizing subjects by ETS exposure In many studies, subjects are categorized based on a single source of ETS exposure (e.g. the spouse) or an exposure at a single point in time (e.g. at the time of the questionnaire in some prospective studies) or during a limited period of time (e.g. adulthood). Although it is well documented that marriage to a smoker and working with a smoker are associated with increased overall ETS exposure, as judged by levels of cotinine in blood, urine or saliva[9], and although it is likely that those who are exposed at one point in their life are more likely to be exposed at another point, it is likely that studies based on a limited assessment of ETS may lack the power to detect any true effect that studies based on a more detailed assessment would have.

  In some case-control studies very detailed questions have been asked about multiple sources of ETS over the whole of the subject's lifetime, and analyses have been conducted using those with no reported exposure as the comparison group. The problem with this approach is that everyone is likely to have had some ETS exposure in their life and the estimates of risk are highly dependent on which subjects happen to get classified in the unexposed comparison group. If, among subjects with a relatively low level of ETS exposure, the cases are more likely to

report this (in an effort to explain their disease) than are controls, such differential recall may cause substantial bias to the estimated effect of ETS. Limitations caused by inadequate characterization of ETS exposure as well as by small sample sizes in some studies have been pointed to by a recent review[10].

- Confounding Many of the studies, particularly those reporting in the 1980s, made at most only limited adjustment for potential confounding variables. Some studies[5-7,11-15] have adjusted for no other variables at all, not even age.

- Misclassification bias In studies of ETS and lung cancer, considerable attention has been given to estimating the magnitude of bias resulting from the inappropriate inclusion of some misclassified current and former smokers among the target population of lifelong nonsmokers. Though it would be expected that bias would also arise for other smoking-associated cancers, this has not been investigated in the literature.

- Publication bias Researchers are more likely to wish to publish, and editors are more likely to accept for publication, results from studies which find a statistically significant association between exposure and disease[16]. As a result the published literature may overstate any true association or produce an apparent association when no true association exists. Two very large prospective studies have reported results relating ETS exposure to lung cancer[17,18] but, with the exception of a recent publication on breast cancer based on one of these[19], have not reported results for any other cancer site.

- Plausibility As discussed below, some studies have reported associations between ETS and cancers not associated with active smoking. Although it is possible to propose mechanisms by which ETS, but not active smoking, could increase risk of cancer of a specific site[20,21], these are speculative and unsupported. It is far more plausible to believe that they represent associations due to chance or bias.

Bearing these points in mind, it is appropriate to consider the results by site.

Cancer of the nasopharynx, head and neck (Table 1) Five studies have reported results specifically for cancer of the nasopharynx. Three of the studies[22-24] provided no evidence of an increase in risk with ETS exposure, one of these[24] even reporting a significant negative trend in relation to childhood exposure. In contrast, two recent studies have reported significant positive associations. In one of these[25] a relationship was noted with childhood but not adulthood ETS exposure. The other[26] reported no significant association with any index of ETS exposure in males but reported significant associations and trends with a wide range of indices in females, all the findings being linked to an unusually low number of cases who reported no ETS exposure from any source, the reference group used in all the relative risk calculations. The heterogeneous nature of the findings and the limitations of the analyses make the overall findings difficult to interpret. For example, the authors of the Chinese study[26] reporting significant associations of nasopharyngeal cancer with ETS exposure in females regard their results as "inconclusive as to whether passive smoking contributes to NPC risk".

Three further studies have also reported results for overall incidence of cancer of the head and neck. Two of these[4,15] reported no significant association of ETS exposure with risk, but one[14], based on analyses which adjusted for no potential confounding variables, and data collected very differently for cases and controls, reported significantly increased risks with ETS exposure at home and at work. Based partly on the evidence from two of these studies[14,15], the Supreme Court of New South Wales, Australia recently decided that ETS exposure can materially contribute to the development of larynx cancer[27]. Since neither of the studies cited presented results specifically for larynx cancer, since both studies would have involved no more than about 10 larynx cancer cases in nonsmokers, since one of the studies[15] found no statistically significant association of ETS with head and neck cancer, and since the one that did[14] had obvious weaknesses, the Supreme Court's decision seems unjustified based on the available data.

Digestive system cancer (Table 2) In general, the data summarized show no indication of a relationship of ETS exposure with digestive system cancer, either overall or by specific sites. Exceptionally, results for colon cancer from one study[28] implausibly reported a significant positive association with ETS exposure in

males and a significant negative association with ETS exposure in females, while results from stomach cancer from one study[29] reported a marginally significant (p=0.03) positive trend for cancers in the cardia subsite, but no indication of an association for cancers in the distal subsite. Clearly, the overall data provide little support for the view that ETS exposure affects incidence of digestive system cancer.

Nasosinus cancer (Table 3) All three studies have reported some evidence of an increased risk of nasosinus cancer in association with ETS exposure. Two studies in Japan[2,12] reported no overall significant increase in risk in relation to spousal or household exposure in females, but a significant dose-related trend in relation to extent of exposure. A third study, in the USA[30], reported an increase in risk in relation to spousal smoking in males that was of marginal statistical significance. Limitations of the studies include the small number of cases studied, the failure in the two Japanese studies to control either for the age of the subject or for any of the wide range of factors known to be associated with nasal cancer, and the reliance in the US study on data collected from next-of-kin. Although some reviewers[10,31] have claimed that ETS exposure is a cause of nasosinus cancer, the evidence does not in fact appear conclusive.

Breast cancer (Table 4) Results relating ETS exposure to risk of breast cancer in women are available from 17 studies. No significant association has been reported in six prospective studies[4,8,19,32-34] including a recent analysis from the American Cancer Society Cancer Prevention Study II which took into account 16 potential confounding variables and reported a relative risk of 1.0. However, five case-control studies[35-39] have reported a significant increase in risk associated with ETS exposure and some others[40-42] have reported a moderate but non-significant increase in risk, though one[34] found a marginally significant reduction in risk. The estimates available for spousal smoking (or nearest equivalent index) from each study show highly significant ($p<0.001$) heterogeneity, with random-effects meta-analyses giving a combined relative risk estimate of 1.18 (95% confidence interval [CI] 1.03-1.36). The results cited above and in Table 4 are for all the women studied; some studies[33,38] have reported an increased risk in premenopausal but not in postmenopausal women, though other studies[34,35,43] did not confirm this finding.

In interpreting this evidence, a number of points should be made:

(i) The great majority of epidemiological studies have reported either no association or a negative association of active smoking with breast cancer risk[10]. It has been suggested[44,45] that a true association might have been missed by failing to use non-ETS exposed nonsmokers as the reference group, but this would not explain why ETS exposure might have an apparent effect at least as large as that from active smoking when it involves so much less exposure to smoke constituents.

(ii) Evidence of a dose-response relationship is very limited. Of three studies claiming to observe a significant trend, one[36] actually reported similar increases in risk regardless of extent of exposure, while another[38] reported increasing risk with increasing exposure only in premenopausal women. Seven other studies[4,19,34,35,37,41,46] which investigated a dose-response did not find one.

(iii) The extent to which confounding might affect the reported relative risks is not clear. Studies have varied considerably as to which other correlates of breast cancer risk have been taken into account in analysis.

(iv) Other biases, such as recall bias in the case-control studies, may also have affected the reported risks associated with ETS.

(v) It has been reported[47] that, after adjustment for various potential confounders, nonsmokers married to smokers are about 40% less likely to attend for breast cancer screening than are nonsmokers married to nonsmokers.

Recent reviews[10,45,48] have taken the view that the evidence on ETS and breast cancer is suggestive of a possible relationship, but more evidence is needed to establish if a causal relationship exists.

Cancer of the cervix (Table 5) Nine studies have reported results relating ETS exposure to risk of cervix cancer (or in two cases to pre-invasive cervical lesions). While five studies[4,8,32,49,50] reported no significant increase associated with ETS exposure, one[51] reported an increased risk in women living with a smoker that was of marginal significance (lower 95% CI stated to be 1.0), two studies[5,52] reported a

significantly increased risk associated with spousal smoking, and another[53] reported a significant dose-related trend in relation to hours of ETS exposure. While a random-effects meta-analysis based on eight independent estimates shows a significant elevation in risk (RR = 1.26, 95% CI = 1.05-1.52), there are a number of difficulties in interpreting the findings. One major problem is that none of the estimates have adjusted for human papilloma virus (HPV) infection, known to be the dominant cause of cervical cancer[54], and only three studies[49,51,53] have adjusted for aspects of sexual activity known to be linked to HPV virus infection. Confounding by HPV infection is considered a plausible explanation of the association of active smoking with cervix cancer[31] and could well bias estimates of the risk of cervix cancer with ETS exposure. It has also been noted[47] that nonsmoking women married to smokers are significantly less likely to undergo screening for cervical cancer than are nonsmoking women married to nonsmokers.

Bladder cancer (Table 6) The results from four studies, three conducted in the 1980s[4,11,55] and one quite recently[56], provide no indication of an effect of ETS on risk of bladder cancer.

Brain cancer (Table 7) No study reported that risk of brain cancer was significantly higher in ETS-exposed individuals, and meta-analyses based on 10 independent estimates also show no significant elevation in risk. Two studies[3,57] have reported a significant dose-related trend in risk with increasing ETS exposure. One of these[3] did not adjust for the age of the subject and the other[57] only reported its results in an abstract with little detail. Few potential confounding variables have been adjusted for in any of the studies. An association of brain cancer risk with ETS exposure has not been clearly demonstrated.

Cancer of other sites (Table 8) The table summarizes the limited results that are available for 10 other cancer sites (or groups of sites). Only two significant differences were reported. One, for kidney cancer in females in relation to hours of ETS exposure at home or work[58], was based on a marginally significant trend statistic where the dose-relationship pattern was actually quite erratic. The other, for endocrine cancer in relation to smoking by the husband[5], is based on only 13 cases

and is unstandardized either for age or sex. These results add little to the evidence on ETS as a potential cause of cancer.

ETS and total cancer incidence (Table 9) Nine studies have reported results relating ETS exposure to total cancer risk, smoking-related cancer risk and/or non smoking-related cancer risk. Some of the analyses include lung cancers but they are generally not more than a small fraction of the cancers analysed. Only one of the studies was published after 1990 and none of the analyses adjusted for more than a very small number of potential confounding variables. Two studies[59,60] reported relative risks, of 6.4 for total cancer and 7.0 for smoking-related cancer, that are so high as to be totally implausible bearing in mind the results for individual sites summarized in Tables 1 to 8. Two studies[2,7], both criticized for weaknesses of design and analysis[1], reported a weaker, but significant association between ETS exposure and total cancer risk, while the other studies[8,50,61-63] did not. Results from a well designed, large prospective study adjusting for relevant confounding variables would be needed before any conclusion could be reached regarding the relationship between ETS exposure and risk of cancers other than the lung. It is notable that neither of the two very large American Cancer Society Cancer Prevention Studies have reported relevant findings here, though they have the potential to do this.

OVERALL CONCLUSIONS

The evidence relating ETS exposure in nonsmokers to risk of cancers of any site other than the lung is relatively limited and subject to a number of sources of bias and confounding. For a number of cancers, including digestive system, bladder and brain, there is little evidence of an association of ETS exposure with risk. Though some studies have reported a relationship with cancers of the breast, cervix and nasopharynx, others have not and the evidence must be regarded as inconclusive. For nasosinus cancer, all three studies have reported a statistically significant relationship with ETS exposure. However, they all suffer from major weaknesses and more evidence is needed to support the existence of a causal relationship.

Taken as a whole, the epidemiology does not demonstrate that, in nonsmokers, ETS exposure causes cancers of any of the sites considered.

ETS AND CANCERS OTHER THAN THE LUNG
THE DATA

The tables that follow summarize the key evidence relating ETS exposure in lifelong nonsmokers to risk of cancers other than the lung:-

1. Nasopharynx, head and neck
2. Digestive system
3. Nasosinus
4. Breast
5. Cervix
6. Bladder
7. Brain
8. Other sites
9. Total cancer incidence

The tables show, for each successive study providing data, relative risks and 95% CIs relating to various indices of ETS exposure. Unless stated otherwise in the notes to the tables, the reference group comprises subjects unexposed to the source of ETS exposure specified. Where appropriate, and the data are available to do this, relative risks and 95% CIs presented by the authors have been recalculated to this standard reference group. The relative risks are adjusted for the potential confounding variables listed in Appendix A, which also gives fuller details of the studies in question. Where necessary, relative risks and/or 95% confidence intervals have been derived from tabular data presented by the authors, by combining independent relative risks by fixed-effects meta-analysis[64], or by combining non-independent relative risks, e.g. for different exposure levels with the same reference group[65].

Where they are reasonable numbers of studies providing independent estimates of risk (Tables 4 to 7), fixed-effects and random-effects meta-analysis[64] have been used to derive an overall relative risk estimates. Where a study provides multiple estimates for a given sex, only one has been used in the overall estimate, as indicated in the notes to the table. Preference has been given to estimates relating to adult rather than childhood exposure and to spousal exposure rather than exposure from a cohabitant or coworker.

TABLE 1 – ETS and Cancer of the Nasopharynx, Head and Neck

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Cancer of the nasopharynx								
Yu[22]	1990	China	Spouse (ever)	M+F	72	0.8(0.4-1.9)	-	ac(1)v
			Cohabitant (ever)	M+F	142	0.7(0.4-1.4)	-	ac(1)
			Mother (childhood age 10)	M+F	63	0.7(0.3-1.5)	-	ac(1)v
			Father (childhood age 10)	M+F	109	0.6(0.3-1.2)	-	ac(1)v
			Cohabitant (childhood age 10)	M+F	59	0.7(0.4-1.3)	-	ac(1)v
Vaughan[23]	1996	USA	Cohabitant (adulthood)	M+F	19	No increase	No	ac(1)q
			Cohabitant (childhood)	M+F	19	No increase	No	ac(1)q
Cheng[24]	1999	Taiwan	Cohabitant (adulthood)	M+F	178	0.7(0.5-1.2)	No	ac(4)
			Cohabitant (childhood)	M+F	178	0.6(0.4-1.0)	d1	ac(4)
Armstrong[25]	2000	Malaysia	Cohabitant (adulthood)	M+F	(282)	No association	-	ac(1)s
			Parent (childhood)	M+F	(282)	2.28(1.21-4.28)	-	ac(1)s
Yuan[26]	2000	China	Spouse (adulthood)	F	156	3.09(1.48-6.46)	d2	ac(9)w
				M	17	1.53(0.26-8.93)	No	ac(9)w
			Coworker (adulthood)	F	139	2.84(1.34-6.00)	d3	ac(9)w
				M	168	1.32(0.63-2.76)	No	ac(9)w
			Cohabitant (adulthood)	F	187	2.88(1.39-5.96)	d4	ac(9)w
				M	63	0.92(0.41-2.03)	No	ac(9)w
			Mother (childhood)	F	44	3.36(1.41-8.05)	d5	ac(9)w
				M	37	1.42(0.56-3.58)	No	ac(9)w
			Father (childhood)	F	151	2.95(1.41-6.19)	d6	ac(9)w
				M	82	1.17(0.54-2.55)	No	ac(9)w
			Cohabitant (childhood)	F	161	2.96(1.42-6.20)	d7	ac(9)w
				M	97	1.26(0.59-2.71)	No	ac(9)w
Head and neck cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	22	Not available	No	c(1)
Tan[14]	1997	USA	Spouse (ever)	F	21	7.34(2.44-22.1)	-	ue
				M	22	1.14(0.41-3.23)	-	ue
			Coworker (ever)	F	18	8.96(2.43-33.0)	-	ue
				M	20	12.0(3.77-38.0)	-	ue
			Spouse or coworker (ever)	F	21	8.00(2.55-25.1)	-	ue
				M	23	3.78(1.37-10.4)	-	ue
Zhang[15]	2000	USA	Spouse or partner (current)	M+F	13	0.9(0.2-5.2)	-	u
			Cohabitant (ever)	M+F	26	2.03(0.77-5.40)	No	ue
			Coworker (ever)	M+F	26	1.86(0.68-5.11)	No	ue

(continued)

TABLE 1 – ETS and Cancer of the Nasopharynx, Head and Neck (continued)

Results are not included for three studies[66-68] as the analyses were not restricted to lifelong nonsmokers.

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers except where stated.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen, "d1", "d2" … "d7" indicate dose-response studied, significant trend with more detailed data as follows:

d1 A significant negative dose-related trend was noted in relation to duration of exposure and cumulative exposure but not in relation to number of smokers in the household (childhood data).

d2 Relative risks 1.0, 3.02, 3.18 for 0, <20, 20+ years lived with smoking spouse (trend p=0.003)

Relative risks 1.0, 3.16, 3.02 for 0, <20, 20+ cigs/day by spouse (trend p=0.004)

Relative risks 1.0, 3.15, 2.45, 6.76 for 0, <20, 20-39, 40+ pack-years by spouse (trend p<0.001)

d3 Relative risks 1.0, 2.47, 3.28 for 0, <3, 3+ hours ETS at work (trend p=0.01)

d4 Relative risks 1.0, 2.65, 2.62, 4.35 for 0, <20, 20-39, 40+ cigs/day by household member (trend p=0.003)

d5 Relative risks 1.0, 2.36, 5.90 for 0, <20, 20+ cigs/day by mother (trend p=0.003)

d6 Relative risks 1.0, 2.46, 3.48 for 0, <20, 20+ cigs/day by father (trend p=0.004)

d7 Relative risks 1.0, 2.33, 3.83, 2.13 for 0, <20, 20-39, 40+ cigs/day by household member (trend p=0.01).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

q results are for differentiated squamous cell carcinoma.

s number of cases in lifelong nonsmokers not known – number given (in brackets) is total for study and includes cancers in smokers.

u unadjusted.

v reference group is never exposed at home from any source.

w reference group is never exposed at home or work from any source.

TABLE 2 – ETS and Digestive System Cancers

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Cancer of the oesophagus								
Hirayama[4]	1987	Japan	Spouse (ever)	F	58	Not available	No	c(1)
Stomach cancer								
Hirayama[2]	1984	Japan	Spouse (ever)	F	854	1.01(0.87-1.18)	No	c(2)e
Jee[32]	1999	Korea	Spouse (ever)	F	197	0.94(0.68-1.29)	No	ac(5)e
Nishino[8]	2001	Japan	Spouse (current)	F	83	0.98(0.59-1.60)	-	ac(6)
			Cohabitant (current)	F	83	0.87(0.54-1.40)	-	ac(6)
Mao[29]	2002	Canada	Cohabitant or	M	31C	4.01(0.90-17.94)	d_1	ac(7)e
			Coworker (ever)	M	101D	0.83(0.48-1.45)	-	ac(7)e
Colon cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	142	Not available	No	c(1)
Sandler II[28]	1988	USA	Cohabitant (ever)	F	215	0.74(0.56-0.97)	-	a
				M	49	2.99(1.77-5.04)	-	a
Nishino[8]	2001	Japan	Spouse (current)	F	48	1.10(0.54-2.40)	-	ac(5)
			Cohabitant (current)	F	48	1.10(0.58-2.20)	-	ac(5)
Cancer of the rectum								
Hirayama[4]	1987	Japan	Spouse (ever)	F	112	Not available	No	c(1)
Nishino[8]	2001	Japan	Spouse (current)	F	31	1.90(0.87-4.20)	-	ac(5)
			Cohabitant (current)	F	31	1.60(0.75-3.40)	-	ac(5)
Liver cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	226	Not available	No	c(1)
Jee[32]	1999	Korea	Spouse (ever)	F	83	0.74(0.46-1.17)	No	ac(5)e
Nishino[8]	2001	Japan	Spouse (current)	F	20	1.20(0.45-3.20)	-	a
Gall bladder cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	91	Not available	No	c(1)
Nishino[8]	2001	Japan	Spouse (current)	F	23	0.66(0.24-1.90)	-	a
Pancreas cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	127	Not available	No	c(1)
Nishino[8]	2001	Japan	Spouse (current)	F	19	1.20(0.45-3.10)	-	a
All digestive cancers								
Sandler I[6]	1985	USA	Mother (childhood)	M+F	13	0.7(0.1-5.6)	-	ue
			Father (childhood)	M+F	12	1.3(0.4-4.2)	-	ue

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers; C indicates cardia, D distal.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend, "d1" indicates dose-response studied, significant trend with more detailed data as follows:
d_1 Relative risks were 1.0, 3.5, 2.8, 5.8 for 0, 1-22, 23-42, 43+ residential plus occupational years exposed (trend p=0.03).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details.

e estimated from data reported.

u unadjusted.

TABLE 3 – ETS and Nasosinus Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Hirayama[2]	1984	Japan	Spouse (ever)	F	28	1.63(0.61-4.35)	d1	c(1)e
Fukuda[12]	1990	Japan	Cohabitant (?)	F	35	1.96(0.84-4.57)	d2	uet
				M	9	No association	No	rt
Zheng[30]	1993	USA	Spouse (ever)	M	28	3.0(1.0-8.9)	-	ac(1)
				M	<28	4.8(0.9-24.7)	No	ac(1)x

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen, "d1", "d2" indicates dose-response studied, significant trend with more detailed data as follows:

d1 Relative risks were 1.00, 1.67, 2.02, 2.55 for 0, 1-14, 15-19, 20+ cigs/day smoked by the husband (one-tailed trend p=0.025).

d2 Relative risks were 1.00, 1.40, 5.73 for 0, 1, 2+ smokers in the household (trend p<0.05).

Key to notes

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

r smoker in the household not included as a significant factor in multiple regression analysis after adjustment for sinusitis and/or polyps and woodworking.

t the source paper does not make clear the time period the ETS exposure relates to.

u unadjusted.

x results are for maxillary cancer only.

TABLE 4 – ETS and Breast Cancer in women

Study	Year	Country	Source (timing) of ETS exposure	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Sandler I[40]	1985	USA	Spouse (ever)	32	1.62(0.76-3.44)	-	am
Sandler I[6]	1985	USA	Mother (childhood)	29	0.9(0.2-3.3)	-	ue
			Father (childhood)	28	0.9(0.4-2.0)	-	ue
Hirayama[4]	1987	Japan	Spouse (ever)	115	1.32(0.83-2.09)	No	c(1)mw
Smith[41]	1994	UK	Spouse (adulthood)	94	1.58(0.81-3.10)	-	ac(9)m
			Coworker (adulthood)	94	1.49(0.76-2.92)	No	ac(9)e
			Cohabitant (childhood)	94	1.18(0.55-2.55)	No	ac(9)e
Hirose[35]	1995	Japan	Spouse (current)	560	1.24(1.03-1.49)	No	ac(1)em
Morabia[36]	1996	Switzerland	Spouse (ever)	90	3.1(1.6-6.1)	d_1	ac(7)mx
			Cohabitant, coworker or in leisure (ever)	98	3.2(1.7-5.9)	d_2	ac(7)x
Jee[32]	1999	Korea	Spouse (ever)	138	1.27(0.91-1.77)	-	ac(5)em
Lash[37]	1999	USA	Cohabitant (ever)	120	2.0(1.1-3.7)	No	ac(6)m
Delfino[42]	2000	USA	Cohabitant (adulthood)	64	1.50(0.79-1.87)	-	ac(2)m
Johnson II[38]	2000	Canada	Cohabitant or coworker (ever)	608	1.43(1.01-2.02)	d_3	ac(10)em
Rookus[69]	2000	Netherlands	Cohabitant or coworker (ever)	(918)	1.2(0.8-1.7)	-	ac(?)smy
Wartenberg[19]	2000	USA	Spouse (ever)	669	1.00(0.84-1.19)	No	ac(16)em
			Cohabitant (current)	669	1.1(0.9-1.3)	-	ac(16)
			Coworker (current)	669	0.8(0.6-1.0)	-	ac(16)
			All sources (current)	669	Not available	No	ac(16)
Woo[33]	2000	USA	Cohabitant (ever)	(706)	1.03(0.81-1.31)	-	ac(1)ms
Nishino[8]	2001	Japan	Spouse (current)	67	0.58(0.32-1.10)	-	ac(8)m
			Cohabitant (current)	67	0.81(0.44-1.50)	-	ac(8)
Egan[34]	2002	USA	Cohabitant or coworker (current)	1158	0.88(0.77-0.99)	No	ac(13)emz
			Mother (childhood)	1222	0.88(0.74-1.04)	-	ac(13)e
			Father (childhood)	1222	1.08(0.96-1.22)	-	ac(13)e
Furber[70]	2002	USA	Cohabitant (ever)	352	0.80(0.55-1.16)	-	ac(2)em
Kropp[39]	2002	Germany	Cohabitant coworker (adulthood)	197	1.65(1.13-2.40)	No	ac(6)em
			Cohabitant (childhood)	197	1.08(0.76-1.53)	No	ac(6)e
			Cohabitant or coworker (lifetime)	197	1.59(1.06-2.39)	d_4	ac(6)
Lash[46]	2002	USA	Cohabitant (ever)	305	0.85(0.63-1.10)	No	ac(8)m
Meta-analyses based on 17 estimates			Fixed effects		1.06(0.99-1.14)		h
			Random effects		1.18(1.03-1.36)		

(continued)

TABLE 4 – ETS and Breast Cancer in women (continued)

Results are not included for three studies[71-74] as the analyses were not restricted to lifelong nonsmokers.

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen, "d1", "d2", "d3" indicates dose-response studied, significant trend, with more detailed data as follows:

d1 relative risks are 1.0, 3.1, 3.2 for 0, 1-50, >50 hours/day – years ETS exposure from spouse (trend $p<0.05$).

d2 relative risks are 1.0, 3.1, 3.2 for 0, 1-50, >50 hours/day – years ETS exposure ever (trend $p<0.05$).

d3 relative risks are 1.0, 1.2, 1.8, 2.0, 3.3, 2.9 for 0, 1-6, 7-16, 17-21, 22-35, 36+ years exposure from spouse (trend $p=0.0007$) – data for premenopausal breast cancer; no trend seen for postmenopausal breast cancer.

d4 relative risks are 1.0, 1.42, 1.83 for 0, 1-50, 51+ hours/day-years exposure in lifetime (trend $p=0.009$).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

h heterogeneity chisquared is 49.68 on 16 degrees of freedom ($p<0.001$).

m relative risk estimate included in meta-analyses.

s number of cases in lifelong nonsmokers not known – number given (in brackets) is total for study and includes cancers in smokers.

x reference group is less than 1 hour/day exposure for 12 consecutive months.

y exposed daily at home or at work for at least 20 years or exposed daily in the bedroom for at least 1 year.

z reference group is none or occasional exposure.

TABLE 5 – ETS and Cancer of the Cervix in women

Study	Year	Country	Source (timing) of ETS exposure		Number of cases	Relative risk (95% CI)	Dose Response	Notes
Sandler I[5]	1985	USA	Spouse (ever)		56	2.1(1.2-3.9)	-	um
Sandler I[6]	1985	USA	Mother (childhood)		40	0.7(0.2-2.5)	-	ue
			Father (childhood)		34	1.7(0.8-3.6)	-	ue
Hirayama[4]	1987	Japan	Spouse (ever)		273	Not available	No	ac(1)
Butler[50]	1988	USA	Spouse (in marriage)		10	2.57(0.70-9.44)	-	ac(1)my
Slattery[53]	1989	USA	Total (last 5 years)		81	1.7(0.8-3.7)	d1	ac(3)e
			Cohabitant (last 5 years)		81	1.2(0.7-2.2)	d2	ac(3)em
			Outside home (last 5 years)		81	1.6(0.7-3.4)	No	ac(3)e
Coker[49]	1992	USA	Spouse (ever)		36	0.9(0.3-2.4)	-	ac(5)em
			Cohabitant (ever)		36	0.9(0.3-2.3)	-	ac(5)e
			Coworker (ever)		36	0.9(0.3-2.3)	-	ac(5)e
			Parent (ever)		36	0.3(0.1-0.9)	-	ac(5)e
Hirose[52]	1996	Japan	Spouse (current)		415	1.30(1.07-1.59)	d3	ac(1)m
Jee[32]	1999	Korea	Spouse (ever)		203	0.90(0.65-1.24)	No	ac(5)em
Scholes[51]	1999	USA	Cohabitant (current)		315	1.4(1.0-2.0)	-	ac(2)m
Nishino[8]	2001	Japan	Spouse (current)		11	1.10(0.26-4.50)	-	a
Meta-analyses based on 8 estimates				Fixed effects		1.26(1.09-1.44)		h
				Random effects		1.26(1.05-1.52)		

Results are not included for four studies[75-78] as the analyses were not restricted to lifelong nonsmokers.

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers except where stated.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen, "d1", "d2", "d3" indicates dose-response studied, significant trend with more detailed data as follows:

d1 Relative risks 1.00, 1.14, 1.57, 3.43 for 0, 0.1-0.9, 1.0-2.9 3.0+ hours/day total ETS exposure (trend p=0.0179)

d2 Relative risks 1.00, 0.62, 2.66 for 0, 0.1-1.5, 1.6+ hours/day ETS exposure at home (trend p=0.0362).

d3 Relative risks 1.00, 1.00, 1.55 for 0, <20, 20+ cigs/day smoked by husband.

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

h heterogeneity chisquared is 9.12 on 7 degrees of freedom (p>0.1).

m relative risk included in meta-analysis.

u unadjusted.

y adjusted for age and education. Butler[50] also gives 3.01(0.83-10.87) adjusted for age and age married and 2.58(0.70-9.56) adjusted for age and spouse occupation.

TABLE 6 – ETS and Bladder Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Kabat[11]	1986	USA	Spouse (ever)	F	35	1.21(0.54-2.69)	-	uem
				M	49	0.77(0.38-1.55)	-	uem
			Cohabitant (?)	F	17	0.63(0.18-2.18)	No	uet
				M	23	1.49(0.48-4.62)	No	uet
			Coworker or in transportation (?)	F	17	2.51(0.63-10.0)	No	uet
				M	23	0.64(0.23-1.75)	No	uet
Hirayama[4]	1987	Japan	Spouse (ever)	F	49	Not available	No	c(1)x
Burch[55]	1989	Canada	Cohabitant (ever)	F	81	0.75(0.33-1.71)	-	ac(1)m
				M	61	0.94(0.45-1.95)	-	ac(1)m
			Coworker (ever)	F	81	0.93(0.48-1.79)	-	ac(1)
				M	61	0.97(0.50-1.91)	-	ac(1)
Zeeger[56]	2002	Netherlands	Spouse (ever)	M+F	48	0.89(0.44-1.80)	-	ac(1)em
			Parents (?)	M+F	52	1.20(0.56-2.40)	-	ac(1)e
			Coworker (?)	M+F	40	1.40(0.70-2.60)	-	ac(1)e
			Cohabitant or coworker (?)	M+F	41	0.67(0.36-1.25)	No	ac(1)e
Meta-analyses based on 5 estimates				Fixed effects		0.89(0.64-1.25)		h
				Random effects		0.89(0.64-1.25)		

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen.

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

h heterogeneity chisquared is 0.91 on 4 degrees of freedom (p>0.1).

t the source paper does not make clear the time period the ETS exposure relates to.

u unadjusted.

x data are for cancer of the urinary organs.

TABLE 7 – ETS and Brain Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Sandler I[6]	1985	USA	Mother (childhood)	M+F	11	0.9(0.1-7.3)	-	um
			Father (childhood)	M+F	9	1.7(0.4-6.5)	-	u
Hirayama[3]	1985	Japan	Spouse (ever)	F	34	2.93(0.82-10.5)	d1	c(1)em
Ryan[79]	1992	Australia	Spouse/partner (ever)	F	(50G)	1.14(0.50-2.59)	-	ams
				M	(60G)	2.01(0.45-9.04)	-	ams
				F	(48N)	2.54(0.94-6.89)	-	ams
				M	(12N)	2.85(0.24-33.7)	-	ams
Hurley[80]	1996	Australia	Cohabitant (adulthood)	M+F	172G	0.97(0.61-1.53)	-	ac(2)m
Blowers[13]	1997	USA	Spouse (ever)	F	(94G)	0.7(0.4-1.4)	-	ums
			Parent (ever)	F	(94G)	1.7(0.8-3.7)	-	us
Johnson[57]	1999	Canada	Cohabitant or coworker (ever)	F	(210)	1.96(0.99-3.9)	d2	nms
				M	(339)	0.97(0.5-1.7)	No	nms
Meta-analyses based on 10 estimates				Fixed effects		1.17(0.91-1.51)		h
				Random effects		1.22(0.91-1.65)		

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers unless indicated otherwise; G indicates glioma, N meningioma

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend seen, "d1", "d2" indicates dose-response studied, significant trend with more detailed data as follows:

d1 Relative risks 1.00, 3.28, 4.92 for husband nonsmoker, ex or 1-19/day and 20+/day (trend p=0.002)

d2 Relative risks 1.00, 1.42, 2.20, 2.67 for 0, 1-24, 25-45 and 46+ years of ETS exposure (trend p=0.001).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

h heterogeneity chisquared is 11.14 on 9 degrees of freedom (p>0.1).

m relative risk estimate included in meta-analyses.

n not known whether estimate adjusted for confounding variable or not.

s numbers of cases in lifelong nonsmokers not known – number given (in brackets) is total for study and includes cancers in smokers.

u unadjusted.

TABLE 8 – ETS and Cancer of Other Sites

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Bone cancer								
Sandler I[6]	1985	USA	Mother (childhood)	M+F	19	1.0(0.2-4.6)	-	ue
			Father (childhood)	M+F	20	0.6(0.2-1.6)	-	ue
Hirayama[4]	1987	Japan	Spouse (ever)	F	17	Not available	No	c(1)
Skin cancer								
Hirayama[4]	1987	Japan	Spouse (ever)	F	23	Not available	No	c(1)
Cancer of the endometrium/corpus uteri								
Hirose[52]	1996	Japan	Spouse (current)	F	125	1.09(0.76-1.57)	No	ac(1)
Nishino[8]	2001	Japan	Spouse (current)	F	13	1.30(0.40-3.90)	-	a
Cancer of the ovary								
Hirayama[4]	1987	Japan	Spouse (ever)	F	54	Not available	No	c(1)
Nishino[8]	2001	Japan	Spouse (current)	F	15	1.70(0.58-5.20)	-	a
Cancer of the kidney								
Kreiger[58]	1993	Canada	Cohabitant or coworker(current)	F	72	0.87(0.50-1.49)	d1	ac(1)er
				M	47	1.09(0.57-2.09)	No	ac(1)er
Female genital cancer								
Sandler I[6]	1985	USA	Mother (childhood)	F	72	1.0(0.4-2.4)	-	ue
			Father (childhood)	F	59	1.3(0.7-2.4)	-	ue
Endocrine gland cancer								
Sandler I[5]	1985	USA	Spouse (ever)	M+F	13	4.4(1.2-17.4)	-	u
Sandler I[6]	1985	USA	Mother (childhood)	M+F	11	1.9(0.4-9.3)	-	ue
			Father (childhood)	M+F	11	1.6(0.5-5.4)	-	ue
Malignant lymphoma								
Hirayama[4]	1987	Japan	Spouse (ever)	F	85	Not available	No	c(1)
Leukaemia								
Hirayama[4]	1987	Japan	Spouse (ever)	F	51	Not available	No	c(1)
All haematopoetic								
Sandler I[6]	1985	USA	Mother (childhood)	M+F	19	2.3(0.7-7.5)	-	ue
			Father (childhood)	M+F	17	2.4(0.9-6.7)	-	ue

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend.

"d1" indicates dose-response studied, significant trend with more detailed data as follows:

1 Relative risks 1.0, 0.6, 1.7 for <3, 3-8, >8 hours/day ETS exposure (trend p=0.03).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

r comparison is of usual exposure 3+ vs <3 hours/day.

u unadjusted.

TABLE 9 – ETS and Total Cancer Incidence

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Total cancer (including lung cancer)								
Hirayama[2]	1984	Japan	Spouse (ever)	F	2705(200)	1.14(1.04-1.25)	d1	c(2)e
Miller I[61]	1984	USA	Spouse (ever)	F	123(5)	0.95(0.57-1.60)	-	ae
Sandler I[5]	1985	USA	Spouse (ever)	F	192(≤2)	1.96(1.30-2.97)	-	uen
				M	39(≤2)	1.53(0.41-5.68)	-	uen
Sandler I[7]	1985	USA	Cohabitant (ever)	M+F	157(≤2)	1.78(1.09-2.91)	d2	uen
Sandler I[6]	1985	USA	Mother (childhood)	M+F	191(1)	1.2(0.7-2.2)	-	ue
			Father (childhood)	M+F	173(1)	1.2(0.8-1.8)	-	ue
Reynolds[60]	1987	USA	Spouse (ever)	F	73(1)	1.68(1.04-2.71)	d3	ac(1)e
Butler[50]	1988	USA	Spouse (in marriage)	F	321(8)	1.20(0.94-1.54)	-	a
Sandler II[62]	1989	USA	Cohabitant (ever)	F	501(?)	1.00(0.82-1.21)	-	ac(3)
				M	115(?)	1.01(0.66-1.53)	-	ac(3)
Miller II[59]	1990	USA	Cohabitant (ever) or long-term exposure outside home	F	82(3)	6.40(2.34-17.5)	-	aex
Nishino[8]	2001	Japan	Spouse (current)	F	426(24)	1.10(0.92-1.40)	-	a
Smoking related cancer (including lung cancer)								
Sandler II[6]	1985	USA	Mother (childhood)	M+F	47(1)	0.8(0.3-2.4)	-	ue
			Father (childhood)	M+F	41(1)	1.7(0.9-3.3)	-	ue
Reynolds[60]	1987	USA	Spouse (ever)	F	<73(1)	7.01(0.73-67.5)	d4	ac(1)e
Butler[50]	1988	USA	Spouse (in marriage)	F	41(8)	1.22(0.61-2.44)	-	a
Sandler II[62]	1989	USA	Cohabitant (ever)	F	76(?)	1.45(0.88-2.40)	-	ac(3)
				M	32(?)	0.96(0.43-2.16)	-	ac(3)
Nishino[8]	2001	Japan	Spouse (current)	F	56(20)	1.70(0.94-2.90)	-	a
Smoking-related cancer (excluding lung cancer)								
Butler[50]	1988	USA	Spouse (in marriage)	F	33(0)	1.06(0.47-2.36)	-	a
Cancer other than the lung								
Gillis[63]	1984	Scotland	Cohabitant (current)	F	43(0)	1.26(0.62-2.56)	-	a
				M	8(0)	0.50(0.10-2.48)	-	a
Cancer other than smoking-related								
Sandler I[6]	1985	USA	Mother (childhood)	F	144(0)	1.3(0.7-2.5)	-	ue
			Father (childhood)	M	132(0)	1.1(0.7-1.7)	-	ue
Sandler II[62]	1989	USA	Cohabitant (ever)	F	425(0)	0.93(0.76-1.54)	-	ac(3)
				M	83(0)	1.03(0.40-2.62)	-	ac(3)

(continued)

TABLE 9 – ETS and Total Cancer Incidence (continued)

Study: described by name of first author of publication – see Appendix A for references.

Year: year of publication of paper reporting results cited.

Number of cases: number among lifelong nonsmokers. Bracketed numbers indicate lung cancers. The number of lung cancers was not known for the Sandler II study.

Relative risk (95% confidence interval = CI): estimated from data provided where necessary – see note e.

Dose response: "-" indicates dose response not studied, "No" indicates dose-response studied but no significant trend. "d1", "d2" … "d4" indicate dose-response studied, significant trend with more detailed data as follows:

d1 Relative risks 1.00, 1.12, 1.23 for husband nonsmoker, ex-smoker or 1-19/day, 20+/day (one-tailed trend p=0.0002).

d2 Relative risks 1.0, 1.5, 2.3, 2.8 for 0, 1, 2, 3+ cohabitants smoking.

d3 A significant trend (p=0.0433) was noted with pack-years ETS exposure but relative risks by level were not given.

d4 A significant trend (p=0.0007) was noted with pack-years ETS exposure but relative risks by level were not given.

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Appendix A for further details).

e estimated from data reported.

n there were a total of 2 nonsmokers with lung cancer but it was not stated how many there were in each sex or how many provided full data on smoking by cohabitants.

u unadjusted.

x results only for unemployed wives included, as no separation by ETS exposure for employed wives.

APPENDIX A – Studies providing data on ETS and cancer other than the lung

Study [ref]	Year[1]	Location	Design[2]	Cancers	Potential confounding variables adjusted for
Gillis[63]	1984	Scotland	P	Total (not lung)	Age
Hirayama[2-4]	1984[3]	Japan, 6 prefectures	P	Total and 18 sites[4]	Age of husband, occupation of husband[5]
Miller I[61]	1984	USA, Pennsylvania	CC	Total	Age
Sandler I[5-7]	1985	USA, N Carolina	CC	Total and 10 categories[6]	None
Kabat[11]	1986	USA, 18 hospitals	CC	Bladder	None
Reynolds[60]	1987	USA, California	P	Total, smoking-related	Age, income
Butler[50]	1988[7]	USA, California	P	Total, smoking-related, cervix	Age
Sandler II[28,62]	1988	USA, Maryland	P	Total, smoking-related, not smoking-related, colon	Age, housing quality, schooling, marital status
Burch[55]	1989	Canada, Alberta and Ontario	CC	Bladder	Age, area of residence
Slattery[53]	1989	USA, Utah	CC	Cervix	Age, education, church attendance, number of sexual partners
Fukuda[12]	1990	Japan, Hokkaido	CC	Nasal cavity	None
Miller II[59]	1990	USA, Pennsylvania	CC	Total	Age
Yu[22]	1990	China, Guangzhou	CC	Nasopharynx	Age, sex
Coker[49]	1992	USA, N Carolina	CC	Cervix[8]	Age, education, race, number of Pap smears, number of partners, genital warts
Ryan[79]	1992	Australia, Adelaide	CC	Brain	Age
Kreiger[58]	1993	Canada, Ontario	CC	Kidney	Age, body mass index
Zheng[30]	1993	USA, National	CC	Nasal cavity	Age, alcohol use
Smith[41]	1994	UK, 11 regions	CC	Breast	Age and 9 others[9]
Hirose[35,52]	1995[10]	Japan, Nagoya	CC	Breast, cervix, endometrium	Age, year of first visit
Hurley[80]	1996	Australia, Melbourne	CC	Brain	Age, sex, reference date
Morabia[36]	1996	Switzerland, Geneva	CC	Breast	Age and 7 others[11]
Vaughan[23]	1996	USA, 5 cancer registries	CC	Nasopharynx	Age, sex
Blowers[13]	1997	USA, California	CC	Brain	None
Tan[14]	1997	USA, Ohio	CC	Head/neck	None
Cheng[24]	1999	Taiwan	CC	Nasopharynx	Age, sex, race, educational level, family history of nasopharynx cancer
Jee[32]	1999	Korea	P	Stomach, liver, breast, cervix	Age, socioeconomic status, residency, husband's age, vegetable consumption, occupation
Johnson I[57]	1999	Canada	CC	Brain	None stated (in abstract)
Lash[37]	1999	USA, Massachusetts	CC	Breast	Age and 6 others[12]
Scholes[51]	1999	USA, Washington State	CS	Cervix[8]	Age, number of sexual partners, age at first intercourse
Armstrong[25]	2000	Malaysia	CC	Nasopharynx	Diet
Delfino[42]	2000	USA, California	CC	Breast	Age, menopausal status, family history of breast cancer
Johnson II[38]	2000	Canada	CC	Breast	Age and 10 others[13]
Rookus[69]	2000	Netherlands	CC	Breast	Lifetime physical activity and other (unstated) confounders
Wartenburg[19]	2000	USA, 50 states[14]	P	Breast	Age and 16 others[15]
Woo[33]	2000	USA, Maryland[16]	P	Breast	Menopausal status
Yuan[26]	2000	China, Shanghai	CC	Nasopharynx	Age and 7 others[17]

APPENDIX A – Studies providing data on ETS and cancer other than the lung (continued)

Study [ref]	Year[1]	Location	Design[2]	Cancers	Potential confounding variables adjusted for
Zhang[15]	2000	USA[18]	CC	Head/neck	None
Nishino[8]	2001	Japan, Miyagi	P	Total, smoking-related and 10 sites[19]	Age and others[20]
Egan[34]	2002	USA	P	Breast	Age and 13 others[21]
Furberg[43,70]	2002[22]	USA, N Carolina	CC	Breast	Age, race and sampling fractions
Kropp[39,81]	2002[23]	German, Freiburg and Rhein-Necker-Odenwald	CC	Breast	Age and 6 others[24]
Lash[46]	2002	USA, Massachusetts	CC	Breast	Age and 8 others[25]
Mao[29]	2002	Canada	CC	Stomach	Age and 7 others[26]
Zeeger[56]	2002	Netherlands	P	Bladder	Age and sex

Notes:

1 Year of first publication.

2 Study design P = prospective CC = case-control CS = cross-sectional.

3 Also 1987.

4 Mouth/pharynx, oesophagus, stomach, colon, rectum, liver, gall bladder, pancreas, nasal cavity, bone, skin, breast, cervix, ovary, bladder, brain, malignant lymphoma, leukaemia.

5 Occupation of husband only adjusted for in analyses of total and stomach cancer.

6 Smoking related, not smoking related, digestive, bone, breast, brain, cervix, female genital, endocrine and hematopoietic.

7 Results for spouse-pairs cohort only considered; AHSMOG cohort includes ex-smokers.

8 Cervical abnormalities only (not cancer).

9 Region, age at menarche, nulliparity, age at first full-term pregnancy, breast feeding, oral contraceptive use, family history of breast cancer, biopsy for benign breast disease, alcohol.

10 Also 1996.

11 Education, body mass index, age at menarche, age at first live birth, oral contraception, breast cancer in mother or sister, history of breast biopsy.

12 Body mass index, parity, history of radiation therapy, mother or sister with breast cancer, history of breast cancer, history of benign breast disease.

13 Province, education, body mass index, alcohol, physical activity, age at menarche, age at end of first pregnancy 5 months or longer, number of live births, months of breastfeeding, height.

14 Also District of Columbia and Puerto Rico.

15 Race, education, family history of breast cancer, age at first live birth, age at menarche, age at menopause, number of spontaneous abortions, oral contraceptive use, oestrogen replacement therapy use, body mass index, history of breast cysts, alcohol, dietary fat, dietary vegetable, occupation of woman, occupation of spouse.

16 Results for same population as Sandler II but based on different follow-up period.

17 Education, preserved food intake, oranges/tangerines intake, exposure to smoke from heated rapeseed oil and from burning coal during cooking, occupational exposure to chemical fumes, history of chronic ear and nose conditions, family history of nasopharynx cancer.

18 Memorial Sloan-Kettering Cancer Centre.

19 Stomach, colon, rectum, liver, gall bladder, pancreas, breast, cervix uteri, corpus uteri, ovary and all smoking-related cancer.

20 Age only for liver, gall bladder, pancreas, cervix uteri, corpus uteri and ovary. For other sites analyses adjusted for age, study area, alcohol, green and yellow vegetables, fruit. For stomach analyses also adjusted for miso-soup, and pickled vegetables. For colon and rectum analyses also adjusted for meat. For breast analyses also adjusted to age at first birth, number of live births, age at menarche, body mass index.

21 Age at menarche, age at first birth, parity, history of benign breast disease, family history of breast cancer, menopausal status, age at menopause, weight at 18 years, adult weight change, adult height, alcohol, carotenoid intake, menopausal hormone use.

22 Results only taken from 2002 reference[70]. The earlier, 1998, paper[43] gives results by menopausal status for only a subset of the cases and controls eventually collected.

23 Results only taken from reference [39]. The other reference[81] gives results by N-acetyltransferase 2 gene status for a smaller sample. The study relates to breast cancer cases aged up to 50 years only.

24 Alcohol, breastfeeding, education, family history of breast cancer, menopausal status, body mass index.

25 History of radiation therapy, body mass index, family history of breast cancer, history of breast cancer, history of benign breast disease, alcohol, parity, age at first birth.

26 Province, education, social class, meat consumption, vegetable consumption, fruit, juices.

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