

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

Executive summary

This review is based on evidence from 85 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 15 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. Seventy-three 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 18 for any one site (cervix), 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 is 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 are significantly raised, there are 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 lung¹ and breast cancer². 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.

Eighty-five 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 reasons³. One study⁴⁻⁶ had incomplete follow-up and used statistical methods of doubtful validity, another⁷⁻⁹ 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 saliva¹², 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 review¹³.

- 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 disease²³. 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 these²⁶, 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. In addition, one study²⁷ reported results in which the association with bladder cancer was stronger in subjects passively exposed to tobacco smoke than in active smokers. Although it is possible to propose mechanisms by which ETS, but not active smoking, could increase risk of cancer of a specific site^{28,29}, 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 August 2012. 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 March 2014. 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-analysis³⁰, or by combining non-independent relative risks, e.g. for different exposure levels with the same reference group³¹.

Where there are five or more studies providing independent estimates of risk, fixed effect and random effects meta-analysis³⁰ 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 85 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. Fifty-four 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 85 studies included in this review, 10^{4-9,14,32-39} were reported in the 1980s, 17^{15-19,40-51} in the 1990s, 43 in the years 2000-9, and 15^{11,27,52-64} were conducted since 2010. Forty-three of the studies were carried out in North America, while 21 studies^{4-6,10,15,16,21,22,41,46,49,50,54,58,59,61,65-71} were conducted in Asia, 13^{11,32,52,55,72-80} in Europe and 3^{43,47,81} in Australasia. Two studies took place in Egypt^{27,82}, one study was located in South America⁶⁰, one study was conducted in Europe, Latin America and the USA⁸³ and one study was carried out in South America, Asia and Europe⁵⁶.

Fifty-nine of the studies were of a case-control design, while 24^{4-6,10,11,32,34-37,50,52,57,58,61,64,72,73,76,77,81,84-89} were prospective cohort studies. The remaining two studies^{51,90} were cross-sectional in design. Seventy-three studies presented results for a single endpoint, while 12 others^{4-11,35-37,46,50,68,79,87,91} considered two or more endpoints, with four of these studies⁴⁻¹¹ 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^{68,76} carried out adjustment but did not specify the factors that had been used to do this. Of the 72 remaining studies, only two^{4-6,65} did not adjust for age, and all but three studies^{65,73,85} 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 ³²	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 ³³	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 ³⁴	1987	USA, California	P	Total, smoking-related	Age, income
Butler ³⁵	1988 ^g	USA, California	P	Total, smoking-related, cervix	Age
Sandler II ^{36,37}	1988	USA, Maryland	P	Total, smoking-related, not smoking-related, colon	Age, housing quality, schooling, marital status
Burch ³⁸	1989	Canada, Alberta and Ontario	CC	Bladder	Age, area of residence
Slattery ³⁹	1989	USA, Utah	CC	Cervix	Age, education, church attendance, number of sexual partners
Fukuda ¹⁵	1990	Japan, Hokkaido	CC	Nasal cavity	None
Miller II ⁴⁰	1990	USA, Pennsylvania	CC	Total	Age
Yu ⁴¹	1990	China, Guangzhou	CC	Nasopharynx	Age, sex
Coker ⁴²	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 ⁴³	1992	Australia, Adelaide	CC	Brain	Age
Kreiger ⁴⁴	1993	Canada, Ontario	CC	Kidney	Age, body mass index
Zheng ⁴⁵	1993	USA, National	CC	Nasal cavity	Age, alcohol use
Hirose ⁴⁶	1996	Japan, Nagoya	CC	Cervix, endometrium	Age, year of first visit
Hurley ⁴⁷	1996	Australia, Melbourne	CC	Brain	Age, sex, reference date
Vaughan ⁴⁸	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 ⁴⁹	1999	Taiwan	CC	Nasopharynx	Age, sex, race, educational level, family history of nasopharynx cancer
Jee ⁵⁰	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 ⁵¹	1999	USA, Washington State	CS	Cervix ^h	Age, number of sexual partners, age at first intercourse
Armstrong ⁶⁵	2000	Malaysia	CC	Nasopharynx	Diet
Yuan ⁶⁶	2000	China, Shanghai	CC	Nasopharynx	Age and 7 others ⁱ
Zhang ²⁰	2000	USA ^j	CC	Head/neck	None
Iribarren ⁹⁰	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 ⁹²	2002	Canada	CC	Stomach	Age and 7 others ⁿ
Zeeger ⁷²	2002	Netherlands	P	Bladder	Age and sex
Goodman ⁹³	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 ⁶⁷	2003	Taiwan	CC	Cervix ^h	Age, education level, number of pregnancies, age at first intercourse, cooking in the kitchen during ages 20-40
You ⁶⁸	2003	China	CC	Oesophagus, stomach, liver	Unspecified but states that "ETS and confounders information was collected ..."
Villeneuve ⁹⁴	2004	Canada	CC	Pancreas	Age, sex, body mass index, income adequacy, province of residence
Chen ⁶⁹	2005	Taiwan	CC	Bladder	Age, BMI, cumulative arsenic, hair dye usage, education
Hu ⁹⁵	2005	Canada	CC	Renal cell	Age, province, education, body mass index, alcohol use, total consumption of meat and of vegetables and fruit
Kasim ⁹⁶	2005	Canada	CC	Leukaemia	Age, sex, BMI, benzene, ionising radiation
McGhee ⁷⁰	2005	Hong Kong	CC	All cancers	Age and education (and sex for sexes-combined analysis)
Phillips ⁹⁷	2005	USA, western Washington State	CC	Intracranial meningioma	Age, sex, education
Trimble ⁸⁴	2005	USA, Washington County	P	Cervix	Age, education, marital status, religious attendance (1963 only)
Baker ⁹⁸	2006	USA, New York state	CC	Ovary	Age, residence, income, usual BMI, history of vaginal infection, year of participation, duration of breastfeeding
Bjerregaard ⁷³	2006	3 European countries	P	Bladder	Age, fruit and vegetables, ETS exposure at the other timepoint
Gallicchio ⁸⁵	2006	USA, Washington County	P	Pancreas	Age, education, marital status
Lilla ⁷⁴	2006	Germany	CC	Colorectum	Age, sex, NSAID use, endoscopy, family history, alcohol, red meat, education, BMI
Samanic ⁷⁵	2006	Spain	CC	Bladder	Age, region, fruit/vegetable consumption, high-risk occupation
Sobti ²¹	2006	India	CC	Cervix	None
Alberg ⁸⁶	2007	USA, Washington County	P	Bladder	Age, education, marital status
Al-Zoughool ⁷⁶	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 ⁹⁹	2007	USA, Texas	CC	Pancreas	Age, sex, race/ethnicity, diabetes, alcohol, education, state of residence, marital status
Hill ⁸¹	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 ¹⁰⁰	2007	USA, Los Angeles County	CC	Bladder	Age, race/ethnicity, education, ETS exposure in other settings
Lo ⁸²	2007	Egypt	CC	Pancreas	Age, sex, residence
Paskett ⁸⁷	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 ⁷¹	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 ⁷⁷	2008	Norway and Sweden	P	Ovary	Age, nulliparous, menopausal status, duration of hormonal contraceptive use
Hassan ¹⁰¹	2008	USA, Texas	CC	Liver	Age, sex, race, education, marital status, residence, HCV, HBV, diabetes, alcohol consumption, family history of cancer
Hooker ⁸⁸	2008	USA, Washington County	P	Rectum	Age, education, marital status
Kordi Tamandani ²²	2008	India, Chandigarh	CC	Cervix	None
Lee I ⁸³	2008	Europe, Latin America and USA	CC	Head/neck	Age, sex, race, study centre, education, alcohol consumption
Ramroth ⁷⁸	2008	Germany	CC	Larynx	Age, sex, alcohol consumption, education
Theis ¹⁰²	2008	USA, Florida/Georgia	CC	Kidney	Age, sex, race, BMI, alcohol consumption
Bao ⁸⁹	2009	USA, nationwide	P	Pancreas	Age, height, diabetes, BMI
Baris ¹⁰³	2009	USA, 3 states	CC	Bladder	Age, race, sex, Hispanic status, state of residence
Duan ⁹¹	2009	USA, Los Angeles County	CC	Oesophagus, stomach	Age, sex, BMI, ethnicity
Lee II ⁷⁹	2009	10 European countries	CC	Head/neck, oesophagus	Age, sex, education, study centre, alcohol consumption, duration of exposure
Verla-Tebit ⁸⁰	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 ⁵²	2010	Netherlands	P	Pancreas	Age, BMI, education
Peppone ⁵³	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 ⁵⁴	2010	China, Shanghai	CC	Bladder	Age, education, tea consumption, vegetable intake
Yang ⁵⁵	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 ⁵⁶	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 ⁵⁷	2011	USA, California	P	Lymphoma	Age, race, alcohol consumption 1 year before study entry
Shekari ⁵⁹	2012	India, Chandigarh	CC	Cervix	Age, oral contraceptives
He ⁵⁸	2012	China, Xi'an	P	Total	Age, sex, marital status, occupation, education, alcohol use, diastolic blood pressure, triglyceride and total cholesterol levels, BMI
Zheng ²⁷	2012	Egypt, 3 areas	CC	Bladder	Age, area of residence, urban/rural residence, education, history of schistosomiasis, history of urinary tract infection, menopausal status in women
Ferreccio ⁶⁰	2013	Chile, 2 regions	CC	Bladder	Age, sex, socioeconomic status, arsenic exposure
Lin ⁶¹	2013	Japan, 45 areas	P	Pancreas	Age, BMI, history of diabetes

(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
Stingone ⁶²	2013	USA, North Carolina	CC	Head/neck	Age, sex, race, education, consumption of fruit/vegetables and alcohol
Troy ⁶³	2013	USA, Pennsylvania	CC	Head/neck	Age, sex, race, recruitment period, drinking status, history of cancer, education
Diver ⁶⁴	2014	USA, nationwide	P	Lymphoma	Age, sex, race, education, family history of hematopoietic cancer, height, BMI, physical activity, alcohol use, use of NSAIDS, hormone replacement therapy use

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^{41,48,49} provided no evidence of an increase in risk with ETS exposure, one of these⁴⁹ even reporting a significant negative trend in relation to childhood exposure. In contrast, two recent studies have reported significant positive associations. In one of these⁶⁵ a relationship was noted with childhood but not adulthood ETS exposure. The other⁶⁶ 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 study⁶⁶ 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 ⁴¹	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 ⁴⁸	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 ⁴⁹	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 ⁶⁵	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 ⁶⁶	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 studies¹⁰⁴⁻¹⁰⁷ 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 USA⁴⁵, 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^{13,108} 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 ⁴⁵	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

Nine further studies have reported results for overall incidence of cancer of the head and neck, details of these being given in Table 4.1.3. Two studies^{11,79} were based on the same participants, and although some overlap may exist in the category “ever exposed at home” used by one study⁷⁹ and “ever exposed during childhood” in the other¹¹, this was felt to be minimal, so both studies were included. Six of the studies^{6,11,20,62,78,83} reported no significant association of ETS exposure with risk, although one⁸³ did find a significantly positive dose-response relationship in subjects exposed to ETS at home only. One study¹⁸, based on unadjusted analyses, and data collected very differently for cases and controls, reported significantly increased risks with ETS exposure at home and at work. One study⁶³ reported a significantly increased risk associated with exposure during childhood to siblings who smoked, but not to any other source of ETS exposure in childhood, and also reported a significantly positive dose-response relationship for those ever exposed in childhood as measured by the number of smokers in the household, but not with cigarettes per day or pack-years of exposure. The final study⁷⁹ found an increase in the risk of cancer of the oral cavity and oropharynx, but not of the larynx and hypopharynx, for subjects exposed at home and/or at work. Statistically significant dose-response relationships, based on categories of 0, 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, based on 10 estimates of risk, gave an overall risk of 1.15 (95% CI 0.99-1.33) using a fixed effect model, and 1.20 (95% CI 0.95-1.52) using a random effects model. Although the heterogeneity is not significant ($p=0.10$), the higher random effects estimate is due to the unusually high contribution of one estimate (7.34 for females in the study Tan¹⁸). Removing the estimates for this study removes the heterogeneity, the fixed effect and random effects estimates both becoming 1.11 (95% CI 0.95-1.29).

Based partly on the evidence from two of the studies^{18,20}, the Supreme Court of New South Wales, Australia decided that ETS exposure can materially contribute to larynx cancer development¹⁰⁹. Since neither study presented results specifically for larynx cancer, both studies would have involved at most about 10 larynx cancer cases in non-smokers, one of the studies²⁰ found no statistically significant association of ETS with head and neck cancer, and the one that did¹⁸ 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 ⁸³	2008	Europe, USA, Latin America	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 ⁷⁸	2008	Germany	Partner or co-worker (ever)	M+F	9L	2.00 (0.39-10.70)	-	ac(3)m
Lee II ⁷⁹	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
Stingone ⁶²	2013	USA	Home (ever)	M+F	125	0.82 (0.53-1.27)	No	ac(5)m
Troy ⁶³	2013	USA	Childhood (ever)	M+F	184	1.19 (0.80-1.76)	d4	ac(6)m
			Childhood (mother)	M+F	119	1.17 (0.72-1.90)	-	ac(6)
			Childhood (father)	M+F	119	1.06 (0.58-1.96)	-	ac(6)
			Childhood (siblings)	M+F	119	3.46 (1.28-9.39)	-	ac(6)
			Childhood (other household members)	M+F	119	0.77 (0.24-2.50)	-	ac(6)
Meta-analyses based on 10 estimates (including Tan)				Fixed effect		1.15 (0.99-1.33)		h1
				Random effects		1.20 (0.95-1.52)		
Meta-analyses based on 8 estimates (excluding Tan)				Fixed effect		1.11 (0.95-1.29)		h2
				Random effects		1.11 (0.95-1.29)		

Results are not included for six studies¹¹⁰⁻¹¹⁵ 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 $p = 0.025$)
- d4 Relative risks were 1.00, 1.06, 6.76 for exposure to 1, 2 3+ household smokers (trend $p = 0.04$). Cigarettes per day and pack-years showed no dose-response relationship

Key to notes

- a adjusted for age
- c adjusted for confounding variables other than age (number of confounders given in brackets – see also Table 3.1).
- e estimated from data reported.
- h1 heterogeneity chisquared is 14.59 on 9 degrees of freedom ($p = 0.10$)
- h2 heterogeneity chisquared is 3.47 on 7 degrees of freedom ($p = 0.84$).
- 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 other⁴⁰ 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 ⁴⁰	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 China⁶⁸ 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 study⁹¹ 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 ⁶⁸	2003	China	Unspecified	M+F	84	1.72 (1.0-3.1)	d1	c(?)
Duan ⁹¹	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 ⁷⁹	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^{116,117} 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. One study¹¹ 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 study⁹² 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 study⁹¹, 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 ⁵⁰	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 ⁹²	2002	Canada	Cohabitant or Co-worker (ever)	M	132	1.08 (0.64-1.82)	d1	ac(7)emn
You ⁶⁸	2003	China	Unspecified	M+F	85	1.33 (0.8-2.3)	d2	c(?)m
Duan ⁹¹	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 study³⁶ 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 one⁸⁸ 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 study⁸⁰ 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 study⁵³, 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 ³⁶	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 ⁸⁷	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 ⁸⁷	2007	USA	Cohabitant or co-worker (ever)	F	≈32	0.63 (0.21-1.84)	-	ac(15)
Hooker ⁸⁸ 1963 cohort	2008	USA	Cohabitant (baseline)	F	56	1.03 (0.58-1.81)	-	ac(2)
			Cohabitant (baseline)	M	12	5.81 (1.84-18.36)	-	ac(2)
			Cohabitant (baseline)	F	54	1.04 (0.54-1.98)	-	ac(2)
			Cohabitant (baseline)	M	13	1.10 (0.24-4.97)	-	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)
			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 ⁷⁴	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 ⁸⁷	2007	USA	Cohabitant or co-worker (ever)	F	284	0.93 (0.61-1.42)	-	ac(15)m
Verla-Tebit ⁸⁰	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 ⁵³	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 studies¹¹⁸⁻¹²⁰ 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 study¹⁰¹, reached statistical significance. In addition, one study⁶⁸ 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 study¹⁰¹ 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 ⁵⁰	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 ⁶⁸	2003	China	Unspecified	M+F	79	1.13 (0.6-1.9)	d1	c(?)
Hassan ¹⁰¹	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
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 11 studies that investigated the association between ETS exposure and the incidence of pancreatic cancer. A study in Egypt⁸² reported a significant 6-fold rise in risk of pancreatic cancer, while another study, based in 10 European countries¹²¹, 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. Thirteen 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. In addition, one study⁶¹ stated that no significant associations between ETS exposure and risk of pancreatic cancer death were observed in never smoking men, but provided no further details. One study¹¹ 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 1.15 (95% CI 0.99-1.34) using the fixed effect model, and 1.16 (95% CI 0.92-1.47) using the random effects model, with significant heterogeneity ($p = 0.04$). Removing the estimate for the study in Egypt⁸² removed the heterogeneity and reduced the overall estimate, with both fixed effect and random effects estimates 1.09 (0.94-1.28). 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 ⁹⁴	2004	Canada	Cohabitant or co-worker: (childhood only)	M+F	23	1.37 (0.46-4.07)	-	ac(4)
				M+F	33	1.01 (0.41-2.50)	-	ac(4)
				M+F	81	1.21 (0.60-2.44)	-	ac(4)
				M+F	105	1.18 (0.60-2.35)	No	ac(4)em
Gallicchio ⁸⁵ : 1963 cohort	2006	USA	Cohabitant (baseline)	M+F	22	1.1 (0.4-2.8)	-	ac(2)m
				M+F	34	0.9 (0.4-2.3)	-	ac(2)m
Hassan ⁹⁹	2007	USA	Childhood, cohabitant or workplace (ever)	M+F	294	1.02 (0.72-1.46)	-	ac(7)m
Lo ⁸²	2007	Egypt	Cohabitant, exposed daily for 1+ years (ever)	M+F	41	6.0 (2.4-14.8)	-	ac(2)m
Bao ⁸⁹	2009	USA	Mother (childhood)	F	95	1.52 (0.97-2.39)	-	ac(3)n
				F	133	0.76 (0.54-1.07)	-	ac(3)n
				F	151	0.94 (0.62-1.41)	-	ac(3)e
				F	151	1.05 (0.76-1.46)	No	ac(3)emo
Heinen ⁵²	2010	Netherlands	Childhood (ever)	F	117	0.90 (0.54-1.50)	-	ac(2)
				F	62	0.78 (0.44-1.39)	-	ac(2)m
				F	87	0.82 (0.51-1.32)	No	ac(2)e
				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)
				M+F	105	1.54 (1.00-2.39)	-	ac(5)fmfp
				M+F	48	3.83 (1.34-10.9)	-	ac(5)fp
Lin ⁶¹	2013	Japan	Home (current)	F	164	1.20 (0.87-1.67)	No	ac(2)m
				F	202	1.21 (0.87-1.68)	-	ac(2)
				F	147	1.13 (0.80-1.58)	No	ac(2)e
				M	53	No association	-	-
Meta-analyses based on 12 estimates (including Lo)				Fixed effect		1.15 (0.99-1.34)		h1
				Random effects		1.16 (0.92-1.47)		
Meta-analyses based on 11 estimates (excluding Lo)				Fixed effect		1.09 (0.94-1.28)		h2
				Random effects		1.09 (0.94-1.28)		

(continued)

Table 4.2.6: ETS and Pancreatic Cancer (continued)

Results are not included for two studies^{122,123} 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 20.38 on 11 degrees of freedom (p = 0.04).
- h2 heterogeneity chisquared is 7.31 on 10 degrees of freedom (p=0.70).
- 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 reference¹²¹
- 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 17 studies reporting results relating ETS exposure to risk of cervix cancer (or, in three studies, of endpoints that also include pre-invasive cervical lesions^{42,51,67} and, in one study, of pre-invasive lesions only⁷¹). Three studies^{7,22,46} reported a significantly increased risk associated with spousal smoking. Another two studies^{21,59} reporting a significantly raised risk gave no definition of exposure. Also, one study⁵¹ reported an increase of marginal significance (lower 95% CI given as 1.0) in women living with a smoker. One study⁸⁴ 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 study⁶⁷ 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^{39,71} 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^{6,10,11,35,42,50,56} reported no significant increase associated with ETS exposure, one of the studies⁴² showing a significantly negative association with exposure to parental smoking.

While a random-effects meta-analysis based on 17 independent estimates shows a significant elevation in risk (RR 1.41, 95% CI 1.26-1.56), there is evidence of heterogeneity ($p = 0.004$), mainly due to the high RR in the first study in India²¹. Excluding this estimate removed much of the heterogeneity, reducing the estimate to 1.40 (95% CI 1.21-1.62). Though this remains statistically significant, there are difficulties of interpretation. Firstly, only one estimate⁷¹ was adjusted for human papilloma virus (HPV) infection, the dominant cause of cervical cancer¹²⁴, and only five studies^{39,42,51,56,71} adjusted for aspects of sexual activity linked to HPV infection. Confounding by HPV infection is considered important in the association of active smoking with cervical cancer¹⁰⁸ 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 cancer¹²⁵. 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 ³⁵	1988	USA	Spouse (in marriage)	10	2.57 (0.70-9.44)	-	ac(1)my	
Slattery ³⁹	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 ⁴²	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 ⁴⁶	1996	Japan	Spouse (current)	415	1.30 (1.07-1.59)	d3	ac(1)m	
Jee ⁵⁰	1999	Korea	Spouse (ever)	203	0.90 (0.65-1.24)	No	ac(5)em	
Scholes ⁵¹	1999	USA	Cohabitant (current)	315	1.4 (1.0-2.0)	-	ac(2)m	
Nishino ¹⁰	2001	Japan	Spouse (current)	11	1.10 (0.26-4.50)	-	am	
Wu ⁶⁷	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 ⁸⁴	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 ⁷¹	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 ⁵⁶	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)	
Shekari ⁵⁹	2012	India	Any (ever)	193	1.43 (1.09-1.88)	-	ac(1)em	

(continued)

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

Meta-analyses based on 17 estimates (including Sobti)	Fixed effect	1.41 (1.26-1.56)	h1
	Random effects	1.51 (1.26-1.81)	
Meta-analyses based on 16 estimates (excluding Sobti)	Fixed effect	1.36 (1.23-1.52)	h2
	Random effects	1.40 (1.21-1.62)	

Results are not included for nine studies¹²⁶⁻¹³⁴ 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 35.40 on 16 degrees of freedom (p=0.004).
- h2 heterogeneity chisquared is 22.14 on 15 degrees of freedom (p=0.10).
- m relative risk included in meta-analysis.
- u unadjusted.
- y adjusted for age and education. Butler³⁵ 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 study¹¹ 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 ⁴⁶	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 ⁷⁶	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 ⁵⁵	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 study⁹⁸ 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 ⁹³	2003	USA	Cohabitant (childhood)	351	0.98 (0.72-1.35)	-	ac(6)m
Baker ⁹⁸	2006	USA	Total (current)	246	0.68 (0.47-0.99)	d1	ac(6)m
Gram ⁷⁷	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 USA¹⁰², reaching statistical significance, and another two, from a study in Canada⁹⁵, just failing to do so. Three of the studies reported significant dose-related trends with ETS exposure. In the first of these⁴⁴, 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 second⁹⁵ showed a non-significant trend for females but a significant positive trend with years of exposure for males. The third study¹⁰² 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 ⁴⁴	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 ⁹⁵	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 ¹⁰²	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 14 studies that reported findings on the association of ETS with bladder cancer. Of these, one study⁶⁹ reported a significant increase in men but not in women, and another study⁸⁶ 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 study¹⁰⁰ 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 study⁷⁵ 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 study⁵⁴ 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, nine studies^{6,11,14,27,38,60,72,73,103} reported no significant association between bladder cancer risk and ETS exposure.

A random-effects meta-analysis based on 21 independent estimates gave a risk estimate of 1.09 (95% CI 0.95-1.26), 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 ³⁸	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 ⁷²	2002	Netherlands	Spouse (ever)	M+F	48	0.89 (0.44-1.80)	-	ac(1)em	
				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	
				M+F	41	0.67 (0.36-1.25)	No	ac(1)et	
Chen ⁶⁹	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 ⁷³	2006	3 European countries	Home and/or work (baseline)	M+F	47	0.82 (0.46-1.48)	-	ac(2)m	
				M+F	47	2.02 (0.94-4.35)	-	ac(2)	
Samanic ⁷⁵	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 ⁸⁶	2007	USA	1963 cohort	Cohabitant (baseline)	F	22	1.8 (0.8-4.5)	-
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
					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 ¹⁰⁰	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 ¹⁰³	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 ⁵⁴	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)em
Zheng ²⁷	2012	Egypt	Home (ever)	M	212	1.41 (0.90-2.20)	-	ac(5)em
				F	337	1.11 (0.82-1.50)	-	ac(6)em
			Outside home (ever)	M	212	1.30 (0.89-1.90)	-	ac(5)e
				F	337	1.40 (0.89-1.22)	-	ac(6)e
			Total (ever)	M	212	1.49 (0.98-2.25)	-	ac(5)e
				F	337	1.08 (0.80-1.47)	-	ac(6)e
Ferreccio ⁶⁰	2013	Chile	Any (ever)	M+F	65	1.25 (0.64-2.42)	-	ac(3)em
Meta-analyses based on 21 estimates				Fixed effect		1.08 (0.95-1.24)		h
				Random effects		1.08 (0.95-1.24)		

Results are not included for one study¹¹⁴ 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 19.37 on 20 degrees of freedom ($p=0.50$).
- 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 study⁹⁷ 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 these⁵ did not adjust for the age of the subject, one¹⁹ only reported its results in an abstract with little detail, while in the third study¹¹, 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 ⁴³	1992	Australia	Spouse/partner (ever)	F	(98)	1.61 (0.82-3.17)	-	aemps
				M	(72)	2.21 (0.58-8.36)	-	aemps
Hurley ⁴⁷	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 (ever)	F	(210)	1.96 (0.99-3.9)	d2	nms
				M	(339)	0.97 (0.5-1.7)	No	nms
Phillips ⁹⁷	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 four studies that reported on lymphoma risk in relation to ETS exposure are given in Table 4.9. Of the 13 relative risks given, eight were below 1.00, one showed no association at all and four were raised, although none reached statistical significance. In addition, one study⁵⁷ 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. No other significant dose-response relationships were seen in this study.

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 ⁵⁷	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
Diver ⁶⁴	2014	USA	Childhood (any)	M+F	591	0.96 (0.79-1.16)	No	ac(10)
			Adulthood (past)	M+F	448	0.96 (0.79-1.17)	-	ac(10)
			Adulthood (current)	M+F	467	0.98 (0.80-1.19)	No	ac(10)
			Adulthood (ever)	M+F	763	0.97 (0.81-1.16)	-	ac(10)
			Home (current)	M+F	205	0.91 (0.66-1.25)	-	ac(10)
			Outside home (current)	M+F	441	0.99 (0.81-1.21)	-	ac(10)
			Any (ever)	M	377	0.90 (0.72-1.24)	-	ac(9)
				F	507	1.00 (0.80-1.27)	-	ac(9)

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 study⁷ was based on only 13 cases and was unstandardized either for age or sex.

In addition, for the endpoint of leukaemia, one study⁹⁶ 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 ⁹⁶	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^{114,135-138} 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 14 studies relating ETS exposure to total, smoking-related and/or non smoking-related cancer risk, see Table 4.11. Some 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 four of the analyses^{11,58,81,90} adjusted for more than a very small number of potential confounding variables.

Two studies^{34,40} reported relative risks, of 6.4 for total cancer and 7.0 for smoking-related cancer, that are 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 criticized for weaknesses of design and analysis³, reported a weaker, but significant association between ETS exposure and total cancer risk. A study in Hong Kong⁷⁰ reported a significant association and significant positive trend, but 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”. A New Zealand study⁸¹ reported a significant increase in cancers other than the lung for females in a 1996 cohort but not in a 1981 cohort, and not for males. A multi-country study¹¹ showed a clear increase in the risk of non-smoking related cancer with ETS exposure, although not reported as statistically significant, but no relationship was seen with total or smoking-related cancer incidence. A study in China⁵⁸ reported a significantly positive dose-response relationship between the risk of total cancer and ETS exposure, but did not find a significant increase in overall risk in either sex. The remaining six studies^{10,32,33,35,37,90} showed no significant association. One⁹⁰ used data from a large study, and adjusted for many confounders.

A meta-analysis of studies reporting ETS and total cancer gave random effects estimates of 1.11 (1.01-1.21) when the extreme relative risk estimate⁴⁰ was excluded, and 1.14 (1.03-1.26) when 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 results¹¹, based on almost 8000 cases, showed no association with total cancer risk (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 ³³	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
				M+F	173	1.2 (0.8-1.8)	-	ue
Reynolds ³⁴	1987	USA	Spouse (ever)	F	73	1.68 (1.04-2.71)	d3	ac(1)em
Butler ³⁵	1988	USA	Spouse (in marriage)	F	321	1.20 (0.94-1.54)	-	am
Sandler II ³⁷	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 ⁴⁰	1990	USA	Cohabitant (ever) or long-term exposure outside home	F	82	6.40 (2.34-17.5)	-	aexm
Iribarren ⁹⁰	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
				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 ⁷⁰	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
He ⁵⁸	2012	China	Home/work (ever)	M	44	1.77 (0.88-3.60)	d5	ac(8)m
				F	25	1.26 (0.49-3.19)	d5	ac(8)m
				M+F	30	2.16 (1.01-4.64)	-	ac(9)
				M+F	38	1.66 (0.86-3.22)	-	ac(9)
Meta-analysis based on 17 estimates (including Miller II)				Fixed effect		1.03 (0.99-1.07)		h1
				Random effects		1.14 (1.03-1.26)		
Meta-analysis based on 16 estimates (excluding Miller II)				Fixed effect		1.03 (0.99-1.07)		h2
				Random effects		1.11 (1.01-1.21)		
Smoking-related cancer (including lung cancer):								
Sandler I ⁸	1985	USA	Mother (childhood)	M+F	47	0.8 (0.3-2.4)	-	uem
				M+F	41	1.7 (0.9-3.3)	-	uem
Reynolds ³⁴	1987	USA	Spouse (ever)	F	<73	7.01 (0.73-67.5)	d6	ac(1)em
Butler ³⁵	1988	USA	Spouse (in marriage)	F	41	1.22 (0.61-2.44)	-	am
Sandler II ³⁷	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

(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		
Meta-analysis based on 8 estimates				Fixed effect		1.11 (0.96-1.29)		h3		
				Random effects		1.23 (0.97-1.55)				
Smoking-related cancer (excluding lung cancer):										
Butler ³⁵	1988	USA	Spouse (in marriage)	F	33	1.06 (0.47-2.36)	-	a		
Cancer other than the lung:										
Gillis ³²	1984	Scotland	Cohabitant (current)	F	43	1.26 (0.62-2.56)	-	a		
				M	8	0.50 (0.10-2.48)	-	a		
Hill ⁸¹ 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		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 ³⁷	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)	d7	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 Relative risks of 1.0, 1.51, 1.50, 3.70 for exposure score 0, 1-2, 3-4, 5-6 for both sexes combined, trend p=0.019. Combined exposure score based on exposure at home (cigarettes per day: 0 = no exposure, 1 = <4 pack-years, 2 = 4 to <8 pack-years, 3 = 8+ pack-years) and exposure at work ((cigarettes per day x years x smokers x hours/day)/100: 0 = no exposure, 1 = <5, 2 = 5 to <15, 3 = 15+).
- d6 A significant trend (p=0.0007) was noted with pack-years ETS exposure but relative risks by level were not given.
- d7 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 47.18 on 16 degrees of freedom (p=0.0001)
- h2 heterogeneity chisquared is 34.51 on 15 degrees of freedom (p=0.003)
- 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 85 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 15 since 2010. Sixty of the studies were of a case-control design, while 24^{4-6,10,11,32,34-37,50,52,57,58,61,64,72,73,76,77,81,84-89} were prospective cohort studies, and two studies^{51,90} 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. Seventy-three of the studies investigated a single endpoint, while 12 others^{4-11,35-37,46,50,68,79,87,91} considered two or more endpoints. Three of these studies⁴⁻¹¹ included 10 or more cancer sites. Thus, the number of studies considering each individual cancer site was limited, and did not exceed 18 for any one site (cervix), 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 44 of the studies that reported on specific cancer sites^{4,11,19,21,22,27,36,41,46,47,49-53,55-57,59,61-66,74,75,77,79,80,83,87,89,91-96,98-100,102,103} including more than 100 cases. The largest study¹¹ 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 study⁴.

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.^{7-9,63}). Elsewhere, there were either low participation rates (e.g.^{53,55,57,80,91,103}), or a substantial difference in response rates between cases and controls (e.g.^{7-9,62,102}). Finally, some studies^{18,21,40,69,82,88,121} 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 only one⁷¹ of the studies adjusts for HPV infection, and only five^{39,42,51,56,71} 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 series¹³⁹. 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 sinus¹⁵, 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^{119,131,133,138}.

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	8 ^a	1.11 (0.95-1.29)	1.11 (0.95-1.29)	3.47	0.84
	10 ^b	1.15 (0.99-1.33)	1.20 (0.95-1.52)	14.59	0.10
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	11 ^c	1.09 (0.94-1.28)	1.07 (0.94-1.28)	7.31	0.70
	12 ^d	1.15 (0.99-1.34)	1.16 (0.92-1.47)	20.38	0.04
Cervix	17 ^e	1.36 (1.23-1.52)	1.40 (1.21-1.62)	22.14	0.10
	18 ^f	1.41 (1.26-1.56)	1.51 (1.26-1.81)	35.40	0.004
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	21	1.08 (0.95-1.24)	1.08 (0.95-1.24)	19.37	0.50
Brain	10	1.19 (0.99-1.44)	1.25 (0.97-1.60)	13.24	0.15
Total (including lung)	16 ^g	1.03 (0.99-1.07)	1.11 (1.01-1.21)	34.51	0.0029
	17 ^h	1.03 (0.99-1.07)	1.14 (1.03-1.26)	47.18	0.0001
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 Tan¹⁸

^b Including study by Tan¹⁸

^c Excluding study by Lo⁸²

^d Including study by Lo⁸²

^e Excluding study by Sobti²¹

^f Including study by Sobti²¹

^g Excluding study by Miller⁴⁰

^h Including study by Miller⁴⁰

Appendix A: Studies excluded from the report

Table A gives details of the 54 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 31 studies^{104-107,110-120,122,123,126-138,140}. Thirteen further papers were either subsets of studies included in the review, or were superseded by later papers¹⁴¹⁻¹⁵³. In addition, 10 studies were excluded because there was either no suitable endpoint¹⁵⁴, or because they were of a design that did not allow relative risks to be calculated¹⁵⁵⁻¹⁶³.

Table A: Studies excluded from the report

Study [ref]	Year ^a	Location	Design ^b	Cancer site(s)	Reasons for exclusion
Buckley ¹²⁶	1981	England, Oxford	CC	Cervix	Results not restricted to never smokers
Hirayama ¹⁴¹	1981	Japan, 6 prefectures	P	Cervix, stomach	Superseded by other papers
Brown ¹²⁷	1982	Canada, Nova Scotia	CC	Cervix	Results not restricted to never smokers
Hellberg ¹²⁸	1983	Sweden, Gothenburg	CC	Cervix	Results not restricted to never smokers
Hirayama ¹⁴²	1984	Japan, 6 prefectures	P	Major (not lung)	Superseded by other papers
Yu ¹⁰⁴	1986	Hong Kong	CC	Nasopharynx	Results not restricted to never smokers
Zunzunegui ¹²⁹	1986	USA, California	CC	Cervix	Results not restricted to never smokers
Chen ¹⁰⁵	1988	Taiwan	CC	Nasopharynx	Results not restricted to never smokers
Hirayama ¹⁴³	1988	Japan, 6 prefectures	P	Brain, nasal sinus	Superseded by other papers
Yu ¹⁰⁶	1988	China, Guangxi	CC	Nasopharynx	Results not restricted to never smokers
Hirayama ¹⁴⁴	1990	Japan, 6 prefectures	P	Total and 17 sites ^c	Superseded by other papers
Hirayama ¹⁴⁵	1990	Japan, 6 prefectures	P	Not lung, respiratory	Superseded by other papers
Tajima ¹³⁰	1990	Japan, Aichi	CC	Cervix	Results not restricted to never smokers
Gerhardsson de Verdier ¹¹⁸	1992	Sweden, Stockholm	CC	Colon, rectum	Results not restricted to never smokers
Guo ¹¹⁰	1995	China, Liaoning	CC	Larynx	Results not restricted to never smokers
Paoff ¹³⁵	1995	USA, California	CC	Thyroid	Results not restricted to never smokers; ETS exposure relates to maternal exposure in-utero
Ogren ¹²²	1996	Sweden, Malmö	P	Pancreas	Results not restricted to never smokers
Clemmesen ¹⁵⁵	1997	6 countries	D	Testis	Ecologic study
Schantz ¹¹¹	1997	USA, New York	CC	Head/neck	Results not restricted to never smokers
Hirose ¹⁴⁶	1998	Japan, Nagoya	CC	Cervix	Based on subset of subjects included in reference ⁴⁶
Coker ¹³¹	2002	USA, N Carolina	CC	Cervix	Results not restricted to never smokers
Escribano Uzcudun ¹¹²	2002	Spain	CC	Pharynx	Results not restricted to never smokers
Enstrom ¹⁵⁴	2003	USA, California	P	-	No suitable endpoint
Kaijser ¹³⁶	2003	Sweden	P	Testis	Results not restricted to never smokers
Slattery ¹¹⁹	2003	USA, California/Utah	CC	Rectum	Results not restricted to never smokers
Glaser ¹³⁷	2004	USA, California	CC	Hodgkin's lymphoma	Results not restricted to never smokers
Pettersson ¹⁵⁶	2004	4 Scandinavian countries	D	Testis	Ecologic study
Settheetham-Ishida ¹³²	2004	Thailand, Khon Kaen	CC	Cervix	Results not restricted to never smokers
Sull ¹³⁴	2004	South Korea	CC	Cervix	Results not restricted to never smokers
Tay ¹³³	2004	Singapore	CC	Cervix	Results not restricted to never smokers
Airoidi ¹¹⁴	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 ¹⁴⁷	2005	USA, Washington County	P	Rectum	Abstract only, superseded by full paper (reference ⁸⁸)
Vineis ¹¹³	2005	10 European countries	P	Head/neck	Results either not restricted to never smokers or included large proportion of lung cancer cases
You ¹⁵³	2005	China, Taixing City	CC	Oesophagus	Based on same subjects as reference ⁶⁸ but published later
McGlynn ¹³⁸	2006	USA	CC	Testis	Results not restricted to never smokers
Tsai ¹⁴⁹	2006	Taiwan	CC	Cervix	Abstract only, superseded by full paper (reference ⁷¹)
Wang ¹¹⁶	2006	China, Huaian	CC	Oesophagus	Results not restricted to never smokers
Dahlstrom ¹⁵⁷	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 ¹⁵⁸	2008	USA, New York State	D	Colorectum	Case series only
Sobti ¹⁵⁰	2008	India, Chandigarh	CC	Cervix	Based on same subjects as reference ²² but published later
Sobti ¹⁵¹	2008	India, Chandigarh	CC	Cervix	Based on subset of subjects included in reference ²²
Sobti ¹⁵²	2008	India, Chandigarh	CC	Cervix	Based on subset of subjects included in reference ²²
Curtin ¹²⁰	2009	USA, California/Utah	CC	Rectum	Results not restricted to never smokers
Karimi Zarchi ¹⁵⁹	2010	Iran, Yazd	D	Cervix	Case series only
Khoshbaten ¹⁶⁰	2010	Iran	D	Oesophagus	Case series only
Nesic ¹⁰⁷	2010	Serbia, Belgrade	CC	Nasopharynx	Results not restricted to never smokers
Sun ¹¹⁷	2010	China, 5 areas	CC	Oesophagus	Results not restricted to never smokers
Leufkens ¹⁴⁸	2011	10 European Centres	P	Colorectum	Superseded by more detailed paper ¹¹
Mallis ¹⁶¹	2011	Greece, Patras	D	Larynx	Case series only
Tranah ¹²³	2011	USA, San Francisco	CC	Pancreas	Results not restricted to never smokers
Wilhelm-Benartzi ¹⁶²	2011	USA, New Hampshire	D	Bladder	Case series only
Natphopsuk ¹⁴⁰	2012	Thailand, Khon Kaen	CC	Cervix	Results not restricted to never smokers
Hofmann ¹⁶³	2013	China, Shanghai	CC	Colorectum	ETS exposure not related to cancer risk and insufficient detail given to allow calculation
Kashigar ¹¹⁵	2013	Canada, Toronto	P	Head/neck	Results not restricted to never smokers; 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.

References

1. Lee PN, Forey BA, Hamling JS. *Epidemiological evidence on environmental tobacco smoke and lung cancer*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2013. www.pnlee.co.uk/Reports.htm [Download LEE2013B]
2. Lee PN, Thornton AJ, Hamling JS. *Epidemiological evidence on environmental tobacco smoke and cancers other than the lung or breast*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2012.
3. Lee PN. *Environmental tobacco smoke and mortality. A detailed review of epidemiological evidence relating environmental tobacco smoke to the risk of cancer, heart disease and other causes of death in adults who have never smoked*. Basel: Karger; 1992.
4. Hirayama T. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med* 1984;**13**:680-90.
5. Hirayama T. Passive smoking - a new target of epidemiology. *Tokai J Exp Clin Med* 1985;**10**:287-93.
6. Hirayama T. Passive smoking and cancer: an epidemiological review. *Gann Monogr Cancer Res* 1987;**33**:127-35.
7. Sandler DP, Everson RB, Wilcox AJ. Passive smoking in adulthood and cancer risk. *Am J Epidemiol* 1985;**121**:37-48.
8. Sandler DP, Everson RB, Wilcox AJ, Browder JP. Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health* 1985;**75**:487-92.
9. Sandler DP, Wilcox AJ, Everson RB. Cumulative effects of lifetime passive smoking on cancer risk. *Lancet* 1985;**1**:312-5.
10. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, *et al*. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control* 2001;**12**:797-802.
11. Chuang S, Gallo V, Michaud D, Overvad K, Tjønneland A, Clavel-Chapelon F, *et al*. Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European prospective investigation into cancer and nutrition. *Cancer Causes Control* 2011;**22**:487-94.
12. Lee PN. Uses and abuses of cotinine as a marker of tobacco smoke exposure. In: Gorrod JW, Jacob P, III, editors. *Analytical determination of nicotine and related compounds and their metabolites*. Amsterdam: Elsevier, 1999;669-719.

13. National Cancer Institute. Shopland DR, Zeise L, Dunn A, editors. *Health effects of exposure to environmental tobacco smoke. The report of the California Environmental Protection Agency*. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 1999. (Smoking and Tobacco Control. Monograph No. 10.) NIH Pub. No. 99-4645.
<http://cancercontrol.cancer.gov/tcrb/monographs/10/index.html>
14. Kabat GC, Dieck GS, Wynder EL. Bladder cancer in nonsmokers. *Cancer* 1986;**57**:362-7.
15. Fukuda K, Shibata A. Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. *Cancer Causes Control* 1990;**1**:165-8.
16. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, *et al.* A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol* 1992;**22**:286-91.
17. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* 1997;**8**:5-12.
18. Tan E-H, Adelstein DJ, Droughton MLT, van Kirk MA, Lavertu P. Squamous cell head and neck cancer in nonsmokers. *Am J Clin Oncol* 1997;**20**:146-50.
19. Johnson KC, Hu J, Fincham S, The Canadian Cancer Registries Epidemiology Research Group. Passive smoking and adult brain cancer in Canada, 1994-1997 [Abstract]. Presented at the 32nd Annual Meeting of the Society for Epidemiologic Research, Baltimore, Maryland, June 10-12, 1999. *Am J Epidemiol* 1999;**149**:S72.
20. Zhang Z-F, Morgenstern H, Spitz MR, Tashkin DP, Yu G-P, Hsu TC, *et al.* Environmental tobacco smoking, mutagen sensitivity, and head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:1043-9.
21. Sobti RC, Kaur S, Kaur P, Singh J, Gupta I, Jain V, *et al.* Interaction of passive smoking with *GST* (*GSTM1*, *GSTT1*, and *GSTP1*) genotypes in the risk of cervical cancer in India. *Cancer Genet Cytogenet* 2006;**166**:117-23.
22. Kordi Tamandani DM, Sobti RC, Shekari M. Association of Fas-670 gene polymorphism with risk of cervical cancer in North Indian population. *Clin Exp Obstet Gynecol* 2008;**35**:183-6.
23. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000;**53**:207-16.
24. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J Natl Cancer Inst* 1981;**66**:1061-6.
25. Cardenas VM, Thun MJ, Austin H, Lally CA, Clark WS, Greenberg RS, *et al.* Environmental tobacco smoke and lung cancer mortality in the American

- Cancer Society's Cancer Prevention Study II. *Cancer Causes Control* 1997;**8**:57-64.
26. Wartenberg D, Calle EE, Thun MJ, Heath CW, Jr., Lally C, Woodruff T. Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* 2000;**92**:1666-73.
 27. Zheng Y-L, Amr S, Saleh DA, Dash C, Ezzat S, Mikhail NN, *et al.* Urinary bladder cancer risk factors in Egypt: a multicenter case-control study. *Cancer Epidemiol Biomarkers Prev* 2012;**21**:537-46.
 28. Wells AJ. An estimate of adult mortality in the United States from passive smoking. *Environ Int* 1988;**14**:249-65.
 29. Remmer H. Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. *Arch Toxicol* 1987;**61**:89-104.
 30. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol* 1991;**44**:127-39.
 31. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;**27**:954-70.
 32. Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur J Respir Dis* 1984;**65**(Suppl 133):121-6.
 33. Miller GH. Cancer, passive smoking and nonemployed and employed wives. *West J Med* 1984;**140**:632-5.
 34. Reynolds P, Kaplan GA, Cohen RD. Passive smoking and cancer incidence: prospective evidence from the Alameda County study. In: *Annual meeting of the Society for Epidemiologic Research, Amherst, MA, 16-19 June 1987*. 1987;1-5.
 35. Butler TL. *The relationship of passive smoking to various health outcomes among Seventh day Adventists in California* [Thesis]. Los Angeles: University of California; 1988.
 36. Sandler RS, Sandler DP, Comstock GW, Helsing KJ, Shore DL. Cigarette smoking and the risk of colorectal cancer in women. *J Natl Cancer Inst* 1988;**80**:1329-33.
 37. Sandler DP, Comstock GW, Helsing KJ, Shore DL. Deaths from all causes in non-smokers who lived with smokers. *Am J Public Health* 1989;**79**:163-7.
 38. Burch JD, Rohan TE, Howe GR, Risch HA, Hill GB, Steele R, *et al.* Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer* 1989;**44**:622-8.

39. Slattery ML, Robison LM, Schuman KL, French TK, Abbott TM, Overall JC, Jr., *et al.* Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *JAMA* 1989;**261**:1593-8.
40. Miller GH. The impact of passive smoking: cancer deaths among nonsmoking women. *Cancer Detect Prev* 1990;**14**:497-503.
41. Yu MC, Garabrant DH, Huang TB, Henderson BE. Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer* 1990;**45**:1033-9.
42. Coker AL, Rosenberg AJ, McCann MF, Hulka BS. Active and passive cigarette smoke exposure and cervical intraepithelial neoplasia. *Cancer Epidemiol Biomarkers Prev* 1992;**1**:349-56.
43. Ryan P, Lee MW, North JB, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer* 1992;**51**:20-7.
44. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control* 1993;**4**:101-10.
45. Zheng W, McLaughlin JK, Chow W-H, Chien HTC, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am J Epidemiol* 1993;**138**:965-72.
46. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, *et al.* Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res* 1996;**87**:1001-9.
47. Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *J Epidemiol Community Health* 1996;**50**:442-6.
48. Vaughan TL, Shapiro JA, Burt RD, Swanson GM, Berwick M, Lynch CF, *et al.* Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev* 1996;**5**:587-93.
49. Cheng Y-J, Hildesheim A, Hsu M-M, Chen I-H, Brinton LA, Levine PH. Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes Control* 1999;**10**:201-7.
50. Jee SH, Ohrr H, Kim IS. Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* 1999;**28**:824-8.
51. Scholes D, McBride C, Grothaus L, Curry S, Albright J, Ludman E. The association between cigarette smoking and low-grade cervical abnormalities in reproductive-age women. *Cancer Causes Control* 1999;**10**:339-44.

52. Heinen MM, Verhage BAJ, Goldbohm A, van den Brandt PA. Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1612-22.
53. Peppone LJ, Reid ME, Moysich KB, Morrow GR, Pascal J-P, Mohile SG, *et al.* The effect of secondhand smoke exposure on the association between active cigarette smoking and colorectal cancer. *Cancer Causes Control* 2010;**21**:1247-55.
54. Tao L, Xiang Y-B, Wang R, Nelson HH, Gao Y-T, Chan KK, *et al.* Environmental tobacco smoke in relation to bladder cancer risk - the Shanghai Bladder Cancer Study. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:3087-95. Erratum appears in *Cancer Epidemiol. Biomarkers Prev.* 2011;**20**(3):411.
55. Yang HP, Brinton LA, Platz EA, Lissowska J, Lacey JV, Jr., Sherman ME, *et al.* Active and passive cigarette smoking and the risk of endometrial cancer in Poland. *Eur J Cancer* 2010;**46**:690-6.
56. Louie KS, Castellsague X, de Sanjose S, Herrero R, Meijer CJ, Shah K, *et al.* Smoking and passive smoking in cervical cancer risk: pooled analysis of couples from the IARC multicentric case-control studies. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:1379-90.
57. Lu Y, Wang SS, Reynolds P, Chang ET, Ma H, Sullivan-Halley J, *et al.* Cigarette smoking, passive smoking, and non-Hodgkin lymphoma risk: evidence from the California teachers study. *Am J Epidemiol* 2011;**174**:563-73.
58. He Y, Jiang B, Li LS, Li LS, Ko L, Wu L, *et al.* Secondhand smoke exposure predicted COPD and other tobacco related mortality in a 17-years cohort study in China. *Chest* 2012;**142**:909-18.
59. Shekari M, Kordi-Tamandani DM, Malekzadeh K, Sobti RC, Karimi S, Suri V. Effect of anti-inflammatory (IL-4, IL-10) cytokine genes in relation to risk of cervical carcinoma. *Am J Clin Oncol* 2012;**35**:514-9.
60. Ferreccio C, Yuan Y, Calle J, Benitez H, Parra RL, Acevedo J, *et al.* Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. *Epidemiology* 2013;**24**:898-905.
61. Lin Y, Yagyu K, Ueda J, Kurosawa M, Tamakoshi A, Kikuchi S. Active and passive smoking and risk of death from pancreatic cancer: findings from the Japan Collaborative Cohort Study. *Pancreatology* 2013;**13**:279-84.
62. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF. Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. *Cancer Causes Control* 2013;**24**:649-64.
63. Troy JD, Grandis JR, Youk AO, Diergaarde B, Romkes M, Weissfeld JL. Childhood passive smoke exposure is associated with adult head and neck cancer. *Cancer Epidemiol* 2013;**37**:417-23.

64. Diver WR, Teras LR, Gaudet MM, Gapstur SM. Exposure to environmental tobacco smoke and risk of non-hodgkin lymphoma in nonsmoking men and women. *Am J Epidemiol* 2014;**179**:987-95.
65. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *Int J Epidemiol* 2000;**29**:991-8.
66. Yuan J-M, Wang X-L, Xiang Y-B, Gao Y-T, Ross RK, Yu MC. Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer* 2000;**85**:364-9.
67. Wu M-T, Lee L-H, Ho C-K, Liu C-L, Wu T-N, Wu S-C, *et al.* Lifetime exposure to environmental tobacco smoke and cervical intraepithelial neoplasms among nonsmoking Taiwanese women. *Arch Environ Health* 2003;**58**:353-9.
68. You NC, Mu LN, Yu SZ, Jiang QW, Cao W, Zhou XF, *et al.* Environmental tobacco smoking and smoking-related susceptibility genes for the risk of esophageal, stomach, and liver cancers [Abstract]. *Ann Epidemiol* 2003;**13**:564.
69. Chen Y-C, Su H-JJ, Guo Y-LL, Houseman EA, Christiani DC. Interaction between environmental tobacco smoke and arsenic methylation ability on the risk of bladder cancer. *Cancer Causes Control* 2005;**16**:75-81.
70. McGhee SM, Ho SY, Schooling M, Ho LM, Thomas GN, Hedley AJ, *et al.* Mortality associated with passive smoking in Hong Kong. *BMJ* 2005;**330**:287-8.
71. Tsai H-T, Tsai Y-M, Yang S-F, Wu K-Y, Chuang H-Y, Wu T-N, *et al.* Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm -a community-based case-control study. *Gynecol Oncol* 2007;**105**:181-8.
72. Zeegers MPA, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control* 2002;**13**:83-90.
73. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, Frederiksen K, Christensen J, Tjønneland A, *et al.* Tobacco smoke and bladder cancer - in the European prospective investigation into cancer and nutrition. *Int J Cancer* 2006;**119**:2412-6.
74. Lilla C, Verla-Tebit E, Risch A, Jäger B, Hoffmeister M, Brenner H, *et al.* Effect of *NAT1* and *NAT2* genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:99-107.
<http://cebp.aacrjournals.org/cgi/reprint/15/1/99>
75. Samanic C, Kogevinas M, Dosemeci M, Malats N, Real FX, Garcia-Closas M, *et al.* Smoking and bladder cancer in Spain: effects of tobacco type, timing,

- environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1348-54.
76. Al-Zoughool M, Dossus L, Kaaks R, Clavel-Chapelon F, Tjønneland A, Olsen A, *et al.* Risk of endometrial cancer in relationship to cigarette smoking: results from the EPIC study. *Int J Cancer* 2007;**121**:2741-7.
 77. Gram IT, Braaten T, Adami H-O, Lund E, Weiderpass E. Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer. *Int J Cancer* 2008;**122**:647-52.
 78. Ramroth H, Dietz A, Becher H. Environmental tobacco smoke and laryngeal cancer: results from a population-based case-control study. *Eur Arch Otorhinolaryngol* 2008;**265**:1367-71.
 79. Lee Y-CA, Marron M, Benhamou S, Bouchardy C, Ahrens W, Pohlabein H, *et al.* Active and involuntary tobacco smoking and upper aerodigestive tract cancer risks in a multicenter case-control study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:3353-61.
 80. Verla-Tebit E, Lilla C, Hoffmeister M, Brenner H, Chang-Claude J. Exposure to environmental tobacco smoke and the risk of colorectal cancer in a case-control study from Germany. *Eur J Cancer Prev* 2009;**18**:9-12.
 81. Hill SE, Blakely T, Kawachi I, Woodward A. Mortality among lifelong nonsmokers exposed to secondhand smoke at home: cohort data and sensitivity analyses. *Am J Epidemiol* 2007;**165**:530-40.
 82. Lo A-C, Soliman AS, El-Ghawalby N, Abdel-Wahab M, Fathy O, Khaled HM, *et al.* Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. *Pancreas* 2007;**35**:120-9.
 83. Lee Y-CA, Boffetta P, Sturgis EM, Wei Q, Zhang Z-F, Muscat J, *et al.* Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:1974-81.
 84. Trimble CL, Genkinger JM, Burke AE, Hoffman SC, Helzlsouer KJ, Diener-West M, *et al.* Active and passive cigarette smoking and the risk of cervical neoplasia. *Obstet Gynecol* 2005;**105**:174-81.
 85. Gallicchio L, Kouzis A, Genkinger JM, Burke AE, Hoffman SC, Diener-West M, *et al.* Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med* 2006;**42**:200-5.
 86. Alberg AJ, Kouzis A, Genkinger JM, Gallicchio L, Burke AE, Hoffman SC, *et al.* A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol* 2007;**165**:660-6.

87. Paskett ED, Reeves KW, Rohan TE, Allison MA, Williams CD, Messina CR, *et al.* Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. *J Natl Cancer Inst* 2007;**99**:1729-35.
88. Hooker CM, Gallicchio L, Genkinger JM, Comstock GW, Alberg AJ. A prospective cohort study of rectal cancer risk in relation to active cigarette smoking and passive smoke exposure. *Ann Epidemiol* 2008;**18**:28-35.
89. Bao Y, Giovannucci E, Fuchs CS, Michaud DS. Passive smoking and pancreatic cancer in women: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:2292-6.
90. Iribarren C, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. *J Epidemiol Community Health* 2001;**55**:721-8.
91. Duan L, Wu AH, Sullivan-Halley J, Bernstein L. Passive smoking and risk of oesophageal and gastric adenocarcinomas. *Br J Cancer* 2009;**100**:1483-5.
92. Mao Y, Hu J, Semenciw R, White K. Active and passive smoking and the risk of stomach cancer, by subsite, in Canada. *Eur J Cancer Prev* 2002;**11**:27-38.
93. Goodman MT, Tung K-H. Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control* 2003;**14**:569-77.
94. Villeneuve PJ, Johnson KC, Mao Y, Hanley AJ. Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. *Can J Public Health* 2004;**95**:32-7.
95. Hu J, Ugnat A-M, The Canadian Cancer Registries Epidemiology Research Group. Active and passive smoking and risk of renal cell carcinoma in Canada. *Eur J Cancer* 2005;**41**:770-8.
96. Kasim K, Levallois P, Abdous B, Auger P, Johnson KC. Environmental tobacco smoke and risk of adult leukemia. *Epidemiology* 2005;**16**:672-80.
97. Phillips LE, Longstreth WT, Jr., Koepsell T, Custer BS, Kukull WA, van Belle G. Active and passive cigarette smoking and risk of intracranial meningioma. *Neuroepidemiology* 2005;**24**:117-22.
98. Baker JA, Odunuga OO, Rodabaugh KJ, Reid ME, Menezes RJ, Moysich KB. Active and passive smoking and risk of ovarian cancer. *Int J Gynecol Cancer* 2006;**16**(Suppl 1):211-8.
99. Hassan MM, Abbruzzese JL, Bondy ML, Wolff RA, Vauthey J-N, Pisters PW, *et al.* Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. *Cancer* 2007;**109**:2547-56.

100. Jiang X, Yuan J-M, Skipper PL, Tannenbaum SR, Yu MC. Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res* 2007;**67**:7540-5.
101. Hassan MM, Spitz MR, Thomas MB, El-Deeb AS, Glover KY, Nguyen NT, *et al.* Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer* 2008;**123**:1883-91.
102. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR. Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. *BMC Cancer* 2008;**8**:387.
103. Baris D, Karagas MR, Verrill C, Johnson A, Andrew AS, Marsit CJ, *et al.* A case-control study of smoking and bladder cancer risk: emergent patterns over time. *J Natl Cancer Inst* 2009;**101**:1553-61.
104. Yu MC, Ho JHC, Lai S-H, Henderson BE. Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. *Cancer Res* 1986;**46**:956-61.
105. Chen C-J, Wang Y-F, Shieh T, Chen J-Y, Liu M-Y. Multifactorial etiology of nasopharyngeal carcinoma. Epstein-Barr virus, familial tendency and environmental cofactors. In: *Head and neck oncology research, Proceedings of the IInd International Head and Neck Oncology Research Conference, Arlington, VA, USA, 10-12 September 1987*. Amsterdam: Kugler, 1988;469-76.
106. Yu MC, Mo CC, Chong WX, Yeh FS, Henderson BE. Preserved foods and nasopharyngeal carcinoma: a case-control study in Guangxi, China. *Cancer Res* 1988;**48**:1954-9.
107. Nešić V, Šipetić S, Vlajinac H, Stošić-Divjak S, Ješić S, Risk factors for the occurrence of undifferentiated carcinoma of nasopharyngeal type: a case-control study. *Srp Arh Celok Lek* 2010;**138**:6-10.
108. Doll R. Cancers weakly related to smoking. *Br Med Bull* 1996;**52**:35-49.
109. Stewart BW, Semmler PCB. *Sharp v Port Kembla RSL Club*: establishing causation of laryngeal cancer by environmental tobacco smoke. *Med J Aust* 2002;**176**:113-6.
110. Guo X, Cheng M, Fei S. A case-control study of the etiology of laryngeal cancer in Liaoning province. *Chin Med J* 1995;**108**:347-50.
111. Schantz SP, Zhang Z-F, Spitz MS, Sun M, Hsu TC. Genetic susceptibility to head and neck cancer: interaction between nutrition and mutagen sensitivity. *Laryngoscope* 1997;**107**:765-81.
112. Escribano Uzcudun A, Rabanal Retolaza I, Garcia Grande A, Miralles Olivar L, Garcia Garcia A, Gonzalez Barón M, *et al.* Pharyngeal cancer prevention:

- evidence from a case-control study involving 232 consecutive patients. *J Laryngol Otol* 2002;**116**:523-31.
113. Vineis P, Airoidi L, Veglia F, Olgiati L, Pastorelli R, Autrup H, *et al.* Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former and never smokers in the EPIC prospective study. *BMJ* 2005;**330**:277-80.
 114. Airoidi L, Vineis P, Colombi A, Olgiati L, Dell'Osta C, Fanelli R, *et al.* 4-aminobiphenyl-hemoglobin adducts and risk of smoking-related disease in never smokers and former smokers in the European Prospective Investigation into Cancer and Nutrition Prospective Study. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2118-24.
 115. Kashigar A, Habbous S, Eng L, Irish B, Bissada E, Irish J, *et al.* Social environment, secondary smoking exposure, and smoking cessation among head and neck cancer patients. *Cancer* 2013;**119**:2701-9.
 116. Wang Z, Tang L, Sun G, Tang Y, Xie Y, Wang S, *et al.* Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China. *BMC Cancer* 2006;**6**:287.
 117. Sun X, Chen W, Chen Z, Wen D, Zhao D, He Y. Population-based case-control study on risk factors for esophageal cancer in five high-risk areas in China. *Asian Pac J Cancer Prev* 2010;**11**:1631-6.
 118. Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM. Occupational exposures and cancer of the colon and rectum. *Am J Ind Med* 1992;**22**:291-303.
 119. Slattery ML, Edwards S, Curtin K, Schaffer D, Neuhausen S. Associations between smoking, passive smoking, *GSTM-1*, *NAT2*, and rectal cancer. *Cancer Epidemiol Biomarkers Prev* 2003;**12**:882-9.
 120. Curtin K, Samowitz WZ, Wolff RK, Herrick J, Caan BJ, Slattery ML. Somatic alterations, metabolizing genes and smoking in rectal cancer. *Int J Cancer* 2009;**125**:158-64.
 121. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, *et al.* Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;**126**:2394-403.
 122. Ögren M, Hedberg M, Berglund G, Borgström A, Janzon L. Risk of pancreatic carcinoma in smokers enhanced by weight gain. *Int J Pancreatol* 1996;**20**:95-101.
 123. Tranah GJ, Holly EA, Wang F, Bracci PM. Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area. *BMC Cancer* 2011;**11**:138.

124. Kjær SK, van den Brule AJC, Bock JE, Poll PA, Engholm G, Sherman ME, *et al.* Human papillomavirus - the most significant risk determinant of cervical intraepithelial neoplasia. *Int J Cancer* 1996;**65**:601-6.
125. Clark MA, Rakowski W, Ehrich B. Breast and cervical cancer screening: associations with personal, spouse's, and combined smoking status. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:513-6.
126. Buckley JD, Doll R, Harris RWC, Vessey MP, Williams PT. Case control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 1981;**ii**:1010-4.
127. Brown DC, Pereira L, Garner JB. Cancer of the cervix and the smoking husband. *Can Fam Physician* 1982;**28**:499-502.
128. Hellberg D, Valentin J, Nilsson S. Smoking as risk factor in cervical neoplasia [Letter]. *Lancet* 1983;**2**:1497.
129. Zunzunegui MV, King M-C, Coria CF, Charlet J. Male influences on cervical cancer risk. *Am J Epidemiol* 1986;**123**:302-7.
130. Tajima K, Hirose K, Ogawa H, Yoshida M, Ohta M. (Hospital epidemiology-a comparative case control study of breast and cervical cancers). *Gan No Rinsho* 1990;**Spec No**:351-64.
131. Coker AL, Bond SM, Williams A, Gerasimova T, Pirisi L. Active and passive smoking, high-risk human papillomaviruses and cervical neoplasia. *Cancer Detect Prev* 2002;**26**:121-8.
132. Settheetham-Ishida W, Singto Y, Yuenyao P, Tassaneeyakul W, Kanjanavirojkul N, Ishida T. Contribution of epigenetic risk factors but not p53 codon 72 polymorphism to the development of cervical cancer in Northeastern Thailand. *Cancer Lett* 2004;**210**:205-11.
133. Tay S-K, Tay K-J. Passive cigarette smoking is a risk factor in cervical neoplasia. *Gynecol Oncol* 2004;**93**:116-20.
134. Sull JW, Jee SH, Yi S, Lee JE, Park JS, Kim S, *et al.* The effect of methylenetetrahydrofolate reductase polymorphism C677T on cervical cancer in Korean women. *Gynecol Oncol* 2004;**95**:557-63.
135. Paoff K, Preston-Martin S, Mack WJ, Monroe K. A case-control study of maternal risk factors for thyroid cancer in young women (California, United States). *Cancer Causes Control* 1995;**6**:389-97.
136. Kaijser M, Akre O, Cnattingius S, Ekblom A. Maternal lung cancer and testicular cancer risk in the offspring. *Cancer Epidemiol Biomarkers Prev* 2003;**12**:643-6.
137. Glaser SL, Keegan THM, Clarke CA, Darrow LA, Gomez SL, Dorfman RF, *et al.* Smoking and Hodgkin lymphoma risk in women - United States. *Cancer Causes Control* 2004;**15**:387-97.

138. McGlynn KA, Zhang Y, Sakoda LC, Rubertone MV, Erickson RL, Graubard BI. Maternal smoking and testicular germ cell tumors. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1820-4.
<http://cebp.aacrjournals.org/cgi/reprint/15/10/1820>
139. International Agency for Research on Cancer. *A review of human carcinogens: Part E: Personal habits and indoor combustions*, Volume 100. Lyon, France: IARC; 2012, (Accessed Jul 2012). (IARC Monographs on the evaluation of carcinogenic risks to humans.)
140. Natphopsuk S, Settheetham-Ishida W, Sinawat S, Pientong C, Yuenyao P, Ishida T. Risk factors for cervical cancer in northeastern Thailand: detailed analyses of sexual and smoking behavior. *Asian Pac J Cancer Prev* 2012;**13**:5489-95.
141. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* 1981;**282**:183-5.
142. Hirayama T. Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P, editors. *Lung cancer: causes and prevention, Proceedings of the International Lung Cancer Update Conference, New Orleans, Louisiana, March 3-5, 1983*. Deerfield Beach, Florida: Verlag Chemie International, Inc, 1984;175-95.
143. Hirayama T. Health effects of active and passive smoking. In: Aoki M, Hisamichi S, Tominaga S, editors. *Smoking and health 1987, Proceedings of the 6th World Conference on Smoking and Health, Tokyo, 9-12 November 1987*. Amsterdam: Elsevier Science Publishers B.V. (Biomedical Division), 1988;75-86. International Congress Series No. 780.
144. Hirayama T. Passive smoking and cancer: The association between husbands smoking and cancer in the lung of non-smoking wives. In: Kasuga H, editor. *Indoor air quality, International Conference on Indoor Air Quality, Tokyo, November 4-6, 1987*. Berlin Heidelberg: Springer-Verlag, 1990;299-311.
145. Hirayama T. *Life-style and mortality: A large scale census based cohort study in Japan.*, Volume 6. Basle: Karger; 1990. (Wahrendorf J, editor. Contributions to epidemiology and biostatistics.)
146. Hirose K, Hamajima N, Takezaki T, Kuroishi T, Kuzuya K, Sasaki S, *et al.* Smoking and dietary risk factors for cervical cancer at different age groups in Japan. *J Epidemiol* 1998;**8**:6-14.
147. Hooker CM, Gallicchio LM, Comstock GW, Alberg AJ. The risk of developing rectal cancer due to active cigarette smoking and passive smoke exposure [Abstract]. *Ann Epidemiol* 2005;**15**:633.
148. Leufkens AM, van Duijnhoven FJB, Siersema PD, Boshuizen HC, Vrieling A, Agudo A, *et al.* Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. *Clin Gastroenterol Hepatol* 2011;**9**:137-44.

149. Tsai H-T, Tsai Y-M, Yang S-F, Wu K-Y, Chuang H-Y, Wu M-T. The relationship between second hand smoke and cervical intraepithelial neoplasm: a community-based case-control study [Abstract (SER)]. *Am J Epidemiol* 2006;**163**(Suppl):S254.
150. Sobti RC, Shekari M, Kordi Tamandani DM, Kaur P, Suri V, Huria A. Effect of *NBS1* gene polymorphism on the risk of cervix carcinoma in a northern Indian population. *Int J Biol Markers* 2008;**23**:133-9.
151. Sobti RC, Shekari M, Kordi Tamandani DM, Malekzadeh K, Suri V. Association of interleukin-18 gene promoter polymorphism on the risk of cervix carcinogenesis in north Indian population. *Oncol Res* 2008;**17**:159-66.
152. Sobti RC, Kordi Tamandani DM, Shekari M, Kaur P, Malekzadeh K, Suri V. Interleukin 1 beta gene polymorphism and risk of cervical cancer. *Int J Gynaecol Obstet* 2008;**101**:47-52.
153. You NC, Mu LN, McAfee T, Yang B, Cao W, Yu SZ, *et al.* Environmental tobacco smoking and smoking-related susceptibility genes for the risk of esophageal cancer [Abstract]. *Am J Epidemiol* 2005;**161**(Suppl):S13.
154. Enstrom JE, Kabat GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;**326**:1057-61. Full version available at <http://bmj.com/cgi/content/full/326/7398/1057>
155. Clemmesen J. Is pregnancy smoking causal to testis cancer in sons? A hypothesis. *Acta Oncol* 1997;**36**:59-63.
156. Pettersson A, Kaijser M, Richiardi L, Askling J, Ekblom A, Akre O. Women smoking and testicular cancer: one epidemic causing another? *Int J Cancer* 2004;**109**:941-4.
157. Dahlstrom KR, Little JA, Zafereo ME, Lung M, Wei Q, Sturgis EM. Squamous cell carcinoma of the head and neck in never smoker-never drinkers: a descriptive epidemiologic study. *Head Neck* 2008;**30**:75-84.
158. Peppone LJ, Mahoney MC, Cummings KM, Michalek AM, Reid ME, Moysich KB, *et al.* Colorectal cancer occurs earlier in those exposed to tobacco smoke: implications for screening [Author Manuscript]. *J Cancer Res Clin Oncol* 2008;**134**:743-51.
159. Karimi Zarchi M, Akhavan A, Gholami H, Dehghani A, Naghshi M, Mohseni F. Evaluation of cervical cancer risk-factors in women referred to Yazd-Iran hospitals from 2002 to 2009. *Asian Pac J Cancer Prev* 2010;**11**:537-8.
160. Khoshbaten M, Naderpour M, Mohammadi G, Alipoor SH, Estakhri R, Fazeli Z. Epidemiology of esophageal lesions in patients with head and neck squamous cell carcinoma. *Asian Pac J Cancer Prev* 2010;**11**:863-5.

161. Mallis A, Jelastopulu E, Mastronikolis NS, Naxakis SS, Kourousis C, Papadas TA. Laryngeal cancer and passive smoking: the neglected factor? *Eur Arch Otorhinolaryngol* 2011;**268**:727-31.
162. Wilhelm-Benartzi CS, Christensen BC, Koestler DC, Andres Houseman E, Schned AR, Karagas MR, *et al.* Association of secondhand smoke exposures with DNA methylation in bladder carcinomas. *Cancer Causes Control* 2011;**22**:1205-13.
163. Hofmann JN, Liao LM, Strickland PT, Shu X-O, Yang G, Ji B-T, *et al.* Polycyclic aromatic hydrocarbons: determinants of urinary 1-hydroxypyrene glucuronide concentration and risk of colorectal cancer in the Shanghai Women's Health Study. *BMC Cancer* 2013;**13**:282.