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

## Executive summary

This review is based on evidence from 77 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, 43 in the years 2000-9, and 7 since 2010. Some 27 individual cancer sites, or groups of sites, were investigated, along with total cancer incidence, and the incidence of smoking-related cancers. Sixty-five of the studies investigated a single endpoint, while 12 others considered two or more endpoints. Four 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 16 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, 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.

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## 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-seven 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 four 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 remaining two[10,11] were 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[12], 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[13].

- Confounding Many of the studies, particularly those reporting in the 1980s, made at most only limited adjustment for potential confounding variables. Some studies[7-9,14-22] 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[23]. 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[24,25] but, with the exception of a publication on breast cancer based on one of these[26], 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[27,28], 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 September 2010. 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 May 2012. 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[29], or by combining non-independent relative risks, e.g. for different exposure levels with the same reference group[30].

Where there are five or more studies providing independent estimates of risk, fixed effect and random effects meta-analysis[29] 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 77 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. Forty-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 77 studies included in this review, 10[4-9,14,31-38] were reported in the 1980s, 17[15-19,39-50] in the 1990s, 43 in the years 2000-9, and seven[11,51-56] were conducted since 2010. Forty of the studies were carried out in North America, while 18 studies[4-6,10,15,16,21,22,40,45,48,49,53,57-63] were conducted in Asia, 13[11,31,51,54,64-72] in Europe and 3[42,46,73] in Australasia. One study took place in Egypt[74], one study was conducted in Europe, Latin America and the USA[75] and one study was carried out in South America, Asia and Europe[55].

Fifty-four of the studies were of a case-control design, while 21[4-6,10,11,31,33-36,49,51,56,64,65,68,69,73,76-81] were prospective cohort studies. The remaining two studies[50,82] were cross-sectional in design. Sixty-five studies presented results for a single endpoint, while 12 others[4-11,34-36,45,49,60,71,79,83] considered two or more endpoints, with four of these studies[4-11] investigating 10 or more cancer sites.

Ten of the studies[7-9,14-22] failed to adjust their results for any potentially confounding variables. Two studies[60,68] carried out adjustment but did not specify the factors that had been used to do this. Of the 65 remaining studies, only two[4-6,57] did not adjust for age, and all but three studies[57,65,77] 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[31] | 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[32] | 1984 | USA, Pennsylvania | CC | Total | Age |
| Sandler I[7-9] | 1985 | USA, N Carolina | CC | Total and 9 categories[f] | None |
| Kabat[14] | 1986 | USA, 18 hospitals | CC | Bladder | None |
| Reynolds[33] | 1987 | USA, California | P | Total, smoking-related | Age, income |
| Butler[34] | 1988[g] | USA, California | P | Total, smoking-related, cervix | Age |
| Sandler II[35,36] | 1988 | USA, Maryland | P | Total, smoking-related, not smoking-related, colon | Age, housing quality, schooling, marital status |
| Burch[37] | 1989 | Canada, Alberta and Ontario | CC | Bladder | Age, area of residence |
| Slattery[38] | 1989 | USA, Utah | CC | Cervix | Age, education, church attendance, number of sexual partners |
| Fukuda[15] | 1990 | Japan, Hokkaido | CC | Nasal cavity | None |
| Miller II[39] | 1990 | USA, Pennsylvania | CC | Total | Age |
| Yu[40] | 1990 | China, Guangzhou | CC | Nasopharynx | Age, sex |
| Coker[41] | 1992 | USA, N Carolina | CC | Cervix[h] | Age, education, race, number of Pap smears, number of partners, genital warts |
| Mizuno[16] | 1992 | Japan | CC | Pancreas | None |
| Ryan[42] | 1992 | Australia, Adelaide | CC | Brain | Age |
| Kreiger[43] | 1993 | Canada, Ontario | CC | Kidney | Age, body mass index |
| Zheng[44] | 1993 | USA, National | CC | Nasal cavity | Age, alcohol use |
| Hirose[45] | 1996 | Japan, Nagoya | CC | Cervix, endometrium | Age, year of first visit |
| Hurley[46] | 1996 | Australia, Melbourne | CC | Brain | Age, sex, reference date |
| Vaughan[47] | 1996 | USA, 5 cancer registries | CC | Nasopharynx | Age, sex |
| Blowers[17] | 1997 | USA, California | CC | Brain | None |
| Tan[18] | 1997 | USA, Ohio | CC | Head/neck | None |
| Cheng[48] | 1999 | Taiwan | CC | Nasopharynx | Age, sex, race, educational level, family history of nasopharynx cancer |
| Jee[49] | 1999 | Korea | P | Stomach, liver, cervix | Age, socioeconomic status, residency, husband's age, vegetable consumption, occupation |
| Johnson I[19] | 1999 | Canada | CC | Brain | None stated (in abstract) |
| Scholes[50] | 1999 | USA, Washington State | CS | Cervix[h] | Age, number of sexual partners, age at first intercourse |
| Armstrong[57] | 2000 | Malaysia | CC | Nasopharynx | Diet |
| Yuan[58] | 2000 | China, Shanghai | CC | Nasopharynx | Age and 7 others[i] |
| Zhang[20] | 2000 | USA[j] | CC | Head/neck | None |
| Iribarren[82] | 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[84] | 2002 | Canada | CC | Stomach | Age and 7 others[n] |
| Zeeger[64] | 2002 | Netherlands | P | Bladder | Age and sex |
| Goodman[85] | 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[59] | 2003 | Taiwan | CC | Cervix[h] | Age, education level, number of pregnancies, age at first intercourse, cooking in the kitchen during ages 20-40 |
| You[60] | 2003 | China | CC | Oesophagus, stomach, liver | Unspecified but states that "ETS and confounders information was collected …" |
| Villenueve[86] | 2004 | Canada | CC | Pancreas | Age, sex, body mass index, income adequacy, province of residence |
| Chen[61] | 2005 | Taiwan | CC | Bladder | Age, BMI, cumulative arsenic, hair dye usage, education |
| Hu[87] | 2005 | Canada | CC | Renal cell | Age, province, education, body mass index, alcohol use, total consumption of meat and of vegetables and fruit |
| Kasim[88] | 2005 | Canada | CC | Leukaemia | Age, sex, BMI, benzene, ionising radiation |
| McGhee[62] | 2005 | Hong Kong | CC | All cancers | Age and education (and sex for sexes-combined analysis) |
| Phillips[89] | 2005 | USA, western Washington State | CC | Intracranial meningioma | Age, sex, education |
| Trimble[76] | 2005 | USA, Washington County | P | Cervix | Age, education, marital status, religious attendance (1963 only) |
| Baker[90] | 2006 | USA, New York state | CC | Ovary | Age, residence, income, usual BMI, history of vaginal infection, year of participation, duration of breastfeeding |
| Bjerregaard[65] | 2006 | 3 European countries | P | Bladder | Age, fruit and vegetables, ETS exposure at the other timepoint |
| Gallicchio[77] | 2006 | USA, Washington County | P | Pancreas | Age, education, marital status |
| Lilla[66] | 2006 | Germany | CC | Colorectum | Age, sex, NSAID use, endoscopy, family history, alcohol, red meat, education, BMI |
| Samanic[67] | 2006 | Spain | CC | Bladder | Age, region, fruit/vegetable consumption, high-risk occupation |
| Sobti[21] | 2006 | India | CC | Cervix | None |
| Alberg[78] | 2007 | USA, Washington County | P | Bladder | Age, education, marital status |
| Al-Zoughool[68] | 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[91] | 2007 | USA, Texas | CC | Pancreas | Age, sex, race/ethnicity, diabetes, alcohol, education, state of residence, marital status |
| Hill[73] | 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[92] | 2007 | USA, Los Angeles County | CC | Bladder | Age, race/ethnicity, education, ETS exposure in other settings |
| Lo[74] | 2007 | Egypt | CC | Pancreas | Age, sex, residence |
| Paskett[79] | 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[63] | 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[69] | 2008 | Norway and Sweden | P | Ovary | Age, nulliparous, menopausal status, duration of hormonal contraceptive use |
| Hassan[93] | 2008 | USA, Texas | CC | Liver | Age, sex, race, education, marital status, residence, HCV, HBV, diabetes, alcohol consumption, family history of cancer |
| Hooker[80] | 2008 | USA, Washington County | P | Rectum | Age, education, marital status |
| Kordi Tamandani[22] | 2008 | India, Chandigarh | CC | Cervix | None |
| Lee I[75] | 2008 | Europe, Latin America and USA | CC | Head/neck | Age, sex, race, study centre, education, alcohol consumption |
| Ramroth[70] | 2008 | Germany | CC | Larynx | Age, sex, alcohol consumption, education |
| Theis[94] | 2008 | USA, Florida/Georgia | CC | Kidney | Age, sex, race, BMI, alcohol consumption |
| Bao[81] | 2009 | USA, nationwide | P | Pancreas | Age, height, diabetes, BMI |
| Baris[95] | 2009 | USA, 3 states | CC | Bladder | Age, race, sex, Hispanic status, state of residence |
| Duan[83] | 2009 | USA, Los Angeles County | CC | Oesophagus, stomach | Age, sex, BMI, ethnicity |
| Lee II[71] | 2009 | 10 European countries | CC | Head/neck, oesophagus | Age, sex, education, study centre, alcohol consumption, duration of exposure |
| Verla-Tebit[72] | 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[51] | 2010 | Netherlands | P | Pancreas | Age, BMI, education |
| Peppone[52] | 2010 | USA, New York State/Buffalo | CC | Colorectal | Age, sex, BMI, place of residence, race, education, income, family history of colorectal cancer, vegetable intake, meat intake, alcohol consumption, aspirin use |
| Tao[53] | 2010 | China, Shanghai | CC | Bladder | Age, education, tea consumption, vegetable intake |
| Yang[54] | 2010 | Poland, Warsaw/Lodz | CC | Endometrium | Age, study site, education, menarche, parity, oral contraceptive use, HRT use, BMI, menopausal status |
| Chuang[11] | 2011 | 10 European countries | P | Total, smoking and non-smoking related and 13 sites[p] | Age, sex and others[q] |
| Louie[55] | 2011 | 5 countries | CC | Cervix | Age, study country, education of husband and wife, lifetime sexual partners of husband, history of sexually transmitted infections, age at first intercourse of wife, oral contraceptives, parity and pap smear history in previous year |
| Lu[56] | 2011 | USA, California | P | Lymphoma | Age, race, alcohol consumption 1 year before study entry |

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

[p] Upper aero-digestive tract, stomach and cardia, colorectal, pancreas, cervix uteri, endometrium, ovary, prostate, bladder, kidney, brain and nervous system, thyroid, lymphoma

q Age and sex only for .For other sites, analyses adjusted for age, sex, study centre, education, alcohol consumption, BMI, physical activity, vegetable intake, fruit intake, non-alcoholic energy intake, adulthood passive smoking. For stomach/cardia, and colorectal analyses also adjusted for red meat intake and processed meat intake. For pancreas analysis also adjusted for self-reported diabetic status. For cervix and endometrium analyses also adjusted for age at menarche, ever use of oral contraceptives, parity and menopausal status

# 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[40,47,48] provided no evidence of an increase in risk with ETS exposure, one of these[48] 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[57] a relationship was noted with childhood but not adulthood ETS exposure. The other[58] 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[58] 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[40] | 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[47] | 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[48] | 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[57] | 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[58] | 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[96-99] 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 Nasosinus cancer

See Table 4.1.2 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[4,15] 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[44], 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[13,100] have claimed that ETS exposure is a cause of nasosinus cancer, the evidence does not in fact appear conclusive.

## Table 4.1.2: 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[15] | 1990 | Japan | Cohabitant (unspecified) | F | 35 | 1.96 (0.84-4.57) | d2 | etu |
| | | | | M | 9 | No association | No | rt |
| Zheng[44] | 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

### 4.1.3. Cancers of the head and neck

Seven further studies have reported results for overall incidence of cancer of the head and neck, and details of these are given in Table 4.1.3. Two of the studies[11,71] were based on the same participants, and although there may be some overlap in the category of "ever exposed at home" used by one study[71] and "ever exposed during childhood" in the other[11], it was felt that this would be minimal and so both studies were included. Five of the studies[6,11,20,70,75] reported no significant association of ETS exposure with risk, but one[18], 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[71] 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 eight estimates of risk, gave an overall risk of 1.20 (95% CI 1.01-1.43) using a fixed effect model, and 1.35 (95% CI 0.98-1.84) using a random effects model. Although the heterogeneity is not significant (p=0.099), the higher random effects estimate is due to the unusually high contribution of one estimate (7.34 for females in the study Tan[18]). Removing the estimates for this study removes the heterogeneity, the fixed effect and random effects estimates both becoming 1.15 (95% CI 0.96-1.37).

Based partly on the evidence from two of these studies[18,20], the Supreme Court of New South Wales, Australia decided that ETS exposure can materially contribute to the development of larynx cancer[101]. 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[20] found no statistically significant association of ETS with head and neck cancer, and since the one that did[18] had obvious weaknesses, the Supreme Court's decision seems unjustified based on the available data.

## Table 4.1.3: 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[18] | 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[20] | 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 [75] | 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[70] | 2008 | Germany | Partner or co-worker (ever) | M+F | 9L | 2.00 (0.39-10.70) | - | ac(3)m |
| Lee II[71] | 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 |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 52 | 1.16(0.63-2.11) | - | ac(1)em |
| Meta-analyses based on 8 estimates (including Tan) | | | | Fixed effect | | 1.20 (1.01-1.43) | | h1 |
| | | | | Random effects | | 1.35 (0.98-1.84) | | |
| Meta-analyses based on 6 estimates (excluding Tan) | | | | Fixed effect | | 1.15 (0.96-1.37) | | h2 |
| | | | | Random effects | | 1.15 (0.96-1.37) | | |

Results are not included for five studies[102-106] 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 12.03 on 7 degrees of freedom (p=0.099)

h2 heterogeneity chisquared is 1.39 on 5 degrees of freedom (p = 0.93).

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[39] 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[39] | 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[60] 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[83] 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[60] | 2003 | China | Unspecified | M+F | 84 | 1.72 (1.0-3.1) | d1 | c(?) |
| Duan[83] | 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[71] | 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 |

Results are not included for two studies[107,108] as the analyses were not restricted to lifelong non-smokers.

### 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 seven studies that considered the endpoint of stomach cancer are given in Table 4.2.3. None of the nine relative risks for overall cancer incidence showed a statistically significant association between stomach cancer and ETS exposure. exposure. One study[11] reported a negative trend for cancers of the stomach and cardia combined, but this was of borderline significance (p=0.05), the relative risks for each exposure group not following a clear pattern of decreasing risk, and being based on data from only two of the 10 countries studied. One study[84] 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[83], 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 seven relative risks, gave an overall estimate of 1.06 (95% CI 0.95-1.19) 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[49] | 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[84] | 2002 | Canada | Cohabitant or Co-worker (ever) | M | 132 | 1.08 (0.64-1.82) | d1 | ac(7)emn |
| You[60] | 2003 | China | Unspecified | M+F | 85 | 1.33 (0.8-2.3) | d2 | c(?)m |
| Duan[83] | 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 |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 109 | 0.87 (0.57-1.31) | d4 | ac(12)m |
| Meta-analyses based on 7 estimates | | | | Fixed effect | | 1.06 (0.95-1.19) | | h |
| | | | | Random effects | | 1.06 (0.95-1.19) | | |

### 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).

d4 Relative risks for stomach/cardia cancer were 1.00, 1.19, 0.34 for never/seldom exposed, few times during week, daily exposure (trend p=0.05). Data from French and Italian centres only

### 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 2.56 on 6 degrees of freedom (p=0.86).

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[35] 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[80] 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.

Eight of the 15 relative risks presented for colorectal cancer showed a negative association with ETS exposure, but in only one study[72] 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. Six other non-significantly increased relative risks were also reported. One study [52], using categories of no exposure, <2 hours/day, 2-7 hours/day or >7 hours/day exposure, reported relative risks of 1.00, 0.84, 1.15 and 1.58 among male participants only. Although it was stated that this relationship was statistically significant, no p value for the trend was given. Meta-analysis of the results for colorectal cancer, based on 7 risk estimates, gave an overall risk of 1.03 (95% CI 0.91-1.16) using a fixed effect model, and 1.06 (95% CI 0.88-1.29) using a random effects model.

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[35] | 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[79] | 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[79] | 2007 | USA | Cohabitant or co-worker (ever) | F | ≈32 | 0.63 (0.21-1.84) | - | ac(15) |
| Hooker[80] | 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[66] | 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)em |
| Paskett[79] | 2007 | USA | Cohabitant or co-worker (ever) | F | 284 | 0.93 (0.61-1.42) | - | ac(15)m |
| Verla-Tebit[72] | 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)em |
| | | | | M | 104 | 0.59 (0.31-1.12) | - | ac(10)em |
| | | | Total (ever) | F | 148 | 1.01 (0.56-1.80) | No | ac(10) |
| | | | | M | 104 | 0.59 (0.31-1.15) | No | ac(9) |
| Peppone[52] | 2010 | USA | Home/work/other locations (current) | F | 284 | 0.97(0.61-1.53) | No | ac(10)mn |
| | | | | M | 205 | 1.58(0.93-2.69) | d1 | ac(10)mn |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 747 | 0.97(0.83-1.14) | No | ac(12)m |
| Meta-analyses based on 7 estimates | | | | Fixed effect | | 1.03 (0.91-1.16) | | h |
| | | | | Random effects | | 1.06 (0.88-1.29) | | |

Results are not included for three studies[109-111] as the analyses were not restricted to lifelong non-smokers.

Dose response

d1 Relative risks were 1.00, 0.84, 1.15, 1.58 for no exposure, <2 hours/day, 2-7 hours/day, >7 hours/day exposure. P value not given but stated to be statistically significant.

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 9.78 on 6 degrees of freedom (p=0.13).

m Relative risk included in meta-analysis

n Subjects exposed to ETS for >7 hours/day

### 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[93], reached statistical significance. In addition, one study[60] 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[93] 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[49] | 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[60] | 2003 | China | Unspecified | M+F | 79 | 1.13 (0.6-1.9) | d1 | c(?) |
| Hassan[93] | 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[74] reported a significant 6-fold rise in risk of pancreatic cancer, while another study, based in 10 European countries[112], 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. One study[11] reported relative risks of 1.00, 1.00 and 2.09 for subjects who were exposed never/seldom, a few times during the week, or daily, to ETS during childhood, and this relationship reached statistical significance (p=0.03).

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[74] 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[16] | 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[86] | 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[77]: 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[91] | 2007 | USA | Childhood, cohabitant or workplace (ever) | M+F | 294 | 1.02 (0.72-1.46) | - | ac(7)m |
| Lo[74] | 2007 | Egypt | Cohabitant, exposed daily for 1+ years (ever) | M+F | 41 | 6.0 (2.4-14.8) | - | ac(2)m |
| Bao[81] | 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[51] | 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 |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 121 | 1.32 (0.85-2.04) | d1 | ac(11) |
| | | | Home/work (ever) | M+F | 105 | 1.54 (1.00-2.39) | - | ac(5)fmp |
| | | | Childhood and home/work (ever) | M+F | 48 | 3.83 (1.34-10.9) | - | ac(5)fp |
| 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 two studies[113,114] as the analyses were not restricted to lifelong non-smokers.

Dose response

d1 Relative risks were 1.00, 1.00, 2.09 for exposed never/seldom, few times during week, daily (p for trend = 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.

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

p data came from reference[112]

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

u unadjusted.

## 4.3. Cervical cancer

See Table 4.3 for details of the 16 studies reporting results relating ETS exposure to risk of cervix cancer (or, in three studies, of endpoints that also include pre-invasive cervical lesions[41,50,59] and, in one study, of pre-invasive lesions only[63]). Three studies[7,22,45] reported a significantly increased risk associated with spousal smoking, while another study[21] reporting a significantly raised risk gave no definition of exposure. Also, one study[50] reported an increase of marginal significance (lower 95% CI given as 1.0) in women living with a smoker. One study[76] 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[59] 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[38,63] 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 seven studies[6,10,11,34,41,49,55] reported no significant increase associated with ETS exposure, one of the studies[41] showing a significantly negative association with exposure to parental smoking.

While a random-effects meta-analysis based on 16 independent estimates shows a significant elevation in risk (RR 1.53, 95% CI 1.25-1.87), there is evidence of heterogeneity ($p = 0.002$), mainly due to the high RR in the first study in India[21]. Excluding this estimate removed much of the heterogeneity, reducing the estimate to 1.41 (95% CI 1.19-1.66). 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[115], and only five studies[38,41,50,55,63] 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[100] 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[116]. 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 4.3: 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[34] | 1988 | USA | Spouse (in marriage) | 10 | 2.57 (0.70-9.44) | - | ac(1)my |
| Slattery[38] | 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[41] | 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[45] | 1996 | Japan | Spouse (current) | 415 | 1.30 (1.07-1.59) | d3 | ac(1)m |
| Jee[49] | 1999 | Korea | Spouse (ever) | 203 | 0.90 (0.65-1.24) | No | ac(5)em |
| Scholes[50] | 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[59] | 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[76] | 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[21] | 2006 | India | Not specified | 102 | 5.13 (2.54-10.4) | - | uem |
| Tsai[63] | 2007 | Taiwan | Any source, 1+ cigarette-years (ever) | 50 | 1.8 (0.9-4.1) | d6 | ac(7)m |
| Kordi Tamandani[22] | 2008 | India | Spouse (ever) | 198 | 1.97 (1.30-3.00) | - | emu |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | 87 | 1.05 (0.66-1.67) | No | ac(14)m |
| Louie[55] | 2011 | 5 countries | Spouse (ever) | 358 | 1.28 (0.88-1.85) | No | ac(10) |
| | | | Spouse (current) | 151 | 1.01 (0.56-1.83) | - | ac(10)m |
| | | | Spouse (ex) | 319 | 1.34 (0.91-1.96) | - | ac(10) |
| Meta-analyses based on 16 estimates (including Sobti) | | | Fixed effect | | 1.40 (1.25-1.57) | | h1 |
| | | | Random effects | | 1.53 (1.25-1.87) | | |
| Meta-analyses based on 15 estimates (excluding Sobti) | | | Fixed effect | | 1.35 (1.20-1.52) | | h2 |
| | | | Random effects | | 1.41 (1.19-1.66) | | |

## Table 4.3 – ETS and Cancer of the Cervix in women (continued)

Results are not included for seven studies[117-123] 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 35.38 on 15 degrees of freedom (p=0.002).

h2 heterogeneity chisquared is 22.00 on 14 degrees of freedom (p=0.08).

m relative risk included in meta-analysis.

u unadjusted.

y adjusted for age and education. Butler[34] 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.

## 4.4. Endometrial cancer

Five studies considered the incidence of cancer of the endometrium in relation to ETS exposure, and details of these are given in Table 4.4. One study[11] found a significantly decreased risk of endometrial cancer in subjects exposed to ETS during childhood, but there was no evidence of a dose-response relationship. None of the remaining studies reported a significant association between risk of the disease and any measure of ETS exposure studied. Meta-analysis of the six available results produced an overall estimate of risk of 0.88 (95% CI 0.78-1.01), using both fixed and random effects models.

Thus, there is no clear association between the risk of endometrial cancer and ETS exposure.

**Table 4.4: 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[45] | 1996 | Japan | Spouse (current) | 125 | 1.09 (0.76-1.57) | No | ac(1)m |
| Nishino[10] | 2001 | Japan | Spouse (current) | 13 | 1.30 (0.40-3.90) | - | am |
| Al-Zoughool[68] | 2007 | 6 European countries | Cohabitant or co-worker (baseline) | x | 1.31 (0.74-2.34) | - | axmp |
| | | | | x | 0.85 (0.65-1.11) | - | axmq |
| Yang[54] | 2010 | Poland | Home (ever) | 358 | 0.86 (0.63-1.17) | - | ac(8)em |
| | | | 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) |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | 396 | 0.80 (0.65-0.99) | No | ac(14)m |
| Meta-analyses based on 6 estimates | | | | Fixed effect | 0.88 (0.78-1.01) | | h |
| | | | | Random effects | 0.88 (0.78-1.01) | | |

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.

h heterogeneity chisquared is 4.49 on 5 degrees of freedom (p=0.48).

m relative risk estimate included in meta-analyses.

p pre-menopausal at baseline.

q post-menopausal at baseline.

x unspecified.

## 4.5. Cancer of the ovary

Details of the six studies that investigated the possible association between ETS exposure and the risk of ovarian cancer are given in Table 4.5. One study[90] 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 five studies failed to find any association between ovarian cancer incidence and exposure to ETS. Meta-analysis of the available results produced an overall risk estimate risk of 0.90 (95% CI 0.77-1.06) using a fixed effect model. Using a random effects model made little difference to this estimate (0.91, 95% CI 0.76-1.09).

There is no convincing evidence of an increase in the risk of ovarian cancer in relation to exposure to ETS.

**Table 4.5: 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) | - | am |
| Goodman[85] | 2003 | USA | Cohabitant (childhood) | 351 | 0.98 (0.72-1.35) | - | ac(6)m |
| Baker[90] | 2006 | USA | Total (current) | 246 | 0.68 (0.47-0.99) | d1 | ac(6)m |
| Gram[69] | 2008 | Norway, Sweden | Cohabitant (baseline) | 109 | 1.1 (0.7-1.6) | - | ac(3)mr |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | 250 | 0.88 (0.68-1.14) | - | ac(1)em |
| Meta-analyses based on 5 estimates | | | | Fixed effect | 0.90 (0.77-1.06) | | h |
| | | | | Random effects | 0.91 (0.76-1.09) | | |

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).

e estimated from data reported.

h heterogeneity chisquared is 4.68 on 4 degrees of freedom (p=0.32).

m relative risk estimate included in meta-analyses.

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).

## 4.6. Cancer of the kidney

See Table 4.6 for details of the four studies that considered this endpoint in relation to ETS exposure. Of the nine relative risks presented, eight were above 1.00, with one of these, from a study in the USA[94], reaching statistical significance, and another two, from a study in Canada[87], just failing to do so. Three of the studies reported significant dose-related trends with ETS exposure. In the first of these[43], 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[87] showed a non-significant trend for females but a significant positive trend with years of exposure for males. The third study[94] 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 4.6: 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[43] | 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[87] | 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[94] | 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 |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 109 | 1.41 (0.93-2.14) | - | ac(1)e |

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

## 4.7. Bladder cancer

Table 4.7 gives details of the 12 studies that reported findings on the association of ETS with bladder cancer. Of these, one study[61] reported a significant increase in men but not in women, and another study[78] 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[92] 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[67] 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. One study[53] reported positive dose-response relationships for every exposure category examined in women, but only for total ETS exposure in men. For both sexes, however, the reported p values for this exposure index failed to reach statistical significance, even though the relative risks given showed a clear increase as the exposure level rose. Finally, seven studies[6,11,14,37,64,65,95] reported no significant association between bladder cancer risk and ETS exposure.

A random-effects meta-analysis based on 18 independent estimates gave a risk estimate of 1.03 (95% CI 0.87-1.22), with no evidence of heterogeneity. Overall, then, no increase in risk has been demonstrated.

## Table 4.7: ETS and Bladder Cancer

| Study | Year | Country | Source (timing) of ETS exposure | Sex | Number of cases | Relative risk (95% CI) | Dose Response | Notes |
|---|---|---|---|---|---|---|---|---|
| Kabat[14] | 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[37] | 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[64] | 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[61] | 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[65] | 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[67] | 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[78] | 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 4.7: 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[92] | 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[95] | 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 |
| Tao[53] | 2010 | China | Childhood (ever) | M | 60 | 1.13 (0.55-2.30) | No | ac(3)ez |
| | | | | F | 58 | 1.83 (0.79-4.24) | d4 | ac(3)ez |
| | | | Spouse (ever) | M | 24 | 0.47 (0.08-2.59) | No | ac(3)mz |
| | | | | F | 61 | 1.84 (0.80-4.25) | d5 | ac(3)mz |
| | | | Other cohabitant (ever) | M | 50 | 1.38 (0.63-3.00) | d6 | ac(3)z |
| | | | | F | 40 | 1.83 (0.72-4.67) | d7 | ac(3)z |
| | | | Co-worker (ever) | M | 70 | 1.05 (0.51-2.14) | No | ac(3)z |
| | | | | F | 36 | 1.65 (0.50-5.39) | d8 | ac(3)z |
| | | | Total (ever) | M | 98 | 1.21 (0.63-2.32) | d9 | ac(3)z |
| | | | | F | 97 | 1.83 (0.82-4.05) | d10 | ac(3)z |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 90 | 1.01 (0.66-1.55) | - | ac(1)e |
| Meta-analyses based on 18 estimates | | | | Fixed effect | | 1.03 (0.88-1.21) | | h |
| | | | | Random effects | | 1.03 (0.87-1.22) | | |

Results are not included for one study[106] 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)

d4 Relative risks 1.00, 1.54, 6.87 for no exposure from any source, smoking by 1 parent, smoking by both parents. Relative risks of 1.00, 1.95, 2.54 for no exposure from any source, father smoked 1-<10, 10+ cpd. Relative risks of 1.00, 2.52, 15.97 for no exposure from any source, mother smoked 1-<10, 10+ cpd.

d5 Relative risks 1.00, 1.44, 2.27 for no exposure from any source, spouse smokes 1-<10, 10+ cpd.

d6 Relative risks 1.00, 1.30, 1.64 for no exposure from any source, other household members smoke 1-<10, 10+ cpd.

d7 Relative risks 1.00, 1.57, 3.62 for no exposure from any source, other household members smoke 1-<10, 10+ cpd.

d8 Relative risks 1.00, 1.46, 2.10 for no exposure from any source, 1-<5, 5+ hours exposure per day.

d9 Relative risks 1.00, 1.15, 2.08 for no exposure from any source, low, high exposure (trend p=0.31)

d10 Relative risks 1.00, 1.75, 3.89 for no exposure from any source, low, high exposure (trend p=0.051)

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 17.48 on 17 degrees of freedom (p=0.42).

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.

z compared to subjects who were unexposed to ETS from any source.

## 4.8. Brain cancer

Details of the eight studies that have reported results relating ETS exposure to brain cancer are given in Table 4.8. Although eight increased relative risks were reported, in only one study[89] 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. Three other studies[5,11,19] 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, one[19] only reported its results in an abstract with little detail, while in the third study[11], although the p value reported reached statistical significance, the actual relative risks given did not show a clear trend of increasing risk in the most highly exposed group. Few potential confounding variables have been adjusted for in any of the studies.

Meta-analysis based on 10 independent estimates gave a relative risk estimate of 1.19 (95% CI 0.99-1.44) using the fixed effect model, and 1.25 (95% CI 0.97-1.60) using the random effects model. Thus, there is no clear evidence for an increase in brain cancer incidence in association with exposure to ETS.

## Table 4.8: 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[42] | 1992 | Australia | Spouse/partner (ever) | F | (98) | 1.61 (0.82-3.17) | - | aemps |
| | | | | M | (72) | 2.21 (0.58-8.36) | - | aemps |
| Hurley[46] | 1996 | Australia | Cohabitant (adulthood) | M+F | 172G | 0.97 (0.61-1.53) | - | ac(2)m |
| Blowers[17] | 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[19] | 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[89] | 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) |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 193 | 1.05 (0.76-1.44) | d4 | ac(10)m |
| Meta-analyses based on 10 estimates | | | | Fixed effect | | 1.19 (0.99-1.44) | | h |
| | | | | Random effects | | 1.25 (0.97-1.60) | | |

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).

d4 Relative risks 1.00, 1.98, 1.71 for exposure never/seldom, few times during week, daily (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.

h Heterogeneity chisquared is 13.24 on 9 degrees of freedom (p=0.15).

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.

## 4.9. Lymphoma

Details of the three studies that reported on lymphoma risk in relation to ETS exposure are given in Table 4.9. Of the five relative risks given, one was below 1.00 and four were raised, although none reached statistical significance. In addition, one study[56] reported three significant dose-response relationships between lymphoma risk and various measures of total ETS exposure. In reality, however, only the relationship with years of exposure showed a truly monotonic relationship, with the pattern of relative risks for ETS intensity, and intensity-years being more erratic.

Therefore, there is little convincing evidence that exposure to ETS increases the risk of lymphoma.

**Table 4.9: ETS and Lymphoma**

| 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 | 85 | Not available | No | c(1) |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 246 | 0.97 (0.74-1.28) | - | ac(1)e |
| Lu[56] | 2011 | USA | Childhood only (ever) | F | 178 | 1.07 (0.80-1.44) | - | ac(2)fn |
| | | | Adulthood only (ever) | F | 163 | 1.18 (0.86-1.61) | - | ac(2)fn |
| | | | Childhood and adulthood (ever) | F | 202 | 1.23 (0.93-1.63) | - | ac(2)fn |
| | | | Total (ever) | F | 371 | 1.15 (0.90-1.46) | d1,d2,d3 | ac(2)fn |

Dose response

d1 Relative risks 1.0, 1.20, 1.24, 1.51 for ≤5, 5.1-20, 20.1-40, >40 years ETS exposure (trend p=0.03)

d2 Relative risks 1.0, 1.39, 1.09, 1.75 for overall intensity of ETS exposure ≤1.0, 1.1-2.0, 2.1-3.0, >3.0 (trend p=0.01)

d3 Relative risks 1.0, 1.18, 1.15, 1.49 for intensity-years ≤5, 5.1-25, 25.1-50, >50 (trend p=0.03)

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.

f compared to subjects with no ETS exposure from any source

n results are for non-Hodgkin lymphoma

## 4.10. Cancer of other sites

Table 4.10 summarizes the limited results that are available for eight 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[88] 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 |
| **Prostate cancer:** | | | | | | | | |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 311 | 0.79 (0.62-0.99) | - | ac(1)e |
| **Thyroid cancer:** | | | | | | | | |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 176 | 0.88 (0.64-1.19) | - | ac(1)e |
| **Leukaemia:** | | | | | | | | |
| Hirayama[6] | 1987 | Japan | Spouse (ever) | F | 51 | Not available | No | c(1) |
| Kasim[88] | 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[106,124-127] 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 13 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 three of the analyses[11,73,82] adjusted for more than a very small number of potential confounding variables.

Two studies[33,39] 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[62] 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". One study in New Zealand[73] 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. Finally, one study[11] showed a clear increase in the risk of non-smoking related cancer with increasing exposure to ETS, although this was not reported as statistically significant, but no relationship was apparent with total or smoking-related cancer incidence. The remaining six studies[10,31,32,34,36,82] showed no significant association. One of these[82] 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 random effects estimates of 1.10 (1.01-1.20) when the extreme relative risk estimate[39] was excluded, and 1.13 (1.02-1.25) when it was included. A meta-analysis of smoking-related cancer (including lung cancer) gave a random effects estimate of 1.23 (0.97-1.55). The largest study presenting results [11], based on just under 8000 cases, indicated no association between total cancer risk and ETS exposure (RR 0.97, 95% CI 0.92-1.02) after adjustment for 11 potential confounders. Results from other well designed, large prospective studies 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[32] | 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[33] | 1987 | USA | Spouse (ever) | F | 73 | 1.68 (1.04-2.71) | d3 | ac(1)em |
| Butler[34] | 1988 | USA | Spouse (in marriage) | F | 321 | 1.20 (0.94-1.54) | - | am |
| Sandler II[36] | 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[39] | 1990 | USA | Cohabitant (ever) or long-term exposure outside home | F | 82 | 6.40 (2.34-17.5) | - | aexm |
| Iribarren[82] | 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[62] | 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 | |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 7808 | 0.97 (0.92-1.02) | No | ac(10)m |
| Meta-analysis based on 15 estimates (including Miller II) | | | | Fixed effect | | 1.03 (0.99-1.07) | | h1 |
| | | | | Random effects | | 1.13 (1.02-1.25) | | |
| Meta-analysis based on 14 estimates (excluding Miller II) | | | | Fixed effect | | 1.03 (0.99-1.07) | | h2 |
| | | | | Random effects | | 1.10 (1.01-1.20) | | |
| **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[33] | 1987 | USA | Spouse (ever) | F | <73 | 7.01 (0.73-67.5) | d5 | ac(1)em |
| Butler[34] | 1988 | USA | Spouse (in marriage) | F | 41 | 1.22 (0.61-2.44) | - | am |
| Sandler II[36] | 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 |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 619 | 1.00 (0.84-1.20) | No | ac(10)m |
| Meta-analysis based on 8 estimates | | | | Fixed effect | | 1.11 (0.96-1.29) | | h3 |
| | | | | Random effects | | 1.23 (0.97-1.55) | | |

(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[34] | 1988 | USA | Spouse (in marriage) | F | 33 | 1.06 (0.47-2.36) | - | a |
| **Cancer other than the lung:** | | | | | | | | |
| Gillis[31] | 1984 | Scotland | Cohabitant (current) | F | 43 | 1.26 (0.62-2.56) | - | a |
| | | | | M | 8 | 0.50 (0.10-2.48) | - | a |
| Hill[73] 1981-84 cohort | 2007 | New Zealand | 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[36] | 1989 | USA | Cohabitant (ever) | F | 425 | 0.93 (0.76-1.54) | - | ac(3) |
| | | | | M | 83 | 1.03 (0.40-2.62) | - | ac(3) |
| Chuang[11] | 2011 | 10 European countries | Childhood (ever) | M+F | 7189 | 0.97 (0.92-1.01) | d6 | ac(10) |

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.

d6 Relative risks 1.0, 1.01, 1.08 for ETS exposure never/seldom, few times during week, daily (trend p=0.08)

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 44.74 on 14 degrees of freedom (p=0.0000)

h2 heterogeneity chisquared is 32.04 on 13 degrees of freedom (p=0.002)

h3 heterogeneity chisquared is 9.38 on 7 degrees of freedom (p=0.23)

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 77 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, 43 in the years 2000-9 and 7 since 2010. Fifty-four of the studies were of a case-control design, while 21[4-6,10,11,31,33-36,49,51,56,64,65,68,69,73,76-81] were prospective cohort studies, and two studies[50,82] were cross-sectional in design.

Some 27 individual cancer sites, or groups of sites, were investigated, along with total cancer incidence, and the incidence of smoking-related cancers. Sixty-five of the studies investigated a single endpoint, while 12 others[4-11,34-36,45,49,60,71,79,83] considered two or more endpoints. Three of these studies[4-11] included 10 or more cancer sites. Thus, the number of studies considering each individual cancer site was limited, and did not exceed 16 for any one site, while several sites were considered by a single study.

Ten of the studies[7-9,14-22] 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 38 of the studies that reported on specific cancer sites[4,11,19,21,22,35,40,45,46,48-52,54-58,66,67,69,71,72,75,79,81,83-88,90-92,94,95] including more than 100 cases. The largest study[11] was based on 7808 cases, but this was for total cancer incidence, with the highest number of cases for a specific site being 854, for stomach cancer, from another study[4].

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.[52,54,56,72,83,95]), or a substantial difference in response rates between cases and controls (e.g.[7-9,94]). Finally, some studies[18,21,39,61,74,80,112] 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 (and only five[38,41,50,55,63] adjust for 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 three of the four 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. For only two endpoints, cervical cancer and total cancer, were these significantly raised, and there were sufficient concerns about the studies included as to render the results inconclusive.

The International Agency for Research on Cancer (IARC) have recently published a review of human carcinogens, including ETS, as part of their Monograph series[128]. In general, their conclusions are similar to those stated here, with the evidence for most cancer sites being described as "conflicting and sparse". They do however report a positive association with cancers of the larynx and pharynx, but state this to be "less than causal". Several problems were noted with their review. For one study of the maxillary sinus[15], the relative risk for women quoted by IARC is in fact the chi-square statistic, and the real relative risk, although raised, was not statistically significant. In addition, for the endpoints of cervical, rectal and testicular cancer, studies were included that are not restricted to never smoking subjects[110,121,123,127].

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 | 6[a] | 1.15 (0.96-1.37) | 1.15 (0.96-1.37) | 1.39 | 0.93 |
| | 8[b] | 1.20 (1.01-1.43) | 1.35 (0.98-1.84) | 12.03 | 0.099 |
| Stomach | 7 | 1.06 (0.95-1.19) | 1.06 (0.95-1.19) | 2.56 | 0.86 |
| Colorectum | 7 | 1.03 (0.91-1.16) | 1.06 (0.88-1.29) | 9.78 | 0.13 |
| Pancreas | 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 |
| Cervix | 15[e] | 1.35 (1.20-1.52) | 1.41 (1.19-1.66) | 22.00 | 0.079 |
| | 16[f] | 1.40 (1.25-1.57) | 1.53 (1.25-1.87) | 35.38 | 0.002 |
| Endometrium | 6 | 0.88 (0.78-1.01) | 0.88 (0.78-1.01) | 4.49 | 0.48 |
| Ovary | 5 | 0.90 (0.77-1.06) | 0.91 (0.76-1.09) | 4.68 | 0.32 |
| Bladder | 18 | 1.03 (0.88-1.21) | 1.03 (0.87-1.22) | 17.49 | 0.42 |
| Brain | 10 | 1.19 (0.99-1.44) | 1.25 (0.97-1.60) | 13.24 | 0.15 |
| Total (including lung) | 14[g] | 1.03 (0.99-1.07) | 1.10 (1.01-1.20) | 32.04 | 0.0024 |
| | 15[h] | 1.03 (0.99-1.07) | 1.13 (1.02-1.25) | 44.74 | 0.0000 |
| Smoking-related (including lung) | 8 | 1.11 (0.96-1.29) | 1.23 (0.97-1.55) | 9.38 | 0.23 |

[a] Excluding study by Tan[18]

[b] Including study by Tan[18]

[c] Excluding study by Lo[74]

[d] Including study by Lo[74]

[e] Excluding study by Sobti[21]

[f] Including study by Sobti[21]

[g] Excluding study by Miller[39]

[h] Including study by Miller[39]

## Appendix A: Studies excluded from the report

Table A gives details of the 49 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 27 studies[96-99,102-111,113,114,117-127]. Thirteen further papers were either subsets of studies included in the review, or were superseded by later papers[129-141]. In addition, nine studies were excluded because there was either no suitable endpoint[142], or because they were of a design that did not allow relative risks to be calculated[143-150].

## Table A: Studies excluded from the report

| Study [ref] | Year[a] | Location | Design[b] | Cancer site(s) | Reasons for exclusion |
|---|---|---|---|---|---|
| Buckley[117] | 1981 | England, Oxford | CC | Cervix | Results not restricted to never smokers |
| Hirayama[129] | 1981 | Japan, 6 prefectures | P | Cervix, stomach | Superseded by other papers |
| Brown[118] | 1982 | Canada, Nova Scotia | CC | Cervix | Results not restricted to never smokers |
| Hellberg[119] | 1983 | Sweden, Gothenburg | CC | Cervix | Results not restricted to never smokers |
| Hirayama[130] | 1984 | Japan, 6 prefectures | P | Major (not lung) | Superseded by other papers |
| Yu[96] | 1986 | Hong Kong | CC | Nasopharynx | Results not restricted to never smokers |
| Zunzunegui[120] | 1986 | USA, California | CC | Cervix | Results not restricted to never smokers |
| Chen[97] | 1988 | Taiwan | CC | Nasopharynx | Results not restricted to never smokers |
| Hirayama[131] | 1988 | Japan, 6 prefectures | P | Brain, nasal sinus | Superseded by other papers |
| Yu[98] | 1988 | China, Guangxi | CC | Nasopharynx | Results not restricted to never smokers |
| Hirayama[132] | 1990 | Japan, 6 prefectures | P | Total and 17 sites[c] | Superseded by other papers |
| Hirayama[133] | 1990 | Japan, 6 prefectures | P | Not lung, respiratory | Superseded by other papers |
| Gerhardsson de Verdier[109] | 1992 | Sweden, Stockholm | CC | Colon, rectum | Results not restricted to never smokers |
| Guo[102] | 1995 | China, Liaoning | CC | Larynx | Results not restricted to never smokers |
| Paoff[124] | 1995 | USA, California | CC | Thyroid | Results not restricted to never smokers; ETS exposure relates to maternal exposure in-utero |
| Ogren[113] | 1996 | Sweden, Malmö | P | Pancreas | Results not restricted to never smokers |
| Clemmesen[143] | 1997 | 6 countries | D | Testis | Ecologic study |
| Schantz[103] | 1997 | USA, New York | CC | Head/neck | Results not restricted to never smokers |
| Hirose[134] | 1998 | Japan, Nagoya | CC | Cervix | Based on subset of subjects included in reference[45] |
| Coker[121] | 2002 | USA, N Carolina | CC | Cervix | Results not restricted to never smokers |
| Escribano Uzcudun[104] | 2002 | Spain | CC | Pharynx | Results not restricted to never smokers |
| Enstrom[142] | 2003 | USA, California | P | - | No suitable endpoint |
| Kaijser[125] | 2003 | Sweden | P | Testis | Results not restricted to never smokers |
| Slattery[110] | 2003 | USA, California/Utah | CC | Rectum | Results not restricted to never smokers |
| Glaser[126] | 2004 | USA, California | CC | Hodgkin's lymphoma | Results not restricted to never smokers |
| Pettersson[144] | 2004 | 4 Scandinavian countries | D | Testis | Ecologic study |
| Settheetham-Ishida[122] | 2004 | Thailand, Khon Kaen | CC | Cervix | Results not restricted to never smokers |
| Tay[123] | 2004 | Singapore | CC | Cervix | Results not restricted to never smokers |
| Airoldi[106] | 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[135] | 2005 | USA, Washington County | P | Rectum | Abstract only, superseded by full paper (reference[80]) |
| Vineis[105] | 2005 | 10 European countries | P | Head/neck | Results either not restricted to never smokers or included large proportion of lung cancer cases |
| You[141] | 2005 | China, Taixing City | CC | Oesophagus | Based on same subjects as reference[60] but published later |
| McGlynn[127] | 2006 | USA | CC | Testis | Results not restricted to never smokers |
| Tsai[137] | 2006 | Taiwan | CC | Cervix | Abstract only, superseded by full paper (reference[63]) |
| Wang[107] | 2006 | China, Huaian | CC | Oesophagus | Results not restricted to never smokers |
| Dahlstrom[145] | 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 |
|---|---|---|---|---|---|
| Peppone[146] | 2008 | USA, New York State | D | Colorectum | Case series only |
| Sobti[138] | 2008 | India, Chandigarh | CC | Cervix | Based on same subjects as reference[22] but published later |
| Sobti[139] | 2008 | India, Chandigarh | CC | Cervix | Based on subset of subjects included in reference[22] |
| Sobti[140] | 2008 | India, Chandigarh | CC | Cervix | Based on subset of subjects included in reference[22] |
| Curtin[111] | 2009 | USA, California/Utah | CC | Rectum | Results not restricted to never smokers |
| Karimi Zarchi [147] | 2010 | Iran, Yazd | D | Cervix | Case series only |
| Khoshbaten[148] | 2010 | Iran | D | Oesophagus | Case series only |
| Nesic[99] | 2010 | Serbia, Belgrade | CC | Nasopharynx | Results not restricted to never smokers |
| Sun[108] | 2010 | China, 5 areas | CC | Oesophagus | Results not restricted to never smokers |
| Leufkens[136] | 2011 | 10 European Centres | P | Colorectum | Superseded by more detailed paper[11] |
| Mallis[149] | 2011 | Greece, Patras | D | Larynx | Case series only |
| Tranah[114] | 2011 | USA, San Francisco | CC | Pancreas | Results not restricted to never smokers |
| Wilhelm-Benartzi[150] | 2011 | USA, New Hampshire | D | Bladder | Case series only |

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.

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