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

Executive summary

This review is based on evidence from 73 studies that presented results relevant to an investigation of the possible association between exposure to environmental tobacco smoke (ETS) and cancers other than the lung or breast. Ten of the studies were reported in the 1980s, 17 in the 1990s, and 46 since 2000. Some 25 individual cancer sites, or groups of sites, were investigated, along with total cancer incidence, and the incidence of smoking-related cancers. Sixty-two of the studies investigated a single endpoint, while 11 others considered two or more endpoints. Three of these studies included 10 or more cancer sites. Thus, the number of studies considering each individual cancer site was limited, and did not exceed 14 for any one site, while some sites were only considered by a very few studies.

Ten of the studies failed to adjust their results for any potential confounding factors. Of the studies that did carry out adjustment, age and sex were the most commonly considered factors, and although data on numerous other potential confounders was collected by the studies, most failed to adjust their results for more than a few of these. Other problems with some studies were noted, including weaknesses in study design, small numbers of cases, limited assessment of ETS exposure, and bias arising from misclassification of exposure. Additionally, there were concerns about the plausibility of some of the results reported.

For none of the cancer sites investigated was there convincing evidence of an association between ETS exposure and the disease in question. Although some of the overall estimates of risk from the meta-analyses performed were significantly raised, these were either based on small numbers of studies, or there were sufficient concerns about the studies included as to render the results inconclusive.

Taken as a whole, the epidemiology does not demonstrate that ETS exposure in non-smokers causes cancers of any of the sites considered by the studies.

Authors: Peter Lee, Alison Thornton and Jan Hamling

Contents

Acknowledgment

This work was supported by the tobacco industry. The accuracy of the material presented and the interpretation of the findings are the responsibility of the authors alone.

Authors: Peter Lee, Alison Thornton and Jan Hamling

1. Introduction

This report is one of a series that assesses the evidence available on the association between environmental tobacco smoke (ETS) exposure and cancers of various sites. Other reports relate to cancer of the lung[1] and breast cancer[2]. This report describes the evidence available on all other cancers in adults. Cancers in childhood are not reported but possible associations between cancers occurring in adulthood and ETS exposure during childhood are discussed.

Seventy-three epidemiological studies have reported results relating ETS exposure in adulthood or childhood to risk of cancers other than the lung or breast in adult non-smokers. 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[3]. One study[4-6] had incomplete follow-up and used statistical methods of doubtful validity, another[7-9] used inappropriate controls and had a substantial difference in response rates between cases and controls, while the third[10] 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[11], 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 discussed elsewhere in a review[12].

- Confounding Many of the studies, particularly those reporting in the 1980s, made at most only limited adjustment for potential confounding variables. Some studies[7-9,13-21] 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 non-smokers. 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 that find a statistically significant association between exposure and disease[22]. 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[23,24] but, with the exception of a publication on breast cancer based on one of these[25], 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[26,27], these are speculative and unsupported. It is far more plausible to believe that they represent associations due to chance or bias.

2. Methods

An online search, using PubMed, was made to identify relevant papers published since the last update of this review in February 2008. The keywords "passive smoking", "environmental tobacco smoke", "involuntary smoking" and "cancer" were used, and the search was conducted to include papers published in the previous three years, up to June 2010. This ensured that any papers published around the time of the previous update of this review would be detected. Studies identified by this search were then examined to see if they contained suitable data, and those that did were selected for inclusion in this review. The references of selected studies were also examined to identify further papers of relevance, as were our existing files. Criteria for the inclusion of studies are given in section 3.

The sections that follow summarize the key evidence relating ETS exposure in lifelong non-smokers to risk of cancers other than the lung, and include tables that are laid out under the following headings. In the column marked "Study", the paper is described by the name of the first author of publication. Full references can be obtained from Table 3.1. "Year" refers to the year of publication of the paper reporting the results cited. In "Source (timing) of ETS exposure", source is given as 'total' when the estimate is for exposure to any one (or more than one) of the sources studied; timing is given as 'ever' when the estimate is for exposure at any time prior to interview. "Number of cases" refers to the number among lifelong non-smokers, unless otherwise indicated. Under "Dose-response", '-' indicates that dose-response was not studied, 'No' indicates that dose-response was studied but that no significant trend was seen, and 'd' followed by a number indicates that dose-response was studied and showed a significant trend, with more detailed data contained in the footnote of that number.

The tables show, for each successive study providing data, relative risks and 95% confidence intervals (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 Table 3.1, 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 effect meta-analysis[28], or by combining non-independent relative risks, e.g. for different exposure levels with the same reference group[29].

Where there are five or more studies providing independent estimates of risk, fixed effect and random effects meta-analysis[28] have been used to derive an overall relative risk estimate. 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, to spousal exposure rather than exposure from a cohabitant or co-worker and to exposure to a cohabitant rather than to co-worker, social or total exposure. Where there is evidence of heterogeneity between the estimates, which can largely be explained by outlying results in one study, the meta-analyses are rerun omitting the study.

3. Studies included and excluded

In order to be included in this review, studies had to provide new evidence relating to an endpoint of cancer other than that of the lung or breast. Results had to be restricted to never smokers and had to be presented as a relative risk, or as data from which a relative risk could be estimated.

Details of the 73 studies that gave data relevant to an investigation of the effect of ETS on cancers other than the lung or breast are given in Table 3.1. Thirty-nine studies were identified that at first appeared to be relevant, but which, on closer inspection, were deemed not suitable for inclusion in this review, and details of these are given in Appendix A, which also includes the reasons for exclusion.

Of the 73 studies included in this review, 10[4-9,13,30-37] were reported in the 1980s, 17[14-18,38-49] in the 1990s, and 46 were conducted either in or since the year 2000. Thirty-eight of the studies were carried out in North America, while 17 studies[4-6,10,14,15,20,21,39,44,47,48,50-56] were conducted in Asia, 13[30,57-68] in Europe and 3[41,45,69] in Australasia. One study took place in Egypt[70] and one study was conducted in Europe, Latin America and the USA[71].

Fifty-one of the studies were of a case-control design, while 20[4-6,10,30,32-35,48,57,58,61,62,66,67,69,72-77] were prospective cohort studies. The remaining two studies[49,78] were cross-sectional in design. Sixty-two studies presented results for a single endpoint, while 11 others[4-10,33-35,44,48,53,64,75,79] considered two or more endpoints, with three of these studies[4-10] investigating 10 or more cancer sites.

Ten of the studies[7-9,13-21] failed to adjust their results for any potentially confounding variables. Two studies[53,61] carried out adjustment but did not specify the factors that had been used to do this. Of the 61 remaining studies, only two[4-6,50] did not adjust for age, and all but three studies[50,58,73] either carried out adjustment for sex, or presented results that were restricted to a single sex only. Although data on a very wide range of other adjustment factors were collected by the studies, only race, area of residence/study, education, body mass index, dietary factors and alcohol consumption were considered by 10 or more studies. On the whole, however, most studies only adjusted for a very few potentially confounding variables.

Table 3.1: Studies providing data on ETS and cancer other than the lung or breast

Study [ref]	Year[a]	Location	Design[b]	Cancer site(s)	Potential confounding variables adjusted for
Gillis[30]	1984	Scotland	P	Total (not lung)	Age
Hirayama[4-6]	1984[c]	Japan, 6 prefectures	P	Total and 17 sites[d]	Age of husband, occupation of husband[e]
Miller I[31]	1984	USA, Pennsylvania	CC	Total	Age
Sandler I[7-9]	1985	USA, N Carolina	CC	Total and 9 categories[f]	None
Kabat[13]	1986	USA, 18 hospitals	CC	Bladder	None
Reynolds[32]	1987	USA, California	P	Total, smoking-related	Age, income
Butler[33]	1988[g]	USA, California	P	Total, smoking-related, cervix	Age
Sandler II[34,35]	1988	USA, Maryland	P	Total, smoking-related, not smoking-related, colon	Age, housing quality, schooling, marital status
Burch[36]	1989	Canada, Alberta and Ontario	CC	Bladder	Age, area of residence
Slattery[37]	1989	USA, Utah	CC	Cervix	Age, education, church attendance, number of sexual partners
Fukuda[14]	1990	Japan, Hokkaido	CC	Nasal cavity	None
Miller II[38]	1990	USA, Pennsylvania	CC	Total	Age
Yu[39]	1990	China, Guangzhou	CC	Nasopharynx	Age, sex
Coker[40]	1992	USA, N Carolina	CC	Cervix[h]	Age, education, race, number of Pap smears, number of partners, genital warts
Mizuno[15]	1992	Japan	CC	Pancreas	None
Ryan[41]	1992	Australia, Adelaide	CC	Brain	Age
Kreiger[42]	1993	Canada, Ontario	CC	Kidney	Age, body mass index
Zheng[43]	1993	USA, National	CC	Nasal cavity	Age, alcohol use
Hirose[44]	1996	Japan, Nagoya	CC	Cervix, endometrium	Age, year of first visit
Hurley[45]	1996	Australia, Melbourne	CC	Brain	Age, sex, reference date
Vaughan[46]	1996	USA, 5 cancer registries	CC	Nasopharynx	Age, sex
Blowers[16]	1997	USA, California	CC	Brain	None
Tan[17]	1997	USA, Ohio	CC	Head/neck	None
Cheng[47]	1999	Taiwan	CC	Nasopharynx	Age, sex, race, educational level, family history of nasopharynx cancer
Jee[48]	1999	Korea	P	Stomach, liver, cervix	Age, socioeconomic status, residency, husband's age, vegetable consumption, occupation
Johnson I[18]	1999	Canada	CC	Brain	None stated (in abstract)
Scholes[49]	1999	USA, Washington State	CS	Cervix[h]	Age, number of sexual partners, age at first intercourse
Armstrong[50]	2000	Malaysia	CC	Nasopharynx	Diet
Yuan[51]	2000	China, Shanghai	CC	Nasopharynx	Age and 7 others[i]
Zhang[19]	2000	USA[j]	CC	Head/neck	None
Iribarren[78]	2001	USA, California	CS	Cancer/tumour	Age and 10 others[k]
Nishino[10]	2001	Japan, Miyagi	P	Total, smoking-related and 9 sites[l]	Age and others[m]
Mao[80]	2002	Canada	CC	Stomach	Age and 7 others[n]
Zeeger[57]	2002	Netherlands	P	Bladder	Age and sex
Goodman[81]	2003	USA	CC	Ovary	Age, ethnicity, education, study site, use of oral contraceptive pill, parity, tubal ligation

(continued)

Table 3.1: Studies providing data on ETS and cancer other than the lung or breast (continued)

Study[ref]	Year[a]	Location	Design[b]	Cancer site(s)	Potential confounding variables adjusted for
Wu[52]	2003	Taiwan	CC	Cervix[h]	Age, education level, number of pregnancies, age at first intercourse, cooking in the kitchen during ages 20-40
You[53]	2003	China	CC	Oesophagus, stomach, liver	Unspecified but states that "ETS and confounders information was collected ..."
Villenueve[82]	2004	Canada	CC	Pancreas	Age, sex, body mass index, income adequacy, province of residence
Chen[54]	2005	Taiwan	CC	Bladder	Age, BMI, cumulative arsenic, hair dye usage, education
Hu[83]	2005	Canada	CC	Renal cell	Age, province, education, body mass index, alcohol use, total consumption of meat and of vegetables and fruit
Kasim[84]	2005	Canada	CC	Leukaemia	Age, sex, BMI, benzene, ionising radiation
McGhee[55]	2005	Hong Kong	CC	All cancers	Age and education (and sex for sexes-combined analysis)
Phillips[85]	2005	USA, western Washington State	CC	Intracranial meningioma	Age, sex, education
Trimble[72]	2005	USA, Washington County	P	Cervix	Age, education, marital status, religious attendance (1963 only)
Baker[86]	2006	USA, New York state	CC	Ovary	Age, residence, income, usual BMI, history of vaginal infection, year of participation, duration of breastfeeding
Bjerregaard[58]	2006	3 European countries	P	Bladder	Age, fruit and vegetables, ETS exposure at the other timepoint
Gallicchio[73]	2006	USA, Washington County	P	Pancreas	Age, education, marital status
Lilla[59]	2006	Germany	CC	Colorectum	Age, sex, NSAID use, endoscopy, family history, alcohol, red meat, education, BMI
Samanic[60]	2006	Spain	CC	Bladder	Age, region, fruit/vegetable consumption, high-risk occupation
Sobti[20]	2006	India	CC	Cervix	None
Alberg[74]	2007	USA, Washington County	P	Bladder	Age, education, marital status
Al-Zoughool[61]	2007	6 European countries	P	Endometrium	Unspecified, but other analyses were adjusted for age, centre, BMI, physical activity, OC use, parity, education, alcohol, HRT use, age at menopause
Hassan[87]	2007	USA, Texas	CC	Pancreas	Age, sex, race/ethnicity, diabetes, alcohol, education, state of residence, marital status
Hill[69]	2007	New Zealand	P	Total (not lung)	Age, ethnicity, marital status, education, labour force status, household equivalized income, household car access, tenure, deprivation index
Jiang[88]	2007	USA, Los Angeles County	CC	Bladder	Age, race/ethnicity, education, ETS exposure in other settings
Lo[70]	2007	Egypt	CC	Pancreas	Age, sex, residence
Paskett[75]	2007	USA, nationwide	P	Colorectum, colon, rectum	Age, ethnicity, study, family history, physical activity, NSAID use, alcohol, hormone therapy use, colonoscopy, diabetes, dietary calcium, fibre and fat, haemoglobin, waist circumference, red meat intake
Tsai[56]	2007	Taiwan	CC	Cervical intraepithelial neoplasm grades 2 and greater (≥CIN2)	Age, education, prior PAP smears, sexual partners, age at first intercourse, family history, cooking oil fume exposure, HPV infection

(continued)

Table 3.1: Studies providing data on ETS and cancer other than the lung or breast (continued)

Study[ref]	Year[a]	Location	Design[b]	Cancer site(s)	Potential confounding variables adjusted for
Gram[62]	2008	Norway and Sweden	P	Ovary	Age, nulliparous, menopausal status, duration of hormonal contraceptive use
Hassan[89]	2008	USA, Texas	CC	Liver	Age, sex, race, education, marital status, residence, HCV, HBV, diabetes, alcohol consumption, family history of cancer
Hooker[76]	2008	USA, Washington County	P	Rectum	Age, education, marital status
Kordi Tamandani[21]	2008	India, Chandigarh	CC	Cervix	None
Lee I[71]	2008	Europe, Latin America and USA	CC	Head/neck	Age, sex, race, study centre, education, alcohol consumption
Ramroth[63]	2008	Germany	CC	Larynx	Age, sex, alcohol consumption, education
Theis[90]	2008	USA, Florida/Georgia	CC	Kidney	Age, sex, race, BMI, alcohol consumption
Bao[77]	2009	USA, nationwide	P	Pancreas	Age, height, diabetes, BMI
Baris[91]	2009	USA, 3 states	CC	Bladder	Age, race, sex, Hispanic status, state of residence
Duan[79]	2009	USA, Los Angeles County	CC	Oesophagus, stomach	Age, sex, BMI, ethnicity
Lee II[64]	2009	10 European countries	CC	Head/neck, oesophagus	Age, sex, education, study centre, alcohol consumption, duration of exposure
Verla-Tebit[65]	2009	Germany	CC	Colorectal	Age, sex, education, family history of colorectal cancer, BMI, fruit/vegetable intake, red meat intake, NSAID use, alcohol consumption, physical activity, colonoscopy, HRT use[o]
Heinen[66]	2010	Netherlands	P	Pancreas	Age, BMI, education
Vrieling[67]	2010	10 European countries	P	Pancreas	Age, sex, study centre, weight, height, history of diabetes
Yang[68]	2010	Poland, Warsaw/Lodz	CC	Endometrium	Age, study site, education, menarche, parity, oral contraceptive use, HRT use, BMI, menopausal status

Notes:

[a] Year of first publication.

[b] Study design P = prospective CC = case-control CS = cross-sectional.

[c] Also 1987.

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

[e] Occupation of husband only adjusted for in analyses of total and stomach cancer.

[f] Smoking related, not smoking related, digestive, bone, brain, cervix, female genital, endocrine and hematopoietic.

[g] Results for spouse-pairs cohort only considered; AHSMOG cohort includes ex-smokers.

[h] Also includes cervical intraepithelial neoplasias that are not cancer.

[i] 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.

[j] Memorial Sloan-Kettering Cancer Centre.

[k] Race/ethnicity, education level, marital status, alcohol consumption, physical activity at work, serum total cholesterol, body mass index, hypertension, diabetes, individual occupational hazards.

[l] Stomach, colon, rectum, liver, gall bladder, pancreas, cervix uteri, corpus uteri, ovary and all smoking-related cancer.

[m] 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.

[n] Province, education, social class, meat consumption, vegetable consumption, fruit, juices.

[o] HRT use was only adjusted for in analyses restricted to female participants

4. Evidence for an association between ETS exposure and cancers other than lung or breast

4.1. Head and Neck Cancers

4.1.1. Nasopharynx cancer

Table 4.1.1 gives details of the five studies that have reported results specifically for cancer of the nasopharynx (NPC). Three of the studies[39,46,47] provided no evidence of an increase in risk with ETS exposure, one of these[47] 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[50] a relationship was noted with childhood but not adulthood ETS exposure. The other[51] 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 reporting 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[51] reporting significant associations of nasopharyngeal cancer with ETS exposure in females regarded their results as "inconclusive as to whether passive smoking contributes to NPC risk".

Table 4.1.1: ETS and Cancer of the Nasopharynx

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Yu[39]	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[46]	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[47]	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[50]	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[51]	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
			Co-worker (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

Results are not included for four studies[92-95] as the analyses were not restricted to lifelong non-smokers.

Dose response

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 Table 3.1 for further details).

q results are for differentiated squamous cell carcinoma.

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

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

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

4.1.2. Cancers of the head and neck

Six further studies have reported results for overall incidence of cancer of the head and neck, and details of these are given in Table 4.1.2. Four of the studies[6,19,63,71] reported no significant association of ETS exposure with risk, but one[17], 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. The final study[64] found an increase in the risk of cancer of the oral cavity and oropharynx, but not of the larynx and hypopharyx, for subjects who were exposed at home and/or at work. Statistically significant dose-response relationships, based on exposure categories of no exposure, 1-15, or 15+ years of exposure, were also found for this endpoint for this source of exposure, and for subjects who were exposed at work only. Meta-analysis of the results for cancer of the head and neck, based on seven estimates of risk, gave an overall risk of 1.20 (95% CI 1.00-1.45) using a fixed effect model, and 1.43 (95% CI 0.97-2.09) using a random effects model. Although the heterogeneity is not quite significant (p=0.062), the higher random effects estimate is due to the unusually high contribution of one estimate (7.34 for females in the study Tan[17]). Removing the estimates for this study removes the heterogeneity, the fixed effect and random effects estimates both becoming 1.14 (95% CI 0.95-1.38).

Based partly on the evidence from two of these studies[17,19], the Supreme Court of New South Wales, Australia decided that ETS exposure can materially contribute to the development of larynx cancer[96]. 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 non-smokers, since one of the studies[19] found no statistically significant association of ETS with head and neck cancer, and since the one that did[17] had obvious weaknesses, the Supreme Court's decision seems unjustified based on the available data.

Table 4.1.2: ETS and Cancers of the Head and Neck

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Hirayama[6]	1987	Japan	Spouse (ever)	F	22	Not available	No	c(1)
Tan[17]	1997	USA	Spouse (ever)	F	21	7.34 (2.44-22.1)	-	uem
				M	22	1.14 (0.41-3.23)	-	uem
			Co-worker (ever)	F	18	8.96 (2.43-33.0)	-	ue
				M	20	12.0 (3.77-38.0)	-	ue
			Spouse or co-worker (ever)	F	21	8.00 (2.55-25.1)	-	ue
				M	23	3.78 (1.37-10.4)	-	ue
Zhang[19]	2000	USA	Spouse or partner (current)	M+F	13	0.9 (0.2-5.2)	-	um
			Cohabitant (ever)	M+F	26	2.03 (0.77-5.40)	No	ue
			Co-worker (ever)	M+F	26	1.86 (0.68-5.11)	No	ue
Lee I [71]	2008	Europe, Latin America, USA	Home/work (ever)	M+F	489	1.07 (0.85-1.34)	-	ac(5)s
			Home (ever)	M+F	484	1.11 (0.89-1.39)	d1	ac(5)ems
			Work (ever)	M+F	484	0.95 (0.76-1.19)	No	ac(5)es
Ramroth[63]	2008	Germany	Partner or co-worker (ever)	M+F	9L	2.00 (0.39-10.70)	-	ac(3)m
Lee II[64]	2009	10 European countries	Home/work (ever)	M+F	111O	1.87 (1.08-3.23)	d2	ac(5)
				M+F	34L	1.98 (0.77-5.07)	No	ac(5)
			Home (ever)	M+F	111O	1.12 (0.72-1.75)	No	ac(5)em
				M+F	34L	1.61 (0.76-3.43)	No	ac(5)em
			Work (ever)	M+F	111O	1.43 (0.92-2.22)	d3	ac(5)e
				M+F	34L	1.35 (0.64-2.87)	No	ac(5)e
Meta-analyses based on 7 estimates (including Tan)				Fixed effect		1.20 (1.00-1.45)		h1
				Random effects		1.43 (0.97-2.09)		
Meta-analyses based on 5 estimates (excluding Tan)				Fixed effect		1.14 (0.95-1.38)		h2
				Random effects		1.14 (0.95-1.38)		

Results are not included for five studies[97-101] as the analyses were not restricted to lifelong non-smokers.

O = oral cavity and oropharynx; L = larynx and hypopharynx

Dose response

d1 Relative risks were 1.00, 1.28, 1.60 for no exposure, 1-15 or >15 years exposure (trend p=<.01). Includes Central Europe, Tampa, Latin America, Los Angeles and Puerto Rico studies only

d2 Relative risks were 1.00, 1.38, 2.15 for no exposure, 1-15 or >15 years exposure (trend p=0.007)

d3 Relative risks were 1.00, 1.04, 1.92 for no exposure, 1.15 or >15 years exposure (trend p=0.025)

Key to notes

a adjusted for age

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

h1 heterogeneity chisquared is 12.02 on 6 degrees of freedom (p=0.062)

h2 heterogeneity chisquared is 1.39 on 4 degrees of freedom (p = 0.85).

m relative risk included in meta-analysis.

s includes Central Europe, Tampa, Latin America, Los Angeles and Houston studies only

u unadjusted.

4.2. Cancers of the Digestive System

4.2.1. All Digestive Cancers

Only two studies considered the risk of all cancers of the digestive system in subjects exposed to ETS, and details of these are shown in Table 4.2.1. While one study failed to find any association, the other[38] reported a 10.8-fold increase in risk for all digestive cancers, a result which seems totally inconsistent with the findings for individual cancers within the digestive system (see sections 4.2.2-4.2.6). This study also reported an implausible 7-fold increase for total cancer risk (see results for Table 4.11 below).

Table 4.2.1: ETS and All Digestive Cancers

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Sandler I[8]	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
Miller II[38]	1990	USA	Cohabitant (ever) or long-term exposure outside home	F	29	10.8 (1.46-79.1)	-	aex

Key to notes

a adjusted for age.

e estimated from data reported.

u unadjusted.

x results relate to unemployed wives only because no separation by ETS exposure for employed wives.

4.2.2. Oesophagus cancer

See Table 4.2.2 for details of the four studies that considered this endpoint. One study in China[53] showed a significantly raised risk of oesophagus cancer, and reported the existence of a positive dose-response relationship, where the risk of the disease increased with increasing exposure to ETS. However, four of the other five relative risks that were presented were below 1.00, although none was significantly so, and while the final risk estimate was raised, it failed to reach statistical significance. In addition, one study[79] reported that the risk of oesophageal cancer decreased as the number of smokers the subject was exposed to in childhood increased, but the significance of this finding was not estimated. Using person-years of exposure, however, the same study reported a positive relationship between oesophageal cancer risk and amount of ETS exposure in adulthood, but this finding failed to reach statistical significance.

From the findings presented, it is not possible to draw any firm conclusions regarding the true nature of the association between the risk of cancer of the oesophagus and exposure to ETS.

Table 4.2.2: ETS and Oesophagus Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Hirayama[6]	1987	Japan	Spouse (ever)	F	58	Not available	No	c(1)
You I[53]	2003	China	Unspecified	M+F	84	1.72 (1.0-3.1)	d1	c(?)
Duan[79]	2009	USA	Childhood (ever)	M+F	38	0.55 (0.27-1.12)	No	ac(3)e
			Adulthood (ever)	M+F	38	1.64 (0.79-3.42)	No	ac(3)ep
Lee II[64]	2009	Europe	Home/work (ever)	M+F	24	0.76 (0.27-2.12)	No	ac(5)
			Home (ever)	M+F	24	0.72 (0.27-1.91)	No	ac(5)e
			Work (ever)	M+F	24	0.96 (0.35-2.61)	No	ac(5)e

Dose response

d1 Relative risks not specified but paper states "There are dose-response relations between total years of ETS exposure and the risk of these three cancers." (i.e. oesophagus, stomach and liver cancers).

Key to notes

a adjusted for age

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported

p use of data for person-years of exposure instead of number of smokers in household made no material difference to relative risk estimate

4.2.3. Stomach Cancer

Details of the six studies that considered the endpoint of stomach cancer are given in Table 4.2.3. None of the eight relative risks for overall cancer incidence showed a statistically significant association between stomach cancer and ETS exposure. One study[80] 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. However, another study[79], using categories of no exposure, <12 or 12+ person-years of exposure, reported relative risks of 1.00, 1.15 and 1.54 for cancers of the distal subsite (trend p=0.03) but no evidence of a dose-response for the gastric cardia subsite. Meta-analysis, based on six relative risks, gave an overall estimate of 1.08 (95% CI 0.96-1.22) for both the fixed effect model and the random effects model.

Overall, there is no compelling evidence that ETS exposure is associated with the risk of stomach cancer.

Table 4.2.3: ETS and Stomach Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Hirayama[4]	1984	Japan	Spouse (ever)	F	854	1.01 (0.87-1.18)	No	c(2)em
Jee[48]	1999	Korea	Spouse (ever)	F	197	0.94 (0.68-1.29)	No	ac(5)em
Nishino[10]	2001	Japan	Spouse (current)	F	83	0.98 (0.59-1.60)	-	ac(6)m
			Cohabitant (current)	F	83	0.87 (0.54-1.40)	-	ac(6)
Mao[80]	2002	Canada	Cohabitant or Co-worker (ever)	M	132	1.08 (0.64-1.82)	d1	ac(7)emn
You[53]	2003	China	Unspecified	M+F	85	1.33 (0.8-2.3)	d2	c(?)m
Duan[79]	2009	USA	Childhood (ever)	M+F	211	0.81 (0.56-1.17)	No	ac(3)eo
			Adulthood (ever)	M+F	226	1.13 (0.79-1.62)	d3	ac(3)emp
Meta-analyses based on 6 estimates				Fixed effect		1.08 (0.96-1.22)		h
				Random effects		1.08 (0.96-1.22)		

Dose response

d1 Relative risks for gastric cardia cancer 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). Relative risks for distal gastric cancer showed no dose response (trend p=0.58).

d2 Relative risks not specified but paper states "There are dose-response relations between total years of ETS exposure and the risk of these three cancers." (i.e. oesophagus, stomach and liver cancers).

d3 Relative risks for distal gastric adenocarcinoma were 1.00, 1.15, 1.54 for no exposure, <12 or ≥12 person-years of exposure (trend p=0.03). Relative risks for distal gastric adenocarcinoma of 1.00, 1.38, 1.23 for no exposure, exposure to 1 or 2+ smokers were also reported. Relative risks for gastric cardia adenocarcinoma showed no dose response (trend p=0.60).

Key to notes

a Adjusted for age.

c Adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e Estimated from data reported.

h Heterogeneity chisquared is 1.58 on 5 degrees of freedom (p=0.9).

m Relative risk included in meta-analysis.

n Estimated from separate, non-independent estimates for gastric cardia cancer and distal gastric cancer. Use of data for person-years of exposure instead of years of exposure (residential plus occupational) made no material difference to the relative risk estimate.

o Estimated from separate, non-independent estimates for gastric cardia adenocarcinoma and distal gastric adenocarcinoma.

p Estimated from separate, non-independent estimates for gastric cardia adenocarcinoma and distal gastric adenocarcinoma. Use of data for person-years of exposure instead of number of smokers in household made no material difference to relative risk estimate.

4.2.4. Colon/Rectal/Colorectal cancer

Table 4.2.4 gives details of the studies that investigated the possible association between ETS exposure and the risk of colon, rectal or colorectal cancers. For colon cancer, one study[34] implausibly reported a significant positive association with ETS exposure in males and a significant negative association with ETS exposure in females. No other statistically significant associations were found for this endpoint.

For rectal cancer, six of the seven relative risks presented were above 1.00, although only one[76] was significantly so. This risk estimate was considerably higher than those found by other authors, but its plausibility is questionable, considering that the other results from this study were only marginally above 1.00, and also given the strength of the association between active smoking and digestive cancers.

Six of the 12 relative risks presented for colorectal cancer showed a negative association with ETS exposure, but in only one study[65] did this reach statistical significance, and then only for males exposed in childhood. Females with the same exposure showed an increased risk of colorectal cancer in this study, although it was not significant. Five other non-significantly increased relative risks were also reported.

Overall, the data provide little support for the view that ETS exposure affects the incidence of colon, rectal, or colorectal cancer.

Table 4.2.4: ETS and Colon/Rectal/Colorectal Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Colon cancer:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	142	Not available	No	c(1)
Sandler II[34]	1988	USA	Cohabitant (ever)	F	215	0.74 (0.56-0.97)	-	a
				M	49	2.99 (1.77-5.04)	-	a
Nishino[10]	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)
Paskett[75]	2007	USA	Cohabitant or co-worker (ever)	F	≈252	1.00 (0.63-1.59)	-	ac(15)
Rectal cancer:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	112	Not available	No	c(1)
Nishino[10]	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)
Paskett[75]	2007	USA	Cohabitant or co-worker (ever)	F	≈32	0.63 (0.21-1.84)	-	ac(15)
Hooker[76]	2008	USA						
1963 cohort			Cohabitant (baseline)	F	56	1.03 (0.58-1.81)	-	ac(2)
			Cohabitant (baseline)	M	12	5.81 (1.84-18.36)	-	ac(2)
1975 cohort			Cohabitant (baseline)	F	54	1.04 (0.54-1.98)	-	ac(2)
			Cohabitant (baseline)	M	13	1.10 (0.24-4.97)	-	ac(2)
Colorectal cancer:								
Lilla[59]	2006	Germany	Childhood, partner or workplace (ever)	M+F	237	0.79 (0.53-1.20)	No	ac(8)
			Childhood (ever)	M+F	237	0.82 (0.57-1.18)	-	ac(8)e
			Partner/workplace (ever)	M+F	237	1.21 (0.84-1.75)	-	ac(8)e
Paskett[75]	2007	USA	Cohabitant or co-worker (ever)	F	284	0.93 (0.61-1.42)	-	ac(15)
Verla-Tebit[65]	2009	Germany	Childhood (ever)	F	148	1.26 (0.77-2.08)	-	ac(10)e
				M	104	0.43 (0.23-0.79)	-	ac(9)e
			Adulthood (ever)	F	148	1.28 (0.77-2.08)	-	ac(10)e
				M	104	1.06 (1.58-1.93)	-	ac(9)e
			Spouse (ever)	F	148	1.58 (0.96-2.61)	No	ac(10)e
				M	104	0.59 (0.31-1.12)	-	ac(10)e
			Total (ever)	F	148	1.01 (0.56-1.80)	No	ac(10)
				M	104	0.59 (0.31-1.15)	No	ac(9)

Results are not included for three studies[102-104] as the analyses were not restricted to lifelong non-smokers.

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

4.2.5. Liver/Gallbladder cancer

See Table 4.2.5 for details of the five studies that presented results for liver and gallbladder cancers. For liver cancer, seven negative associations with ETS exposure were found, and two of these, from the same study[89], reached statistical significance. In addition, one study[53] reported the presence of "dose-response relations", assumed to be positive, between total years of ETS exposure and liver cancer risk but did not give relative risks, while another study[89] reported negative dose-response relationships for childhood and adulthood exposure in males, and adulthood exposure in both sexes combined, but did not attempt to estimate the significance of these findings. Although two studies reported an increase in liver cancer risk in subjects with ETS exposure, in neither study did this finding reach statistical significance.

No association was found between ETS exposure and the risk of gallbladder cancer.

Overall, the data do not convincingly demonstrate an association between ETS exposure and the risk of cancers of the liver and gallbladder.

Table 4.2.5: ETS and Liver/Gallbladder Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Liver cancer:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	226	Not available	No	c(1)
Jee[48]	1999	Korea	Spouse (ever)	F	83	0.74 (0.46-1.17)	No	ac(5)e
Nishino[10]	2001	Japan	Spouse (current)	F	20	1.20 (0.45-3.20)	-	a
You[53]	2003	China	Unspecified	M+F	79	1.13 (0.6-1.9)	d1	c(?)
Hassan[89]	2008	USA	Childhood (ever)	F	47	0.70 (0.36-1.37)	No	ac(10)e
				M	41	0.31 (0.11-0.84)	d2	ac(10)e
			Adulthood (ever)	F	47	0.89 (0.45-1.75)	No	ac(10)e
				M	41	0.43 (0.17-1.08)	d3	ac(10)e
			Lifetime (ever)	F	47	0.71 (0.34-1.49)	No	ac(10)e
				M	41	0.19 (0.08-0.45)	d4	ac(10)e
Gall bladder cancer:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	91	Not available	No	c(1)
Nishino[10]	2001	Japan	Spouse (current)	F	23	0.66 (0.24-1.90)	-	a

Dose response

d1 Relative risks not specified but paper states "There are dose-response relations between total years of ETS exposure and the risk of these three cancers." (i.e. oesophagus, stomach and liver cancers).

d2 Relative risks were 1.00, 0.4, 0.2 for no exposure, ≤10 or >10 years exposure

d3 Relative risks were 1.00, 0.5, 0.1 for no exposure, ≤20 or >20 years exposure

d4 Relative risks were 1.00, 0.1, 0.3 for no exposure, ≤20 or >20 years exposure

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

4.2.6. Pancreatic cancer

Table 4.2.6 gives details of the 10 studies that investigated the association between ETS exposure and the incidence of pancreatic cancer. A study in Egypt[70] reported a significant 6-fold rise in risk of pancreatic cancer, while another study, based in 10 European countries[67], reported that the risk of pancreatic cancer was increased nearly fourfold in subjects who had ever been exposed to ETS during their lifetime. The relative risks for childhood exposure and exposure at home/work in this study were also above 1.00, with the risk estimate for home/work exposure being of marginal statistical significance. Ten other non-significantly raised relative risks were presented for this endpoint in relation to various measures of ETS exposure, with eight negative associations being reported, none of which was significantly so.

Meta-analysis of the available results produced an overall estimate of the risk for pancreatic cancer of 1.13 (95% CI 0.95-1.35) using the fixed effect model, and 1.16 (95% CI 0.88-1.54) using the random effects model, with significant heterogeneity ($p = 0.027$). Removing the estimate for the study in Egypt[70] removed the heterogeneity and reduced the overall estimate, with both fixed effect and random effects estimates 1.07 (0.89-1.27). Whichever overall estimates are selected, it is clear that the evidence for an association between the incidence of pancreatic cancer and exposure to ETS is not convincing.

Table 4.2.6: ETS and Pancreatic Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Hirayama[6]	1987	Japan	Spouse (ever)	F	127	Not available	No	c(1)
Mizuno[15]	1992	Japan	Home (childhood)	F	35	0.72 (0.28-1.86)	-	eum
				M	5	0.11 (0.005-2.60)	-	erum
Nishino[10]	2001	Japan	Spouse (current)	F	19	1.20 (0.45-3.10)	-	am
Villeneuve[82]	2004	Canada	Cohabitant or co-worker:					
			(childhood only)	M+F	23	1.37 (0.46-4.07)	-	ac(4)
			(adult only)	M+F	33	1.01 (0.41-2.50)	-	ac(4)
			(childhood and adult)	M+F	81	1.21 (0.60-2.44)	-	ac(4)
			(combined)	M+F	105	1.18 (0.60-2.35)	No	ac(4)em
Gallicchio[73]: 1963 cohort	2006	USA	Cohabitant (baseline)	M+F	22	1.1 (0.4-2.8)	-	ac(2)m
1975 cohort			Cohabitant (baseline)	M+F	34	0.9 (0.4-2.3)	-	ac(2)m
Hassan[87]	2007	USA	Childhood, cohabitant or workplace (ever)	M+F	294	1.02 (0.72-1.46)	-	ac(7)m
Lo[70]	2007	Egypt	Cohabitant, exposed daily for 1+ years (ever)	M+F	41	6.0 (2.4-14.8)	-	ac(2)m
Bao[77]	2009	USA	Mother (childhood)	F	95	1.52 (0.97-2.39)	-	ac(3)n
			Father (childhood)	F	133	0.76 (0.54-1.07)	-	ac(3)n
			Workplace/home (current)	F	151	0.94 (0.62-1.41)	-	ac(3)e
			Cohabitant (adulthood)	F	151	1.05 (0.76-1.46)	No	ac(3)emo
Heinen[66]	2010	Netherlands	Childhood (ever)	F	117	0.90 (0.54-1.50)	-	ac(2)
			Spouse (current)	F	62	0.78 (0.44-1.39)	-	ac(2)m
			Workplace (ever)	F	87	0.82 (0.51-1.32)	No	ac(2)e
			Workplace/home (current)	F	101	1.11 (0.72-1.71)	No	ac(2)e
Vrieling[67]	2010	10 European countries	Childhood (ever)	M+F	105	1.33 (0.86-2.07)	No	ac(5)f
			Home/work (ever)	M+F	105	1.54 (1.00-2.39)	-	ac(5)fm
			Childhood and home/work (ever)	M+F	48	3.83 (1.34-10.9)	-	ac(5)f
Meta-analyses based on 11 estimates (including Lo)				Fixed effect		1.13 (0.95-1.35)		h1
				Random effects		1.16 (0.88-1.54)		
Meta-analyses based on 10 estimates (excluding Lo)				Fixed effect		1.07 (0.89-1.27)		h2
				Random effects		1.07 (0.89-1.27)		

(continued)

Table 4.2.6: ETS and Pancreatic Cancer (continued)

Results are not included for one study[105] as the analyses were not restricted to lifelong non-smokers.

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

f compared to subjects who were never exposed to ETS from any source

h1 heterogeneity chisquared is 20.29 on 10 degrees of freedom (p = 0.027).

h2 heterogeneity chisquared is 6.92 on 9 degrees of freedom (p=0.65).

m relative risk included in meta-analysis.

n compared to neither parent being a smoker

o compared to <5 years living with a smoker in adulthood

r relative risk estimated by adding 0.5 to each cell as one cell had value of 0

u unadjusted.

4.3 Nasosinus cancer

See Table 4.3 for details of the studies that considered this endpoint. All three studies have reported some evidence of an increased risk of nasosinus cancer in association with ETS exposure. Two studies in Japan[4,14] 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[43], 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[12,106] have claimed that ETS exposure is a cause of nasosinus cancer, the evidence does not in fact appear conclusive.

Table 4.3: ETS and Nasosinus Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Hirayama[4]	1984	Japan	Spouse (ever)	F	28	1.63 (0.61-4.35)	d1	c(1)e
Fukuda[14]	1990	Japan	Cohabitant (unspecified)	F	35	1.96 (0.84-4.57)	d2	etu
				M	9	No association	No	rt
Zheng[43]	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

Dose response

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

a adjusted for age

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 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

4.4. Cervical cancer

See Table 4.4 for details of the 14 studies reporting results relating ETS exposure to risk of cervix cancer (or, in three studies, of endpoints that also include pre-invasive cervical lesions[40,49,52] and, in one study, of pre-invasive lesions only[56]). Three studies[7,21,44] reported a significantly increased risk associated with spousal smoking, while another study[20] reporting a significantly raised risk gave no definition of exposure. Also, one study[49] reported an increase of marginal significance (lower 95% CI given as 1.0) in women living with a smoker. One study[72] showed a significantly raised risk for living with a smoker when using data from a 1963 cohort, but not using equivalent data from a 1975 cohort. One study[52] reported a significantly increased risk and dose-related trend for ETS exposure at home during adulthood and a significant dose-related trend for lifetime exposure, while two further studies[37,56] reported a significant dose-related trend in relation to hours per day and pack-years respectively of ETS exposure, although neither study found a significant association with overall exposure. The remaining five studies[6,10,33,40,48] reported no significant increase associated with ETS exposure, one of the studies[40] showing a significantly negative association with exposure to parental smoking.

While a random-effects meta-analysis based on 14 independent estimates shows a significant elevation in risk (RR 1.63, 95% CI 1.30-2.05), there is evidence of heterogeneity ($p = 0.002$), mainly due to the high RR in the first study in India[20]. Excluding this estimate removed much of the heterogeneity, reducing the estimate to 1.48 (95% CI 1.23-1.78). Though this remains statistically significant, there are difficulties of interpretation. Firstly, no estimate was adjusted for human papilloma virus (HPV) infection, the dominant cause of cervical cancer[107], and only four studies[37,40,49,56] adjusted for aspects of sexual activity linked to HPV infection. Confounding by HPV infection is considered important in the association of active smoking with cervix cancer[106] and could bias estimates of risk for ETS exposure. Another difficulty is that, among non-smokers, those married to smokers are significantly less likely to undergo screening for cervical cancer[108]. The earlier lesions are detected and treated the better the expected outcome, so women who are less likely to be screened may be at greater risk of developing or dying from cancer.

Although there appears to be an increase in the risk of cervical cancer associated with ETS exposure, the results should be interpreted with caution.

Table 4.4: 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[7]	1985	USA	Spouse (ever)	56	2.1 (1.2-3.9)	-	um
Sandler I[8]	1985	USA	Mother (childhood)	40	0.7 (0.2-2.5)	-	ue
			Father (childhood)	34	1.7 (0.8-3.6)	-	ue
Hirayama[6]	1987	Japan	Spouse (ever)	273	Not available	No	ac(1)
Butler[33]	1988	USA	Spouse (in marriage)	10	2.57 (0.70-9.44)	-	ac(1)my
Slattery[37]	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[40]	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
			Co-worker (ever)	36	0.9 (0.3-2.3)	-	ac(5)e
			Parent (ever)	36	0.3 (0.1-0.9)	-	ac(5)e
Hirose[44]	1996	Japan	Spouse (current)	415	1.30 (1.07-1.59)	d3	ac(1)m
Jee[48]	1999	Korea	Spouse (ever)	203	0.90 (0.65-1.24)	No	ac(5)em
Scholes[49]	1999	USA	Cohabitant (current)	315	1.4 (1.0-2.0)	-	ac(2)m
Nishino[10]	2001	Japan	Spouse (current)	11	1.10 (0.26-4.50)	-	am
Wu[52]	2003	Taiwan	Cohabitant (adult)	89	2.73 (1.31-5.67)	d4	ac(4)m
			Co-worker (adult)	89	1.56 (0.83-2.92)	No	ac(4)
			Cohabitant (childhood)	89	0.99 (0.54-1.83)	No	ac(4)
			Co-worker (childhood)	89	1.03 (0.47-2.26)	No	ac(4)
			Lifetime exposure (pack-years)	89	2.30 (0.91-5.84)	d5	ac(4)e
Trimble[72]	2005	USA					
1963 cohort			Spouse (baseline)	81	2.0 (1.2-3.3)	-	ac(3)m
			Any cohabitant (baseline)	94	2.1 (1.3-3.3)	-	ac(3)
			Cohabitant but not spouse (baseline)	43	2.3 (1.1-4.9)	-	ac(3)
1975 cohort			Spouse (baseline)	49	1.6 (0.8-3.2)	-	ac(2)m
			Any cohabitant (baseline)	55	1.4 (0.8-2.4)	-	ac(2)
			Cohabitant but not spouse (baseline)	41	1.3 (0.6-3.2)	-	ac(2)
Sobti[20]	2006	India	Not specified	102	5.13 (2.54-10.4)	-	uem
Tsai[56]	2007	Taiwan	Any source, 1+ cigarette-years (ever)	50	1.8 (0.9-4.1)	d6	ac(7)m
Kordi Tamandani[21]	2008	India	Spouse (ever)	198	1.97 (1.30-3.00)	-	emu
Meta-analyses based on 14 estimates (including Sobti)			Fixed effect		1.45 (1.28-1.63)		h1
			Random effects		1.63 (1.30-2.05)		
Meta-analyses based on 13 estimates (excluding Sobti)			Fixed effect		1.39 (1.23-1.58)		h2
			Random effects		1.48 (1.23-1.78)		

(continued)

Table 4.4 – ETS and Cancer of the Cervix in women (continued)

Results are not included for six studies[109-114] as the analyses were not restricted to lifelong non-smokers.

Dose response

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=0.02)

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=0.04).

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

d4 Relative risks 1.00, 2.13, 3.97 for 0, 1-10, >10 cigs/day smoked at home (trend p=0.002).

d5 Relative risks 1.00, 1.90, 2.99 for 0, 1-20, >21 pack-years ETS exposure (trend p=0.02).

d6 Relative risks 1.00, 1.3, 2.1, 7.2 for 0, 1-10, 11-20, >20 pack-years ETS exposure (estimated trend p=0.00003).

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported

h1 heterogeneity chisquared is 32.44 on 13 degrees of freedom (p=0.002).

h2 heterogeneity chisquared is 19.69 on 12 degrees of freedom (p=0.07).

m relative risk included in meta-analysis.

u unadjusted.

y adjusted for age and education. Butler[33] 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.

4.5. Bladder cancer

Table 4.5 gives details of the 10 studies that reported findings on the association of ETS with bladder cancer. Of these, one study[54] reported a significant increase in men but not in women, and another study[74] reported a significant increase among those exposed to cohabitants other than the spouse in the 1963 cohort but not among those exposed to the spouse only or to any cohabitant in that cohort, and not for any index of exposure in the 1975 cohort. One study[88] reported significant dose-related trends with childhood exposure and total exposure in women but no significant results for other exposures in women and none for men, and one study[60] reported a significant increase in risk and a significant dose-related trend with exposure of women at work but not with other exposures of women and none among men. Finally, six studies[6,13,36,57,58,91] reported no significant increase associated with ETS exposure.

A random-effects meta-analysis based on 15 independent estimates gave a risk estimate of 1.02 (95% CI 0.84-1.23), with no evidence of heterogeneity. Overall, then, no increase in risk has been demonstrated.

Table 4.5: ETS and Bladder Cancer

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Kabat[13]	1986	USA	Spouse (ever)	F	35	1.21 (0.54-2.69)	-	uem
				M	49	0.77 (0.38-1.55)	-	uem
			Cohabitant (unspecified)	F	17	0.63 (0.18-2.18)	No	uet
				M	23	1.49 (0.48-4.62)	No	uet
			Co-worker or in transportation (unspecified)	F	17	2.51 (0.63-10.0)	No	uet
				M	23	0.64 (0.23-1.75)	No	uet
Hirayama[6]	1987	Japan	Spouse (ever)	F	49	Not available	No	c(1)x
Burch[36]	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
			Co-worker (ever)	F	81	0.93 (0.48-1.79)	-	ac(1)
				M	61	0.97 (0.50-1.91)	-	ac(1)
Zeegers[57]	2002	Netherlands	Spouse (ever)	M+F	48	0.89 (0.44-1.80)	-	ac(1)em
			Parents (unspecified)	M+F	52	1.20 (0.56-2.40)	-	ac(1)et
			Co-worker (unspecified)	M+F	40	1.40 (0.70-2.60)	-	ac(1)et
			Cohabitant or co-worker (unspecified)	M+F	41	0.67 (0.36-1.25)	No	ac(1)et
Chen[54]	2005	Taiwan	Any (unspecified)	F	6	1.09 (0.42-2.80)	-	ac(4)tm
				M	6	7.16 (1.87-27.4)	-	ac(4)tm
Bjerregaard[58]	2006	3 European countries	Home and/or work (baseline)	M+F	47	0.82 (0.46-1.48)	-	ac(2)m
			Total (childhood)	M+F	47	2.02 (0.94-4.35)	-	ac(2)
Samanic[60]	2006	Spain	Childhood (ever)	F	105	0.67 (0.33-1.38)	No	ac(3)e
				M	55	1.12 (0.60-2.10)	No	ac(3)e
			Cohabitant (ever)	F	106	1.38 (0.63-3.01)	No	ac(3)emv
				M	54	1.06 (0.56-2.00)	No	ac(3)emv
			Co-worker (ever)	F	106	2.03 (1.07-3.87)	d1	ac(3)ew
				M	55	0.37 (0.16-0.81)	No	ac(3)ew
			Total (ever)	M+F	161	0.7 (0.3-2.3)	-	ac(3)
Alberg[74]	2007	USA						
1963 cohort			Cohabitant (baseline)	F	22	1.8 (0.8-4.5)	-	ac(2)m
			Spouse only (unspecified)	F	15	1.1 (0.3-3.8)	-	ac(2)ty
			Other cohabitant only (unspecified)	F	18	3.0 (1.2-7.9)	-	ac(2)ty
1975 cohort			Cohabitant (baseline)	F	23	0.9 (0.3-2.2)	-	ac(2)m
			Spouse only (unspecified)	F	29	1.2 (0.4-3.6)	-	ac(2)ty
			Other cohabitant only (unspecified)	F	25	0.4 (0.1-3.3)	-	ac(2)ty

(continued)

Table 4.5: ETS and Bladder Cancer (continued)

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose Response	Notes
Jiang[88]	2007	USA	Childhood (ever)	F	41	1.64 (0.73-3.69)	d2	ac(3)e
				M	106	0.75 (0.46-1.21)	No	ac(3)e
			Cohabitant (ever)	F	42	1.33 (0.61-2.90)	No	ac(3)em
				M	106	0.73 (0.45-1.19)	No	ac(3)em
			Co-worker (ever)	F	40	1.39 (0.65-2.97)	No	ac(3)e
				M	98	0.89 (0.54-1.47)	No	ac(3)e
			Social (ever)	F	42	0.88 (0.39-2.00)	No	ac(3)e
				M	106	1.14 (0.68-1.91)	No	ac(3)e
			Total (ever)	F	42	4.24 (0.90-20.04)	d3	ac(3)e
				M	106	1.15 (0.56-2.38)	No	ac(3)e
Baris[91]	2009	USA	Childhood (ever)	M+F	145	1.10 (0.72-1.68)	No	ac(4)e
			Cohabitant (ever)	M+F	145	1.09 (0.67-1.77)	No	ac(4)em
			Co-worker (ever)	M+F	145	1.18 (0.80-1.74)	No	ac(4)e
			Total (ever)	M+F	145	1.06 (0.52-2.14)	No	ac(4)e
Meta-analyses based on 15 estimates				Fixed effect		1.02 (0.85-1.22)		h
				Random effects		1.02 (0.84-1.23)		

Results are not included for one study[101] as the analyses were not restricted to lifelong non-smokers.

Dose response

d1 Relative risks 1.0, 1.7, 1.7, 3.3 for 0, >0-135, >135-240 or >240 smoker-years occupational exposure (trend p=0.03)

d2 Relative risks 1.00, 0.99, 3.08 for no childhood exposure, exposure to 1 smoker or exposure to 2+ smokers (trend p=0.02)

d3 Relative risks 1.00, 3.34, 5.48 for no exposure, intermediate exposure or high exposure using an index of exposure over all the sources studied (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 Table 3.1 for further details).

e estimated from data reported.

h heterogeneity chisquared is 14.81 on 14 degrees of freedom (p=0.39).

m relative risk included in meta-analysis.

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

u unadjusted.

v the authors give results for the sexes separately and combined. The result for the sexes combined (RR 2.1, 95% CI 0.5-8.8) is clearly inconsistent with the data provided for the separate sexes.

w the authors give results for the sexes separately and combined. The result for the sexes combined (RR 0.7, 95% CI 0.2-2.4) is somewhat inconsistent with the data provided for the separate sexes.

x data are for cancer of the urinary organs.

y subjects with exposure from both their spouse and other cohabitants were not reported except for a note that this category did not contain any bladder cancers.

4.6. Brain cancer

Details of the seven studies that have reported results relating ETS exposure to brain cancer are given in Table 4.6. Although seven increased relative risks were reported, in only one study[85] did the risk associated with ETS exposure reach statistical significance. This result related to exposure from the spouse, with no significant increase seen for ETS from other cohabitants or co-workers. This study, which also found a significant positive trend for years of exposure to spousal ETS, reported a significant positive association with active smoking for men but a significant negative association with active smoking for women. Two other studies[5,18] also reported a significantly positive dose-related trend in risk with increasing ETS exposure. However, one of these[5] did not adjust for the age of the subject and the other[18] only reported its results in an abstract with little detail. Few potential confounding variables have been adjusted for in any of the studies.

Meta-analysis based on nine independent estimates gave a relative risk estimate of 1.27 (95% CI 1.01-1.60) using the fixed effect model, and 1.32 (95% CI 0.97-1.80) using the random effects model. Thus, the evidence for an increase in brain cancer incidence in association with exposure to ETS is not compelling.

Table 4.6: 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[8]	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[5]	1985	Japan	Spouse (ever)	F	34	2.93 (0.82-10.5)	d1	c(1)em
Ryan[41]	1992	Australia	Spouse/partner (ever)	F	(98)	1.61 (0.82-3.17)	-	aemps
				M	(72)	2.21 (0.58-8.36)	-	aemps
Hurley[45]	1996	Australia	Cohabitant (adulthood)	M+F	172G	0.97 (0.61-1.53)	-	ac(2)m
Blowers[16]	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[18]	1999	Canada	Cohabitant or co-worker	F	(210)	1.96 (0.99-3.9)	d2	nms
			(ever)	M	(339)	0.97 (0.5-1.7)	No	nms
Phillips[85]	2005	USA	Spouse (10+ years earlier)	M+F	95M	2.0 (1.1-3.5)	d3	ac(2)m
			Cohabitant, not spouse (10+ years earlier)	M+F	95M	0.7 (0.4-1.1)	No	ac(2)
			Co-worker (10+ years earlier)	M+F	95M	0.7 (0.4-1.2)	No	ac(2)
Meta-analyses based on 9 estimates				Fixed effect		1.27 (1.01-1.60)		h
				Random effects		1.32 (0.97-1.80)		

G = glioma M = meningioma

Dose response

d1 Relative risks 1.00, 3.28, 4.92 for husband non-smoker, 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)

d3 Relative risks 1.0, 1.4, 2.3, 2.7 for 0, <13, 13-28, >28 years exposure to spousal ETS (trend p=0.02).

Key to notes

a Adjusted for age.

c Adjusted for confounding variables other than age (number of confounders given in brackets – see Table 3.1 for further details).

e Estimated from data reported.

h Heterogeneity chisquared is 12.33 on 8 degrees of freedom (p=0.14).

m Relative risk estimate included in meta-analyses.

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

p Estimated from separate, non-independent estimates for glioma and meningioma.

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

u Unadjusted.

4.7. Endometrial cancer

Four studies considered the incidence of cancer of the endometrium in relation to ETS exposure, and details of these are given in Table 4.7. None of the studies reported a significant association between risk of the disease and any measure of ETS exposure studied.

Table 4.7: ETS and Cancer of the Endometrium

Study	Year	Country	Source (timing) of ETS exposure	Number of cases	Relative risk (95% CI)	Dose response	Notes
Hirose[44]	1996	Japan	Spouse (current)	125	1.09 (0.76-1.57)	No	ac(1)
Nishino[10]	2001	Japan	Spouse (current)	13	1.30 (0.40-3.90)	-	a
Al-Zoughool[61]	2007	6 European countries	Cohabitant or co-worker (baseline)	x	1.31 (0.74-2.34)	-	axp
				x	0.85 (0.65-1.11)	-	axq
Yang[68]	2010	Poland	Home (ever)	358	0.86 (0.63-1.17)	-	ac(8)e
			Work (ever)	358	1.00 (0.75-1.34)	-	ac(8)e
			Home and/or work (ever)	358	0.92 (0.65-1.29)	No	ac(8)

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of additional confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

p pre-menopausal at baseline.

q post-menopausal at baseline.

x unspecified.

4.8. Cancer of the ovary

Details of the five studies that investigated the possible association between ETS exposure and the risk of ovarian cancer are given in Table 4.8. One study[86] reported a significant reduction in risk and a significant negative dose-related trend with total ETS exposure. This study reported a similar result for current smokers. The remaining four studies failed to find any association between ovarian cancer incidence and exposure to ETS.

Table 4.8: ETS and Cancer of the Ovary

Study	Year	Country	Source (timing) of ETS exposure	Number of cases	Relative risk (95% CI)	Dose response	Notes
Hirayama[6]	1987	Japan	Spouse (ever)	54	Not available	No	c(1)
Nishino[10]	2001	Japan	Spouse (current)	15	1.70 (0.58-5.20)	-	a
Goodman[81]	2003	USA	Cohabitant (childhood)	351	0.98 (0.72-1.35)	-	ac(6)
Baker[86]	2006	USA	Total (current)	246	0.68 (0.47-0.99)	d1	ac(6)
Gram[62]	2008	Norway, Sweden	Cohabitant (baseline)	109	1.1 (0.7-1.6)	-	ac(3)r

Dose response

d1 Relative risks 1.00, 0.68, 0.54, 0.39 for 0, <2, 2-8, >8 hours/day ETS exposure (trend p=0.04)

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of additional confounders given in brackets – see Table 3.1 for further details).

r results quoted above are for all tumours. The study also reports results by type of tumour: invasive tumours RR 1.1 (0.7-1.7), borderline tumours RR 1.1 (0.5-2.7), serous tumours RR 1.4 (0.8-2.3) and mucinous tumours RR 1.1 (0.4-3.0).

4.9. Cancer of the kidney

See Table 4.9 for details of the three studies that considered this endpoint in relation to ETS exposure. Of the eight relative risks presented, seven were above 1.00, with one of these, from a study in the USA[90], reaching statistical significance, and another two, from a study in Canada[83], just failing to do so. All three of the studies reported significant dose-related trends with ETS exposure. In the first study[42], a positive trend was reported in females in relation to hours of ETS exposure at home or work. This was based on a marginally significant trend statistic where the dose-relationship pattern was actually quite erratic. The second[83] showed a non-significant trend for females but a significant positive trend with years of exposure for males. The third study[90] showed positive trends for all measures of ETS exposure considered, although no estimate of the significance of the trend for public/private ETS exposure was made. Again, the pattern of relative risks for this trend was erratic, as were those for exposure at home and at work in this study, although both of these were reported to be statistically significant. Only the relationship between exposure at home and/or work showed a clear increase in kidney cancer risk with increasing exposure.

Although the data considered here indicate an increase in the risk of kidney cancer in association with exposure to ETS, there are too few studies reporting for any firm conclusions to be drawn.

Table 4.9: ETS and Cancer of the Kidney

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Kreiger[42]	1993	Canada	Cohabitant or co-worker (current)	F	72	0.87 (0.50-1.49)	d1	ac(1)es
				M	47	1.09 (0.57-2.09)	No	ac(1)es
Hu[83]	2005	Canada	Residential and/or occupational (ever)	F	171	1.75 (0.99-3.08)	d2	ac(6)e
				M	89	2.55 (0.99-6.58)	d3	ac(6)e
Theis[90]	2008	USA	Home (ever)	M+F	129	1.32 (0.76-2.29)	d4,d5	ac(3)e
			Work (ever)	M+F	129	1.57 (0.96-2.59)	No	ac(3)e
			Public/private (ever)	M+F	128	1.53 (0.90-2.60)	No	ac(4)et
			Home/work (ever)	M+F	128	1.94 (1.07-3.52)	d6	ac(3)ex

Dose response

d1 Relative risks 1.0, 0.6, 1.7 for <3, 3-8, >8 hours/day ETS exposure (trend p=0.03)

d2 Relative risks 1.0, 1.7, 1.7, 1.8 for never, 1-22, 23-42 and ≥43 years exposure (sum of years residential exposure and years occupation exposure) (trend p=0.09)

d3 Relative risks 1.0, 1.5, 2.5, 3.9 for never, 1-22, 23-42 and ≥43 years exposure (sum of years residential exposure and years occupation exposure) (trend p=0.001)

d4 Relative risks 1.00, 0.86, 2.18 for no exposure, 1-20 or >20 years exposure (trend p=0.010)

d5 Relative risks 1.00, 0.83, 2.37 for no exposure, 1-29999 or 30000+ hours exposure (trend p= 0.008)

d6 Relative risks 1.33, 1.92, 3.04 for 0-6569, 6570-24454, 24455-67707 or 67708+ hours exposure (trend p=0.020)

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of additional confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

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

t compared to exposure of <1 hour per week

x compared to 0-6569 hours exposure

4.10. Cancer of other sites

Table 4.10 summarizes the limited results that are available for seven cancer sites (or groups of sites).

Although a significant association of endocrine cancer with exposure to smoking by the spouse was reported, this study[7] was based on only 13 cases and was unstandardized either for age or sex.

In addition, for the endpoint of leukaemia, one study[84] reported significant positive dose-related trends for exposure to cohabitants and to co-workers.

No other significant associations were reported. These results add little to the evidence on ETS as a potential cause of cancer. Even for endocrine cancer and leukaemia, more studies are clearly needed before any assessment can be made.

Table 4.10: 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[8]	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[6]	1987	Japan	Spouse (ever)	F	17	Not available	No	c(1)
Skin cancer:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	23	Not available	No	c(1)
Female genital cancer:								
Sandler I[8]	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[7]	1985	USA	Spouse (ever)	M+F	13	4.4 (1.2-17.4)	-	u
Sandler I[8]	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[6]	1987	Japan	Spouse (ever)	F	85	Not available	No	c(1)
Leukaemia:								
Hirayama[6]	1987	Japan	Spouse (ever)	F	51	Not available	No	c(1)
Kasim[84]	2005	Canada	Cohabitant (ever)	M+F	266	0.99 (0.69-1.42)	d1	ac(4)e
			Co-worker (ever)	M+F	244	1.20 (0.88-1.64)	d2	ac(4)e
All haematopoietic:								
Sandler I[8]	1985	USA	Mother (childhood)	M+F	19	2.3 (0.7-7.5)	-	ue
				M+F	17	2.4 (0.9-6.7)	-	ue

Results are not included for five studies[101,115-118] as the analyses were not restricted to lifelong non-smokers.

Dose response

d1 Relative risks 1.00, 0.68, 0.98, 1.32 for never, <22, 22-39 and >39 years exposure (trend p=0.004)

d2 Relative risks 1.00, 0.98, 1.26, 1.57 for never, <15, 15-21 and >21 years exposure (trend p=0.001)

Key to notes

a adjusted for age.

c adjusted for confounding variables other than age (number of additional confounders given in brackets – see Table 3.1 for further details).

e estimated from data reported.

u unadjusted.

4.11. Total cancer incidence

For details of the 12 studies reporting results relating ETS exposure to total cancer risk, smoking-related cancer risk and/or non smoking-related cancer risk, see Table 4.11. Some of the analyses include lung cancers but they are generally not more than a small fraction of the cancers analysed. Most of the studies were published before 1990 and only two of the analyses[69,78] adjusted for more than a very small number of potential confounding variables.

Two studies[32,38] 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 the earlier tables. Two further studies, both from the 1980s[4,7-9], and both criticized for weaknesses of design and analysis[3], reported a weaker, but significant association between ETS exposure and total cancer risk. A more recent study in Hong Kong[55] reported a significant association and significant positive trend. However, this study used a strange design that asked the person reporting a cancer death to quantify ETS exposure 10 years earlier for both the case and a living person "who was well known to the informant". Finally, one study in New Zealand[69] reported a significant increase in cancers other than the lung for females in a 1996 cohort but not for females in a 1981 cohort and not for males. The remaining six studies[10,30,31,33,35,78] showed no significant association. One of these[78] used data from a large study, with the analyses adjusted for a wide range of possible confounders.

A meta-analysis of studies reporting ETS and total cancer gave a random effects estimates of 1.13 (1.02-1.24) when the extreme relative risk estimate[38] was excluded, and 1.16 (1.04-1.31) when it was included. A meta-analysis of smoking-related cancer (including lung cancer) gave a random effects estimate of 1.41 (1.08-1.84). 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 total cancer risk. 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.

Table 4.11: 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[4]	1984	Japan	Spouse (ever)	F	2705	1.14 (1.04-1.25)	d1	c(2)em
Miller I[31]	1984	USA	Spouse (ever)	F	123	0.95 (0.57-1.60)	-	aem
Sandler I[7]	1985	USA	Spouse (ever)	F	192	1.96 (1.30-2.97)	-	uenm
				M	39	1.53 (0.41-5.68)	-	uenm
Sandler I[9]	1985	USA	Cohabitant (ever)	M+F	157	1.78 (1.09-2.91)	d2	uen
Sandler I[8]	1985	USA	Mother (childhood)	M+F	191	1.2 (0.7-2.2)	-	ue
			Father (childhood)	M+F	173	1.2 (0.8-1.8)	-	ue
Reynolds[32]	1987	USA	Spouse (ever)	F	73	1.68 (1.04-2.71)	d3	ac(1)em
Butler[33]	1988	USA	Spouse (in marriage)	F	321	1.20 (0.94-1.54)	-	am
Sandler II[35]	1989	USA	Cohabitant (ever)	F	501	1.00 (0.82-1.21)	-	ac(3)m
				M	115	1.01 (0.66-1.53)	-	ac(3)m
Miller II[38]	1990	USA	Cohabitant (ever) or long-term exposure outside home	F	82	6.40 (2.34-17.5)	-	aexm
Iribarren[78]	2001	USA	Cohabitant (current)	F	1220	0.94 (0.82-1.08)	No	ac(10)m
				M	239	0.93 (0.65-1.31)	No	ac(10)m
			Total (current)	F	1220	0.95 (0.84-1.08)	No	ac(10)
				M	239	1.28 (0.94-1.75)	No	ac(10)
Nishino[10]	2001	Japan	Spouse (current)	F	426	1.10 (0.92-1.40)	-	am
McGhee[55]	2005	Hong Kong	Cohabitants (10 years earlier)	F	764	1.35 (1.03-1.76)	-	ac(1)m
				M	851	1.16 (0.85-1.60))	-	ac(1)m
				M+F			d4	
Meta-analysis based on 13 estimates (including Miller II)				Fixed effect		1.11 (1.05-1.18)		h1
				Random effects		1.16 (1.04-1.31)		
Meta-analysis based on 12 estimates (excluding Miller II)				Fixed effect		1.10 (1.04-1.17)		h2
				Random effects		1.13 (1.02-1.24)		
Smoking-related cancer (including lung cancer):								
Sandler I[8]	1985	USA	Mother (childhood)	M+F	47	0.8 (0.3-2.4)	-	uem
			Father (childhood)	M+F	41	1.7 (0.9-3.3)	-	uem
Reynolds[32]	1987	USA	Spouse (ever)	F	<73	7.01 (0.73-67.5)	d5	ac(1)em
Butler[33]	1988	USA	Spouse (in marriage)	F	41	1.22 (0.61-2.44)	-	am
Sandler II[35]	1989	USA	Cohabitant (ever)	F	76	1.45 (0.88-2.40)	-	ac(3)m
				M	32	0.96 (0.43-2.16)	-	ac(3)m
Nishino[10]	2001	Japan	Spouse (current)	F	56	1.70 (0.94-2.90)	-	am
Meta-analysis based on 7 estimates				Fixed effect		1.41 (1.08-1.84)		h3
				Random effects		1.41 (1.08-1.84)		

(continued)

Table 4.11: ETS and Total Cancer Incidence (continued)

Study	Year	Country	Source (timing) of ETS exposure	Sex	Number of cases	Relative risk (95% CI)	Dose response	Notes
Smoking-related cancer (excluding lung cancer):								
Butler[33]	1988	USA	Spouse (in marriage)	F	33	1.06 (0.47-2.36)	-	a
Cancer other than the lung:								
Gillis[30]	1984	Scotland	Cohabitant (current)	F	43	1.26 (0.62-2.56)	-	a
				M	8	0.50 (0.10-2.48)	-	a
Hill[69]	2007	New Zealand						
1981-84 cohort			Cohabitant (baseline)	F	≈1285	1.04 (0.90-1.21)	-	ac(8)
				M	≈548	1.19 (0.95-1.49)	-	ac(8)
1996-99 cohort			Cohabitant (baseline)	F	≈1693	1.21 (1.05-1.40)	-	ac(8)
				M	≈1070	0.98 (0.80-1.20)	-	ac(8)
Cancer other than smoking-related:								
Sandler I[8]	1985	USA	Mother (childhood)	F	144	1.3 (0.7-2.5)	-	ue
			Father (childhood)	M	132	1.1 (0.7-1.7)	-	ue
Sandler II[35]	1989	USA	Cohabitant (ever)	F	425	0.93 (0.76-1.54)	-	ac(3)
				M	83	1.03 (0.40-2.62)	-	ac(3)

Dose response

d1 Relative risks 1.00, 1.12, 1.23 for husband non-smoker, 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=0.04) was noted with pack-years ETS exposure but relative risks by level were not given.

d4 Relative risks 1.0, 1.14, 1.74 for 0, 1 and 2+ smoking cohabitants (sexes combined), trend p=0.003.

d5 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 Table 3.1 for further details).

e estimated from data reported.

h1 heterogeneity chisquared is 33.10 on 13 degrees of freedom (p=0.002)

h2 heterogeneity chisquared is 21.42 on 12 degrees of freedom (p=0.045)

h3 heterogeneity chisquared is 4.86 on 6 degrees of freedom (p=0.56)

m relative risk included in meta-analyses.

n there were a total of 2 non-smokers 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 relate to unemployed wives only because no separation by ETS exposure for employed wives.

5. Conclusions

This review is based on evidence from 73 studies that presented results relevant to an investigation of the possible association between exposure to environmental tobacco smoke (ETS) and cancers other than the lung or breast. Ten of the studies were reported in the 1980s, 17 in the 1990s, and 46 since 2000. Fifty-one of the studies were of a case-control design, while 20[4-6,10,30,32-35,48,57,58,61,62,66,67,69,72-77] were prospective cohort studies, and two studies[49,78] were cross-sectional in design.

Some 25 individual cancer sites, or groups of sites, were investigated, along with total cancer incidence, and the incidence of smoking-related cancers. Sixty-two of the studies investigated a single endpoint, while 11 others[4-10,33-35,44,48,53,64,75,79] considered two or more endpoints. Three of these studies[4-10] included 10 or more cancer sites. Thus, the number of studies considering each individual cancer site was limited, and did not exceed 14 for any one site, while several sites were considered by a single study.

Ten of the studies[7-9,13-21] failed to adjust their results for any potential confounding factors. Of the studies that did carry out adjustment, age and sex were the most commonly considered factors, and although data on numerous other potential confounders was collected by the studies, most failed to adjust their results for more than a few of these.

Other problems with the studies were also noted. Many of the studies were based on small numbers of cases, with only 35 of the studies that reported on specific cancer sites[4,18,20,21,34,39,44,45,47-51,59,60,62,64-68,71,75,77,79-84,86-88,90,91] including more than 100 cases. The largest study[4] was based on 2705 cases, but this was for total cancer incidence, with the highest number of cases for a specific site being 854, for stomach cancer, also from this study.

Other weaknesses in study design that were noted included incomplete follow-up and the use of statistical methods of doubtful validity (e.g.[4-6]), and the use of inappropriate controls (e.g.[7-9]). Elsewhere, there were either low participation rates (e.g.[65,68,79,91]), or a substantial difference in response rates between cases and controls (e.g.[7-9,90]). Finally, some studies[17,20,38,54,67,70,76] reported significantly raised relative risks that appeared to be implausibly large, given the associations between active smoking and the cancer site in question. The reasons for these findings are unclear, but suggest possible sources of bias in these studies.

For most of the cancer sites considered in this review, including head and neck cancers, the digestive system, bladder and brain, there is little or no evidence of an increase in risk in association with ETS exposure. Indeed, the evidence for liver cancer was more suggestive of a negative relationship. Though some studies have reported an association with cancers of the cervix, others have not and the evidence must be regarded as inconclusive, particularly as none of the studies adjust for HPV infection (or sexual activity). Some studies have also reported an increased risk of cancer of the nasopharynx associated with ETS exposure, but here the evidence is heterogeneous and no firm conclusion can be reached. 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. More evidence is also needed for kidney cancer, where all three of the studies conducted so far report some evidence of dose-response; and for leukaemia, where one of only two studies reports evidence of dose-response.

Where there were sufficient studies reporting to allow meta-analysis of the results to be carried out, the overall estimates of risk are summarized in Table 5.1. Although some of these were significantly raised, they were either based on small numbers of studies, or there were sufficient concerns about the studies included as to render the results inconclusive.

Taken as a whole, the epidemiology does not demonstrate that ETS exposure in non-smokers causes cancers of any of the sites considered by the studies.

Table 5.1: Summary of meta-analysis results for ETS exposure and cancers other than lung and breast

Cancer site	Number of estimates	Overall risk estimate (95% CI)		Heterogeneity chisquared	P value
		Fixed effect	Random effects		
Head/neck	5[a]	1.14 (0.95-1.38)	1.14 (0.95-1.38)	1.39	0.85
	7[b]	1.20 (1.00-1.45)	1.43 (0.97-2.09)	12.02	0.062
Stomach	6	1.08 (0.96-1.22)	1.08 (0.96-1.22)	1.58	0.90
Pancreatic	10[c]	1.07 (0.89-1.27)	1.07 (0.89-1.27)	6.92	0.65
	11[d]	1.13 (0.95-1.35)	1.16 (0.88-1.54)	20.29	0.027
Cervical	13[e]	1.39 (1.23-1.58)	1.48 (1.23-1.78)	19.69	0.073
	14[f]	1.45 (1.28-1.63)	1.63 (1.30-2.05)	32.44	0.002
Bladder	15	1.02 (0.85-1.22)	1.02 (0.84-1.23)	14.81	0.39
Brain	9	1.27 (1.01-1.60)	1.32 (0.97-1.80)	12.33	0.14
Total (including lung)	13[g]	1.10 (1.04-1.17)	1.13 (1.02-1.24)	21.42	0.045
	14[h]	1.11 (1.05-1.18)	1.16 (1.04-1.31)	33.10	0.002
Smoking-related (including lung)	7	1.41 (1.08-1.84)	1.41 (1.08-1.84)	4.86	0.56

[a] Excluding study by Tan[17]

[b] Including study by Tan[17]

[c] Excluding study by Lo[70]

[d] Including study by Lo[70]

[e] Excluding study by Sobti[20]

[f] Including study by Sobti[20]

[g] Excluding study by Miller[38]

[h] Including study by Miller[38]

Appendix A: Studies excluded from the report

Table A gives details of the 39 studies that were excluded from this report, and the reasons why they were excluded. The most common reason for rejection was a failure to restrict the results to never smokers, which accounted for the exclusion of some 23 studies[92-95,97-105,109-118]. Thirteen further papers were either subsets of studies included in the review, or were superseded by later papers[119-130]. In addition, four studies were excluded because there was either no suitable endpoint[131], or because they were of a design that did not allow relative risks to be calculated[132-134].

Table A: Studies excluded from the report

Study [ref]	Year[a]	Location	Design[b]	Cancer site(s)	Reasons for exclusion
Hirayama[119]	1981	Japan, 6 prefectures	P	Cervix, stomach	Superseded by other papers
Brown[109]	1982	Canada, Nova Scotia	CC	Cervix	Results not restricted to never smokers
Hellberg[110]	1983	Sweden, Gothenburg	CC	Cervix	Results not restricted to never smokers
Hirayama[120]	1984	Japan, 6 prefectures	P	Major (not lung)	Superseded by other papers
Yu[92]	1986	Hong Kong	CC	Nasopharynx	Results not restricted to never smokers
Zunzunegui[111]	1986	USA, California	CC	Cervix	Results not restricted to never smokers
Chen[93]	1988	Taiwan	CC	Nasopharynx	Results not restricted to never smokers
Hirayama[121]	1988	Japan, 6 prefectures	P	Brain, nasal sinus	Superseded by other papers
Yu[94]	1988	China, Guangxi	CC	Nasopharynx	Results not restricted to never smokers
Hirayama[122]	1990	Japan, 6 prefectures	P	Total and 17 sites[c]	Superseded by other papers
Hirayama[123]	1990	Japan, 6 prefectures	P	Not lung, respiratory	Superseded by other papers
Gerhardsson de Verdier[102]	1992	Sweden, Stockholm	CC	Colon, rectum	Results not restricted to never smokers
Guo[97]	1995	China, Liaoning	CC	Larynx	Results not restricted to never smokers
Paoff[115]	1995	USA, California	CC	Thyroid	Results not restricted to never smokers; ETS exposure relates to maternal exposure in-utero
Ogren[105]	1996	Sweden, Malmö	P	Pancreas	Results not restricted to never smokers
Clemmesen[132]	1997	6 countries	D	Testis	Ecologic study
Schantz[98]	1997	USA, New York	CC	Head/neck	Results not restricted to never smokers
Hirose[124]	1998	Japan, Nagoya	CC	Cervix	Based on subset of subjects included in reference[44]
Coker[112]	2002	USA, N Carolina	CC	Cervix	Results not restricted to never smokers
Escribano Uzcudun[99]	2002	Spain	CC	Pharynx	Results not restricted to never smokers
Enstrom[131]	2003	USA, California	P	-	No suitable endpoint
Kaijser[116]	2003	Sweden	P	Testis	Results not restricted to never smokers
Slattery[103]	2003	USA, California/Utah	CC	Rectum	Results not restricted to never smokers
Glaser[117]	2004	USA, California	CC	Hodgkin's lymphoma	Results not restricted to never smokers
Pettersson[133]	2004	4 Scandinavian countries	D	Testis	Ecologic study
Settheetham-Ishida[113]	2004	Thailand, Khon Kaen	CC	Cervix	Results not restricted to never smokers
Tay[114]	2004	Singapore	CC	Cervix	Results not restricted to never smokers
Airoldi[101]	2005	10 European countries	P	3 sites[d]	Results not restricted to never smokers and biomarker used is not good measure of ETS exposure
Hooker[125]	2005	USA, Washington County	P	Rectum	Abstract only, superseded by full paper (reference[76])
Vineis[100]	2005	10 European countries	P	Head/neck	Results either not restricted to never smokers or included large proportion of lung cancer cases
You[130]	2005	China, Taixing City	CC	Oesophagus	Based on same subjects as reference[53] but published later
McGlynn[118]	2006	USA	CC	Testis	Results not restricted to never smokers
Tsai[126]	2006	Taiwan	CC	Cervix	Abstract only, superseded by full paper (reference[56])
Dahlstrom[134]	2008	USA, Houston	D	Head/neck	Case series only

(continued)

Table A: Studies excluded from the report (continued)

Study [ref]	Year[a]	Location	Design[b]	Cancer site(s)	Reasons for exclusion
Sobti[127]	2008	India, Chandigarh	CC	Cervix	Based on same subjects as reference[21] but published later
Sobti[128]	2008	India, Chandigarh	CC	Cervix	Based on subset of subjects included in reference[21]
Sobti[129]	2008	India, Chandigarh	CC	Cervix	Based on subset of subjects included in reference[21]
Curtin[104]	2009	USA, California/Utah	CC	Rectum	Results not restricted to never smokers
Nesic[95]	2010	Serbia, Belgrade	CC	Nasopharynx	Results not restricted to never smokers

Notes:

[a] Year of first publication.

[b] Study design CC = case-control CS = cross-sectional. D = descriptive NCC = nested case-control P = prospective

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

[d] Bladder, leukemias, oral cancer.

REFERENCES

1. Lee PN, Forey BA, Hamling JS. *Epidemiological evidence on environmental tobacco smoke and lung cancer*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2006. www.pnlee.co.uk/reflist.htm [Download LEE2006G]

2. Lee PN, Hamling JS. *Epidemiological evidence on environmental tobacco smoke and breast cancer. A review with meta-analyses*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2008. www.pnlee.co.uk/reflist.htm [Download LEE2008]

3. Lee PN. *Environmental tobacco smoke and mortality. A detailed review of epidemiological evidence relating environmental tobacco smoke to the risk of cancer, heart disease and other causes of death in adults who have never smoked*. Basel: Karger; 1992.

4. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 1984;**13**:680-90.

5. Hirayama T. Passive smoking - a new target of epidemiology. *Tokai J Exp Clin Med* 1985;**10**:287-93.

6. Hirayama T. Passive smoking and cancer: an epidemiological review. *Gann Monogr Cancer Res* 1987;**33**:127-35.

7. Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;**121**:37-48.

8. Sandler DP, Everson RB, Wilcox AJ, Browder JP. Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health* 1985;**75**:487-92.

9. Sandler DP, Wilcox AJ, Everson RB. Cumulative effects of lifetime passive smoking on cancer risk. *Lancet* 1985;**1**:312-5.

10. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, *et al.* Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control* 2001;**12**:797-802.

11. Lee PN. Uses and abuses of cotinine as a marker of tobacco smoke exposure. In: Gorrod JW, Jacob P, III, editors. *Analytical determination of nicotine and related compounds and their metabolites*. Amsterdam: Elsevier, 1999;669-719.

12. National Cancer Institute. Shopland DR, Zeise L, Dunn A, editors. *Health effects of exposure to environmental tobacco smoke. The report of the California Environmental Protection Agency*. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 1999. (Smoking and Tobacco Control. Monograph No. 10.) NIH Pub. No. 99-4645. http://cancercontrol.cancer.gov/tcrb/monographs/10/index.html

13. Kabat GC, Dieck GS, Wynder EL. Bladder cancer in nonsmokers. *Cancer* 1986;**57**:362-7.

14. Fukuda K, Shibata A. Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. *Cancer Causes Control* 1990;**1**:165-8.

15. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, *et al.* A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol* 1992;**22**:286-91.

16. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* 1997;**8**:5-12.

17. Tan E-H, Adelstein DJ, Droughton MLT, van Kirk MA, Lavertu P. Squamous cell head and neck cancer in nonsmokers. *Am J Clin Oncol* 1997;**20**:146-50.

18. Johnson KC, Hu J, Fincham S, The Canadian Cancer Registries Epidemiology Research Group. Passive smoking and adult brain cancer in Canada, 1994-1997 [Abstract]. Presented at the 32nd Annual Meeting of the Society for Epidemiologic Research, Baltimore, Maryland, June 10-12, 1999. *Am J Epidemiol* 1999;**149**:S72.

19. Zhang Z-F, Morgenstern H, Spitz MR, Tashkin DP, Yu G-P, Hsu TC, *et al.* Environmental tobacco smoking, mutagen sensitivity, and head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:1043-9.

20. Sobti RC, Kaur S, Kaur P, Singh J, Gupta I, Jain V, *et al.* Interaction of passive smoking with *GST* (*GSTM1, GSTT1,* and *GSTP1*) genotypes in the risk of cervical cancer in India. *Cancer Genet Cytogenet* 2006;**166**:117-23.

21. Kordi Tamandani DM, Sobti RC, Shekari M. Association of Fas-670 gene polymorphism with risk of cervical cancer in North Indian population. *Clin Exp Obstet Gynecol* 2008;**35**:183-6.

22. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000;**53**:207-16.

23. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J Natl Cancer Inst* 1981;**66**:1061-6.

24. Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, *et al.* Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study II. *Cancer Causes Control* 1997;**8**:57-64.

25. Wartenberg D, Calle EE, Thun MJ, Heath CW, Jr., Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* 2000;**92**:1666-73.

26. Wells AJ. An estimate of adult mortality in the United States from passive smoking. *Environ Int* 1988;**14**:249-65.

27. Remmer H. Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. *Arch Toxicol* 1987;**61**:89-104.

28. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol* 1991;**44**:127-39.

29. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;**27**:954-70.

30. Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Respir Dis* 1984;**65(suppl 133)**:121-6.

31. Miller GH. Cancer, passive smoking and nonemployed and employed wives. *West J Med* 1984;**140**:632-5.

32. Reynolds P, Kaplan GA, Cohen RD. Passive smoking and cancer incidence: prospective evidence from the Alameda County study. In: *Annual meeting of the Society for Epidemiologic Research, Amherst, MA, 16-19 June 1987.* 1987;1-5.

33. Butler TL. *The relationship of passive smoking to various health outcomes among Seventh day Adventists in California* [Thesis]. Los Angeles: University of California; 1988.

34. Sandler RS, Sandler DP, Comstock GW, Helsing KJ, Shore DL. Cigarette smoking and the risk of colorectal cancer in women. *J Natl Cancer Inst* 1988;**80**:1329-33.

35. Sandler DP, Comstock GW, Helsing KJ, Shore DL. Deaths from all causes in non-smokers who lived with smokers. *Am J Public Health* 1989;**79**:163-7.

36. Burch JD, Rohan TE, Howe GR, Risch HA, Hill GB, Steele R, *et al.* Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer* 1989;**44**:622-8.

37. Slattery ML, Robison LM, Schuman KL, French TK, Abbott TM, Overall JC, Jr., *et al.* Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *JAMA* 1989;**261**:1593-8.

38. Miller GH. The impact of passive smoking: cancer deaths among nonsmoking women. *Cancer Detect Prev* 1990;**14**:497-503.

39. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer* 1990;**45**:1033-9.

40. Coker AL, Rosenberg AJ, McCann MF, Hulka BS. Active and passive cigarette smoke exposure and cervical intraepithelial neoplasia. *Cancer Epidemiol Biomarkers Prev* 1992;**1**:349-56.

41. Ryan P, Lee MW, North JB, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer* 1992;**51**:20-7.

42. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control* 1993;**4**:101-10.

43. Zheng W, McLaughlin JK, Chow W-H, Chien HTC, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am J Epidemiol* 1993;**138**:965-72.

44. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, *et al.* Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res* 1996;**87**:1001-9.

45. Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *J Epidemiol Community Health* 1996;**50**:442-6.

46. Vaughan TL, Shapiro JA, Burt RD, Swanson GM, Berwick M, Lynch CF, *et al.* Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev* 1996;**5**:587-93.

47. Cheng Y-J, Hildesheim A, Hsu M-M, Chen I-H, Brinton LA, Levine PH. Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes Control* 1999;**10**:201-7.

48. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* 1999;**28**:824-8.

49. Scholes D, McBride C, Grothaus L, Curry S, Albright J, Ludman E. The association between cigarette smoking and low-grade cervical abnormalities in reproductive-age women. *Cancer Causes Control* 1999;**10**:339-44.

50. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *Int J Epidemiol* 2000;**29**:991-8.

51. Yuan J-M, Wang X-L, Xiang Y-B, Gao Y-T, Ross RK, Yu MC. Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer* 2000;**85**:364-9.

52. Wu M-T, Lee L-H, Ho C-K, Liu C-L, Wu T-N, Wu S-C, *et al.* Lifetime exposure to environmental tobacco smoke and cervical intraepithelial neoplasms among nonsmoking Taiwanese women. *Arch Environ Health* 2003;**58**:353-9.

53. You NC, Mu LN, Yu SZ, Jiang QW, Cao W, Zhou XF, *et al.* Environmental tobacco smoking and smoking-related susceptibility genes for the risk of esophageal, stomach, and liver cancers [Abstract]. *Ann Epidemiol* 2003;**13**:564.

54. Chen Y-C, Su H-JJ, Guo Y-LL, Houseman EA, Christiani DC. Interaction between environmental tobacco smoke and arsenic methylation ability on the risk of bladder cancer. *Cancer Causes Control* 2005;**16**:75-81.

55. McGhee SM, Ho SY, Schooling M, Ho LM, Thomas GN, Hedley AJ, *et al.* Mortality associated with passive smoking in Hong Kong. *BMJ* 2005;**330**:287-8.

56. Tsai H-T, Tsai Y-M, Yang S-F, Wu K-Y, Chuang H-Y, Wu T-N, *et al.* Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm -a community-based case-control study. *Gynecol Oncol* 2007;**105**:181-8.

57. Zeegers MPA, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control* 2002;**13**:83-90.

58. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, Frederiksen K, Christensen J, Tjønneland A, *et al.* Tobacco smoke and bladder cancer - in the European prospective investigation into cancer and nutrition. *Int J Cancer* 2006;**119**:2412-6.

59. Lilla C, Verla-Tebit E, Risch A, Jäger B, Hoffmeister M, Brenner H, *et al.* Effect of *NAT1* and *NAT2* genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:99-107. http://cebp.aacrjournals.org/cgi/reprint/15/1/99

60. Samanic C, Kogevinas M, Dosemeci M, Malats N, Real FX, Garcia-Closas M, *et al.* Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1348-54.

61. Al-Zoughool M, Dossus L, Kaaks R, Clavel-Chapelon F, Tjønneland A, Olsen A, *et al.* Risk of endometrial cancer in relationship to cigarette smoking: results from the EPIC study. *Int J Cancer* 2007;**121**:2741-7.

62. Gram IT, Braaten T, Adami H-O, Lund E, Weiderpass E. Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer. *Int J Cancer* 2008;**122**:647-52.

63. Ramroth H, Dietz A, Becher H. Environmental tobacco smoke and laryngeal cancer: results from a population-based case-control study. *Eur Arch Otorhinolaryngol* 2008;**265**:1367-71.

64. Lee Y-CA, Marron M, Benhamou S, Bouchardy C, Ahrens W, Pohlabeln H, *et al.* Acitve and involuntary tobacco smoking and upper aerodigestive tract

cancer risks in a multicenter case-control study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:3353-61. Cancer Epidemiology, Biomarkers & Prevention.

65. Verla-Tebit E, Lilla C, Hoffmeister M, Brenner H, Chang-Claude J. Exposure to environmental tobacco smoke and the risk of colorectal cancer in a case-control study from Germany. *Eur J Cancer Prev* 2009;**18**:9-12.

66. Heinen MM, Verhage BAJ, Goldbohm A, van den Brandt PA. Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1612-22.

67. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, *et al.* Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;**126**:2394-403.

68. Yang HP, Brinton LA, Platz EA, Lissowska J, Lacey JV, Jr., Sherman ME, *et al.* Active and passive cigarette smoking and the risk of endometrial cancer in Poland. *Eur J Cancer* 2010;**46**:690-6.

69. Hill SE, Blakely T, Kawachi I, Woodward A. Mortality among lifelong nonsmokers exposed to secondhand smoke at home: cohort data and sensitivity analyses. *Am J Epidemiol* 2007;**165**:530-40.

70. Lo A-C, Soliman AS, El-Ghawalby N, Abdel-Wahab M, Fathy O, Khaled HM, *et al.* Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. *Pancreas* 2007;**35**:120-9.

71. Lee Y-CA, Boffetta P, Sturgis EM, Wei Q, Zhang Z-F, Muscat J, *et al.* Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:1974-81.

72. Trimble CL, Genkinger JM, Burke AE, Hoffman SC, Helzlsouer KJ, Diener-West M, *et al.* Active and passive cigarette smoking and the risk of cervical neoplasia. *Obstet Gynecol* 2005;**105**:174-81.

73. Gallicchio L, Kouzis A, Genkinger JM, Burke AE, Hoffman SC, Diener-West M, *et al.* Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med* 2006;**42**:200-5.

74. Alberg AJ, Kouzis A, Genkinger JM, Gallicchio L, Burke AE, Hoffman SC, *et al.* A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol* 2007;**165**:660-6.

75. Paskett ED, Reeves KW, Rohan TE, Allison MA, Williams CD, Messina CR, *et al.* Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. *J Natl Cancer Inst* 2007;**99**:1729-35.

76. Hooker CM, Gallicchio L, Genkinger JM, Comstock GW, Alberg AJ. A prospective cohort study of rectal cancer risk in relation to active cigarette smoking and passive smoke exposure. *Ann Epidemiol* 2008;**18**:28-35.

77. Bao Y, Giovannucci E, Fuchs CS, Michaud DS. Passive smoking and pancreatic cancer in women: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:2292-6.

78. Iribarren C, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. *J Epidemiol Community Health* 2001;**55**:721-8.

79. Duan L, Wu AH, Sullivan-Halley J, Bernstein L. Passive smoking and risk of oesophageal and gastric adenocarcinomas. *Br J Cancer* 2009;**100**:1483-5.

80. Mao Y, Hu J, Semenciw R, White K. Active and passive smoking and the risk of stomach cancer, by subsite, in Canada. *Eur J Cancer Prev* 2002;**11**:27-38.

81. Goodman MT, Tung K-H. Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control* 2003;**14**:569-77.

82. Villeneuve PJ, Johnson KC, Mao Y, Hanley AJ. Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. *Can J Public Health* 2004;**95**:32-7.

83. Hu J, Ugnat A-M, The Canadian Cancer Registries Epidemiology Research Group. Active and passive smoking and risk of renal cell carcinoma in Canada. *Eur J Cancer* 2005;**41**:770-8.

84. Kasim K, Levallois P, Abdous B, Auger P, Johnson KC. Environmental tobacco smoke and risk of adult leukemia. *Epidemiology* 2005;**16**:672-80.

85. Phillips LE, Longstreth WT, Jr., Koepsell T, Custer BS, Kukull WA, van Belle G. Active and passive cigarette smoking and risk of intracranial meningioma. *Neuroepidemiology* 2005;**24**:117-22.

86. Baker JA, Odunuga OO, Rodabaugh KJ, Reid ME, Menezes RJ, Moysich KB. Active and passive smoking and risk of ovarian cancer. *Int J Gynecol Cancer* 2006;**16(Suppl 1)**:211-8.

87. Hassan MM, Abbruzzese JL, Bondy ML, Wolff RA, Vauthey J-N, Pisters PW, *et al.* Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. *Cancer* 2007;**109**:2547-56.

88. Jiang X, Yuan J-M, Skipper PL, Tannenbaum SR, Yu MC. Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res* 2007;**67**:7540-5.

89. Hassan MM, Spitz MR, Thomas MB, El-Deeb AS, Glover KY, Nguyen NT, *et al.* Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer* 2008;**123**:1883-91.

90. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. *BMC Cancer* 2008;**8**:387.

91. Baris D, Karagas MR, Verrill C, Johnson A, Andrew AS, Marsit CJ, *et al.* A case-control study of smoking and bladder cancer risk: emergent patterns over time. *J Natl Cancer Inst* 2009;**101**:1553-61.

92. Yu MC, Ho JHC, Lai S-H, Henderson BE. Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. *Cancer Res* 1986;**46**:956-61.

93. Chen C-J, Wang Y-F, Shieh T, Chen J-Y, Liu M-Y. Multifactorial etiology of nasopharyngeal carcinoma. Epstein-Barr virus, familial tendency and environmental cofactors. In: *Head and neck oncology research, Proceedings of the IInd International Head and Neck Oncology Research Conference, Arlington, VA, USA, 10-12 September 1987.* Amsterdam: Kugler, 1988;469-76.

94. Yu MC, Mo CC, Chong WX, Yeh FS, Henderson BE. Preserved foods and nasopharyngeal carcinoma: a case-control study in Guangxi, China. *Cancer Res* 1988;**48**:1954-9.

95. Nešić V, Šipetić S, Vlajinac H, Stošić-Divjak S, Ješić S. Risk factors for the occurrence of undifferentiated carcinoma of nasopharyngeal type: a case-control study. *Srp Arh Celok Lek* 2010;**138**:6-10.

96. Stewart BW, Semmler PCB. *Sharp v Port Kembla RSLClub:* establishing causation of laryngeal cancer by environmental tobacco smoke. *Med J Aust* 2002;**176**:113-6.

97. Guo X, Cheng M, Fei S. A case-control study of the etiology of laryngeal cancer in Liaoning province. *Chin Med J* 1995;**108**:347-50.

98. Schantz SP, Zhang Z-F, Spitz MS, Sun M, Hsu TC. Genetic susceptibility to head and neck cancer: interaction between nutrition and mutagen sensitivity. *Laryngoscope* 1997;**107**:765-81.

99. Escribano Uzcudun A, Rabanal Retolaza I, Garcia Grande A, Miralles Olivar L, Garcia Garcia A, Gonzalez Barón M, *et al.* Pharyngeal cancer prevention: evidence from a case-control study involving 232 consecutive patients. *J Laryngol Otol* 2002;**116**:523-31.

100. Vineis P, Airoldi L, Veglia F, Olgiati L, Pastorelli R, Autrup H, *et al.* Environmental tobacco smoke and risk of respiratory cancer and chronic

obstructive pulmonary disease in former and never smokers in the EPIC prospective study. *BMJ* 2005;**330**:277-80.

101. Airoldi L, Vineis P, Colombi A, Olgiati L, Dell'Osta C, Fanelli R, *et al.* 4-aminobiphenyl-hemoglobin adducts and risk of smoking-related disease in never smokers and former smokers in the European Prospective Investigation into Cancer and Nutrition Prospective Study. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2118-24.

102. Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM. Occupational exposures and cancer of the colon and rectum. *Am J Ind Med* 1992;**22**:291-303.

103. Slattery ML, Edwards S, Curtin K, Schaffer D, Neuhausen S. Associations between smoking, passive smoking, *GSTM-1*, *NAT2*, and rectal cancer. *Cancer Epidemiol Biomarkers Prev* 2003;**12**:882-9.

104. Curtin K, Samowitz WZ, Wolff RK, Herrick J, Caan BJ, Slattery ML. Somatic alterations, metabolizing genes and smoking in rectal cancer. *Int J Cancer* 2009;**125**:158-64.

105. Ögren M, Hedberg M, Berglund G, Borgström A, Janzon L. Risk of pancreatic carcinoma in smokers enhanced by weight gain. *Int J Pancreatol* 1996;**20**:95-101.

106. Doll R. Cancers weakly related to smoking. *Br Med Bull* 1996;**52**:35-49.

107. Kjær SK, van den Brule AJC, Bock JE, Poll PA, Engholm G, Sherman ME, *et al.* Human papillomavirus - the most significant risk determinant of cervical intraepithelial neoplasia. *Int J Cancer* 1996;**65**:601-6.

108. Clark MA, Rakowski W, Ehrich B. Breast and cervical cancer screening: associations with personal, spouse's, and combined smoking status. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:513-6.

109. Brown DC, Pereira L, Garner JB. Cancer of the cervix and the smoking husband. *Can Fam Physician* 1982;**28**:499-502.

110. Hellberg D, Valentin J, Nilsson S. Smoking as risk factor in cervical neoplasia [Letter]. *Lancet* 1983;**2**:1497.

111. Zunzunegui MV, King M-C, Coria CF, Charlet J. Male influences on cervical cancer risk. *Am J Epidemiol* 1986;**123**:302-7.

112. Coker AL, Bond SM, Williams A, Gerasimova T, Pirisi L. Active and passive smoking, high-risk human papillomaviruses and cervical neoplasia. *Cancer Detect Prev* 2002;**26**:121-8.

113. Settheetham-Ishida W, Singto Y, Yuenyao P, Tassaneeyakul W, Kanjanavirojkul N, Ishida T. Contribution of epigenetic risk factors but not p53 codon 72 polymorphism to the development of cervical cancer in Northeastern Thailand. *Cancer Lett* 2004;**210**:205-11.

114. Tay S-K, Tay K-J. Passive cigarette smoking is a risk factor in cervical neoplasia. *Gynecol Oncol* 2004;**93**:116-20.

115. Paoff K, Preston-Martin S, Mack WJ, Monroe K. A case-control study of maternal risk factors for thyroid cancer in young women (California, United States). *Cancer Causes Control* 1995;**6**:389-97.

116. Kaijser M, Akre O, Cnattingius S, Ekbom A. Maternal lung cancer and testicular cancer risk in the offspring. *Cancer Epidemiol Biomarkers Prev* 2003;**12**:643-6.

117. Glaser SL, Keegan THM, Clarke CA, Darrow LA, Gomez SL, Dorfman RF, *et al.* Smoking and Hodgkin lymphoma risk in women - United States. *Cancer Causes Control* 2004;**15**:387-97.

118. McGlynn KA, Zhang Y, Sakoda LC, Rubertone MV, Erickson RL, Graubard BI. Maternal smoking and testicular germ cell tumors. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1820-4. http://cebp.aacrjournals.org/cgi/reprint/15/10/1820

119. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* 1981;**282**:183-5.

120. Hirayama T. Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P, editors. *Lung cancer: causes and prevention, Proceedings of the International Lung Cancer Update Conference, New Orleans, Louisiana, March 3-5, 1983.* Deerfield Beach, Florida: Verlag Chemie International, Inc, 1984;175-95.

121. Hirayama T. Health effects of active and passive smoking. In: Aoki M, Hisamichi S, Tominaga S, editors. *Smoking and health 1987, Proceedings of the 6th World Conference on Smoking and Health, Tokyo, 9-12 November 1987.* Amsterdam: Elsevier Science Publishers B.V. (Biomedical Division), 1988;75-86. International Congress Series No. 780.

122. Hirayama T. Passive smoking and cancer: The association between husbands smoking and cancer in the lung of non-smoking wives. In: Kasuga H, editor. *Indoor air quality, International Conference on Indoor Air Quality, Tokyo, November 4-6, 1987.* Berlin Heidelberg: Springer-Verlag, 1990;299-311.

123. Hirayama T. Wahrendorf J, editor. *Life-style and mortality: A large scale census based cohort study in Japan. Contributions to epidemiology and biostatistics.* Basle: Karger; 1990. 6.

124. Hirose K, Hamajima N, Takezaki T, Kuroishi T, Kuzuya K, Sasaki S, *et al.* Smoking and dietary risk factors for cervical cancer at different age groups in Japan. *J Epidemiol* 1998;**8**:6-14.

125. Hooker CM, Gallicchio LM, Comstock GW, Alberg AJ. The risk of developing rectal cancer due to active cigarette smoking and passive smoke exposure [Abstract]. *Ann Epidemiol* 2005;**15**:633.

126. Tsai H-T, Tsai Y-M, Yang S-F, Wu K-Y, Chuang H-Y, Wu M-T. The relationship between second hand smoke and cervical intraepithelial neoplasm: a community-based case-control study [Abstract (SER)]. *Am J Epidemiol* 2006;**163(Suppl)**:S254.

127. Sobti RC, Shekari M, Kordi Tamandani DM, Kaur P, Suri V, Huria A. Effect of *NBS1* gene polymorphism on the risk of cervix carcinoma in a northern Indian population. *Int J Biol Markers* 2008;**23**:133-9.

128. Sobti RC, Shekari M, Kordi Tamandani DM, Malekzadeh K, Suri V. Association of interleukin-18 gene promoter polymorphism on the risk of cervix carcinogenesis in north Indian population. *Oncol Res* 2008;**17**:159-66.

129. Sobti RC, Kordi Tamandani DM, Shekari M, Kaur P, Malekzadeh K, Suri V. Interleukin 1 beta gene polymorphism and risk of cervical cancer. *Int J Gynaecol Obstet* 2008;**101**:47-52.

130. You NC, Mu LN, McAfee T, Yang B, Cao W, Yu SZ, *et al.* Environmental tobacco smoking and smoking-related susceptibility genes for the risk of esophageal cancer [Abstract]. *Am J Epidemiol* 2005;**161(Suppl)**:S13.

131. Enstrom JE, Kabat GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;**326**:1057-61. Full version available at http://bmj.com/cgi/content/full/326/7398/1057

132. Clemmesen J. Is pregnancy smoking causal to testis cancer in sons? A hypothesis. *Acta Oncol* 1997;**36**:59-63.

133. Pettersson A, Kaijser M, Richiardi L, Askling J, Ekbom A, Akre O. Women smoking and testicular cancer: one epidemic causing another? *Int J Cancer* 2004;**109**:941-4.

134. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. *Head Neck* 2008;**30**:75-84.