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REVIEW ARTICLE

Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women. An updated review and meta-analysis

Peter N. Lee and Jan S. Hamling

P.N. Lee Statistics and Computing Ltd, Sutton, UK

Abstract

Context: In 2006, we reviewed the evidence on environmental tobacco smoke (ETS) and breast cancer in nonsmoking women. Since then various studies and reviews have been published but opinion remains divided.
Objective: To provide an updated review.
Methods: We extracted study details, derived relative risk (RR) estimates with confidence intervals (CIs) for various ETS exposure indices, and conducted meta-analyses.
Results: The update increased the number of studies from 22 to 47. Using an index for each study most closely equivalent to "spouse ever smoked", a weak but significant association was seen (random-effects RR = 1.15, 95% CI = 1.07–1.23). However, the estimates were heterogeneous: higher for Asian studies than for North American or European studies, higher for studies adjusting for fewer potential confounding variables, and close to 1.0 for prospective studies, regardless of whether or not they asked detailed questions on ETS exposure. The RR for eight prospective studies asking detailed questions was 1.003, 95% CI = 0.96–1.05. Risk was increased in premenopausal women (RR = 1.36, 95% CI = 1.15–1.60), but not postmenopausal women. Dose–response findings were similarly heterogeneous. No significant increase was seen for childhood or workplace exposure, but an increase was seen for total exposure (RR = 1.22, 95% CI = 1.09–1.37).
Conclusions: Increases mainly derived from case-control studies are prone to recall bias. Study weaknesses and possible publication bias limit interpretation. Considering also the weak association of smoking with breast cancer, and the much lower exposures from ETS than from smoking, our analyses do not clearly demonstrate that ETS exposure increases risk of breast cancer in nonsmokers. More research is needed.

Keywords

Breast cancer, meta-analysis, passive smoking, publication bias, recall bias, smoking

History

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Introduction

In 2006, we published a review with meta-analyses (Lee & Hamling, 2006) of the evidence relating environmental tobacco smoking (ETS) exposure to risk of breast cancer in women who had never smoked (''nonsmokers''). Based on results from 22 epidemiological cohort and case-control studies, we noted a weak, but significant, association (random-effects relative risk (RR) = 1.12, 95% confidence interval (95% CI) = 1.02–1.24). However, the estimates were heterogeneous, with risk close to 1.0 for prospective, North American and larger studies, for studies adjusting for many potential confounding variables, and for postmenopausal women. Dose–response analyses were also heterogeneous, and no significant increase was seen for ETS exposure in childhood, in the workplace or specifically from the spouse, though an increase was seen for total exposure. At that time, we noted that increases mainly derived from case-control studies asking detailed histories, where RRs depend heavily on who was classified as having no reported exposure from any of the ETS sources considered, so may be prone to recall bias, and we emphasized the need for results from prospective studies with similar histories. We also noted the implausibility that ETS exposure might cause breast cancer, given the RR for active smoking was so close to 1, and felt that, at that time, one could not confidently conclude that ETS exposure increased risk in nonsmokers.

We also commented on two related major reviews associated with the California EPA Report (California Environmental Protection Agency, 2005; Johnson, 2005), noting our disagreement with their conclusion that the evidence is consistent with a causal association in younger, primarily premenopausal women. Since then, a number of other expert groups have drawn their own conclusions, which show a considerable degree of disagreement. Thus, while the Canadian Expert Group (Collishaw et al., 2009; Johnson et al.,

Address for correspondence: Peter N. Lee, P.N. Lee Statistics and Computing Ltd, 17 Cedar Road, Sutton, Surrey SM2 5DA, UK. Tel: +44 20 8642 8265. E-mail: PeterLee@pnlee.co.uk

2011) essentially agreed with the California Environmental Protection Agency that the data demonstrate a causal relationship in premenopausal women, a more recent report (US Surgeon General, 2014) states that ''the evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer,'' while the IARC (International Agency for Research on Cancer, 2012; Secretan et al., 2009) note that the ''evidence for breast cancer remains inconclusive'' and do not include breast cancer in the list of cancers for which ''sufficient evidence'' has been demonstrated of a causal relationship with ETS. The review by the Oxford Group (Pirie et al., 2008) is even more dismissive of a causal relationship, noting (consistently with a more recent review – Yang et al., 2013) that the ''aggregate results from studies with prospectively reported information show that the incidence of breast cancer is similar in women who did and did not report passive smoke exposure to tobacco smoke whether as a child or as an adult'' and that ''the aggregate results from the retrospective studies may have been distorted by some women becoming more likely to report past exposures because they knew that they had breast cancer.''

Since our earlier review (Lee & Hamling, 2006), studies providing data have proliferated, and none of the later reviews mentioned above cite publications later than 2011. It seems timely, therefore, to carry out an updated review incorporating more recent publications. The methodology used is essentially as described earlier.

As before, and as is usual in studies of ETS and health for reasons discussed elsewhere (Lee, 1992), we restrict attention to studies where the relationship between ETS exposure and breast cancer mortality or incidence has been studied in nonsmokers. This requirement means that some publications which might at first seem relevant have not been considered. These include a number of studies in China considered in two recent reviews (Chen et al., 2014, 2015) as well as various other studies (Bradbury et al., 2006; Gao et al., 2013; Hirose et al., 1995; Hosseinzadeh et al., 2014; Hsieh et al., 2014; Hu et al., 2013; Kruk, 2007; Marcus et al., 2000; Marufu et al., 2015; Qi et al., 2014; Sanderson et al., 1996; Wang et al., 2000, 2014; Weiss et al., 1997; Zhao et al., 1999).

Methods

The methods used, essentially as described earlier (Lee & Hamling, 2006), are summarized below. In June 2015, publications describing results of studies relating breast cancer risk in lifelong nonsmoking women to ETS exposure were sought from MEDLINE searches, in-house files and reference lists of papers retrieved. The search terms ''(passive smoking OR environmental tobacco smoke OR involuntary smoking) AND breast cancer'' were used. Studies not in humans, of ecological design, or not providing results for nonsmokers were rejected. Studies included in our previous review (Lee & Hamling, 2006) were included.

From the selected studies, details were extracted of study location and design and of potential confounding variables considered. Where available, RR estimates and their 95% CI were extracted for various sources of ETS exposure: at home, at work, in adulthood, in childhood and throughout life. As before, we use the term ''relative risk'' to include odds ratios from case-control studies, as well as hazard ratios from prospective studies. For each exposure, the RR adjusted for the most potential confounding variables was selected for analysis. Overall RRs were estimated from RRs given by grouped level of exposure (e.g. 1–2, 3–5, 6 + h/day), genetic type, or other subgroup as described earlier (Lee & Hamling, 2006). For a given source of exposure (e.g. at work), RRs generally compared women who were exposed or unexposed to the specific source, exceptions, where the reference group included women with a low exposure, being noted in the tables. RRs were also extracted by subgroup, where available. We also determined whether studies provided dose–response data, and if so, whether there was significant ($p < 0.05$) evidence of a trend within the exposed groups.

Fixed-effect and random-effects meta-analyses were conducted (Fleiss & Gross, 1991), with tests of publication bias also carried out (Egger et al., 1997). We also tested whether the results from a specific study could be regarded as an outlier, by treating the drop in deviance (chi-squared) from excluding the result divided by the mean deviance for the remaining studies as an F statistic, and rerunning the meta-analysis excluding the study if the associated probability was <0.01.

These methods of analysis were applied separately to data for six ETS exposure indices; from the spouse, at home, at the workplace, overall adulthood, in childhood and total during lifetime. They were also applied in a ''principal'' meta-analysis in which one result was selected from each study, based first on source of exposure (choosing spouse as the highest preference, then partner, cohabitant, exposure at home or work) and second on time of exposure (for spouse or partner preferring ever to current, and, for other types of exposures, preferring adulthood to ever in life). This was intended to produce an index most closely equivalent to ''spouse ever smoked''. For these seven indices, additional analyses were also conducted by study type separated into two groups (prospective or nested case-control studies, and other case-control studies) reflecting whether ETS exposure was or was not determined before disease onset. For the principal meta-analysis, further subgroup analyses were conducted by region (North America, Asia, Europe), study size (>500, <500 cases), confounders adjusted for (age and 9+ others, <9 or 9+ but not including age), detailed exposure assessment (yes, no), and study type × detailed assessment. A study was regarded as having made a detailed assessment if it separately asked questions about childhood exposure, at home exposure in adulthood (spousal or any cohabitant) and other sources of exposure in adulthood (e.g. workplace). Subgroup analyses were also conducted excluding studies published only as abstracts, by length of follow-up for prospective studies ($\leq$10, 11+ years) and by type of control for case-control studies (population, other).

For each study included in the principal meta-analysis which provided results by level of adjustment for potential confounding variables, the ratio was calculated of the most-adjusted RR estimate (as used in the principal meta-analysis) to the corresponding least-adjusted RR estimate. The overall effect of confounding, in these studies was then estimated from the geometric mean of these ratios.

Unless otherwise indicated, the word ''significant'' is taken to indicate significance at $p < 0.05$.

Results

The studies

Some details of the 47 studies are summarized in Table 1. Two studies were published in the 1980s, four in the 1990s, 16 from 2000 to 2005, 14 from 2006 to 2010, and 11 from 2011 to June 2015, reflecting increasing interest in the possibility that ETS might cause breast cancer. Four studies (Chilian-Herrera et al., 2010; Rookus et al., 2000; Woo et al., 2000; Zhu et al., 2006) were published only as abstracts. Young et al. (2009) reports a combination of two studies, one reported extensively by Anderson et al. (2012). To avoid overlap no result from Young et al. (2009) is included in the principal meta-analysis.

The 47 studies included all the 22 that had been considered in our earlier review – those 15 with a main publication year up to 2002, four published in 2004 or 2005 (Gammon et al., 2004; Gram et al., 2005; Hanaoka et al., 2005; Shrubsole et al., 2004) and three were results from a later publication that has since become available (Mechanic et al., 2006; Reynolds et al., 2009; Xue et al., 2011).

Twenty-two of the 47 studies were conducted in North America, 14 in Asia and 11 in Europe.

Thirty of the studies were of case-control design, six with upper age limits: of 36 years (Smith et al., 1994), 45 years (Roddam et al., 2007), 50 years (Gram et al., 2005; Kropp & Chang-Claude, 2002), 54 years (Rookus et al., 2000) and 55 years (Liu et al., 2000). The remaining case-control studies included older women.

Fifteen studies were prospective, with follow-up ranging from 3.5 to 24 years. Most concerned breast cancer onset, but Hirayama (1987) and Wartenberg et al. (2000) were of mortality, based on death certificates. Two further studies (Alberg et al., 2004; Woo et al., 2000) were case-control studies nested within prospective studies.

The case-control studies mainly used population controls. However, Sandler et al. (1985) used friends of cases as controls, possibly unrepresentative of the population, since friends, compared to random members of the population, tend to be more similar in respect of various factors, such as education and alcohol consumption. Also seven case-control studies used hospital-based controls: benign breast disease patients (Delfino et al., 2000), patients with ''other diseases'' (Ilic et al., 2013) and patients without cancer (Li et al., 2015; Liu et al., 2000; Nishino et al., 2014; Tang et al., 2013; Tong et al., 2014). Most case-control studies obtained the information from the subject, but Lash & Aschengrau (1999, 2002) used proxy interviews for deceased cases and their matched controls.

Results for various ETS exposure indices were reported. Seven studies (Alberg et al., 2004; Hirayama, 1987; Jee et al., 1999; Nishino et al., 2014; Roddam et al., 2007; Tong et al., 2014; Wada et al., 2015) only recorded exposure from the spouse or partner, while 10 further studies (Delfino et al., 2000; Gammon et al., 2004; Gram et al., 2005; Lash & Aschengrau, 1999, 2002; Lin et al., 2008; Mechanic et al., 2006; Pirie et al., 2008; Sandler et al., 1985; Woo et al., 2000) only considered at-home exposure. The other studies collected more extensive information.

Twenty-five of the studies, indicated by an asterisk in the ETS sources column in Table 1, collected data on ETS exposure in childhood, in adulthood at home and in adulthood at work (or outside the home), though a number of these did not report results for a combined index based on all their exposure sources. These 25 studies have been classified, for the purposes of subgroup analysis, as providing ''detailed'' ETS data. Other studies either clearly did not collect detailed data, as defined, or provided insufficient information to confirm that they did.

While most studies presented results comparing women exposed or unexposed to the source of interest, some required a minimum level of exposure to count as exposed. Thus, Morabia et al. (1996) and Kropp and Chang-Claude (2002) required at least an hour a day exposure for a year, Johnson et al. (2000) required women to be in the presence, specifically, of regular smokers, and Rookus et al. (2000) defined exposure as ''exposed daily to the smoke of housemates or colleagues during at least 20 years or if someone smoked daily in their bedroom during more than one year.'' Also, Chilian-Herrera et al. (2010) presented results for ''t3 versus t1'' with no explanation beyond that the reference group consisted of never active smokers with no history of passive smoking exposure, Rosenberg et al. (2013) required exposure for at least an hour a day for at least 12 consecutive months and restricted attention to exposure up to age 30, and Tong et al. (2014) required exposure for at least a year and excluded women living with more than one smoker.

Supplementary item 1 lists the potential confounding variables adjusted for. The studies published only as abstracts (Chilian-Herrera et al., 2010; Rookus et al., 2000; Woo et al., 2000; Zhu et al., 2006) did not clarify which variables had been adjusted for, while the presentation in Conlon et al. (2010) allowed only unadjusted results to be used. Of the others, all adjusted for age except for Hirayama (1987) (which adjusted for age of the husband), De Silva et al. (2010) and Ilic et al. (2013). Sandler et al. (1985), Hirayama (1987) and Young et al. (2009) adjusted for no other variables, but the other studies adjusted for between two and 16 variables. Other variables adjusted for in at least 10 studies included age at menarche, age at pregnancy (or birth), parity (or numbers of births), family history of breast cancer, personal history of benign breast disease, alcohol consumption, menopausal status (or age at menopause), body mass index (or other similar indices of obesity), physical activity, education (or socio-economic status) and hormone use. These are all well-established breast cancer risk factors (Gammon et al., 2002; Madigan et al., 1995). Other less commonly considered variables included aspects of diet and breastfeeding.

RR estimates and meta-analyses for different sources of ETS exposure

Tables 2–7 give RRs for six different sources of ETS exposure and Table 8 gives results of meta-analyses based on these data.

As shown in Table 2, 14 studies provide RRs specifically for the spouse (or partner), with significantly ($p < 0.05$) increased risks seen in two (Morabia et al., 1996; Tong et al., 2014). Combining these 14 studies (and selecting the RR for spouse ever smoked from Wartenberg et al., 2000) gives a fixed-effect meta-analysis estimate of 1.08 (95%

Table 1. Studies providing data on ETS and breast cancer.

Study[a]	Year[b]	Location	Design[c]	ETS sources[d]	Subgroup analysis[e]
Sandler et al., 1985; Wells, 1991; Wells, 1998	1985	USA, North Carolina	CC-F	Sp, Ch	Yes
Hirayama, 1987; Wells, 1991; Wells, 1998	1987	Japan, six prefectures	P(16)	Sp	Yes
Smith et al., 1994	1994	UK, 11 regions	CC-P	Sp, Oc, Wk, Aa, Ch, To,*	–
Morabia et al., 1996; Morabia et al., 1998; Morabia et al., 2000	1996	Switzerland, Geneva	CC-P	Sp, To[f],*	Yes
Jee et al., 1999	1999	Korea, nationwide	P(6)	Sp	–
Lash & Aschengrau, 1999	1999	USA, Massachusetts	CC-P	Co, Ch	–
Delfino et al., 2000	2000	USA, California	CC-B	Co	Yes
Johnson et al., 2000	2000	Canada, eight provinces	CC-P	Aa, Ch, To,*	Yes
Liu et al., 2000	2000	China, Chongqing	CC-H	Co, Wk, Ch,*	–
Rookus et al., 2000	2000	Netherlands, Amsterdam	CC-P	To,*	Yes
Wartenberg et al., 2000	2000	USA, 50 states[g]	P(12)	Sp, Co, Wk, Aa,*	Yes
Woo et al., 2000	2000	USA, Maryland	NCC	Co	Yes
Nishino et al., 2001	2001	Japan, Miyagi	P(9)	Sp, Oc	–
Chang-Claude et al., 2002; Kropp & Chang-Claude, 2002; Lilla et al., 2005	2002	Germany, two regions	CC-P	Aa, Ch, To,*	Yes
Lash & Aschengrau, 2002	2002	USA, Massachusetts	CC-P	Co, Ch	–
Alberg et al., 2004	2004	USA, Washington County	NCC	Sp	Yes
Gammon et al., 2004; Gaudet et al., 2005; Mordukhovich et al., 2010	2004	USA, New York	CC-P	Co	Yes
Shrubsole et al., 2004	2004	China, Shanghai	CC-P	Sp, Wk, Aa	Yes
Bonner et al., 2005	2005	USA, New York state	CC-P	Co, Wk, Ch,*	Yes
Gram et al., 2005	2005	Norway and Sweden	P(10)	Co	–
Hanaoka et al., 2005	2005	Japan, 14 districts	P(10)	Co, Wk, To,*	Yes
Metsola et al., 2005; Sillanpää et al., 2005	2005	Finland, Kuopio	CC-P	To,*	Yes
Lissowska et al., 2006, 2007	2006	Poland, Warsaw and Łódź	CC-P	Co, Wk, To,*	Yes
Furberg et al., 2002; Mechanic et al., 2006; Millikan et al., 1998	2006	USA, North Carolina	CC-P	Co	Yes
Zhu et al., 2006	2006	China, Shanghai	P(7)	To	Yes
Roddam et al., 2007	2007	UK, three regions	CC-G	Sp	Yes
Lin et al., 2008	2008	Japan, nationwide	P(13)	Co, Ch,*	–
Pirie et al., 2008	2008	UK, nationwide	P(3.5)	Sp, Ch, To	Yes
Rollison et al., 2008	2008	USA, Delaware	CC-P	Co, Wk, Ch, To,*	–
Slattery et al., 2008	2008	USA, four states	CC-P	Ch, To,*	Yes
Ahern et al., 2009	2009	USA, Massachusetts	CC-P	Aa, Ch, To,*	–
Reynolds et al., 2009, 2004, 2006	2009	USA, California	P(10)	Co, Wk, Aa, Ch, To,*	Yes
Young et al., 2009	2009	Canada, Ontario[h]	CC-P	To,*	–
Chilian-Herrera et al., 2010	2010	Mexico, US border states	CC-P	To,*	Yes
Conlon et al., 2010	2010	Canada, Ontario	CC-P	To,*	Yes
De Silva et al., 2010	2010	Sri Lanka, Western province	CC-P	To[i]	–
Luo et al., 2011	2011	USA, nationwide	P(10)	Co, Wk, Aa, Ch, To,*	Yes
Egan et al., 2002; Xue et al., 2011	2011	USA, 11 states	P(24)	Co, Wk, Aa, Ch,*	Yes
Anderson et al., 2012	2012	Canada, Ontario	CC-P	Co, Wk, Aa, Ch,*	Yes
Ilic et al., 2013	2013	Serbia, Kragujevac	CC-H	Aa	–
Rosenberg et al., 2013	2013	USA, Nationwide	P(14)	To,*	Yes
Tang et al., 2013	2013	China, Guangzhou	CC-H	Co, Wk, Aa	Yes
Chuang et al., 2011; Dossus et al., 2014	2014	Europe, 10 countries	P(18)	Co, Wk, Aa, Ch, To,*	–
Nishino et al., 2014	2014	Japan, Miyagi Prefecture	CC-H	Sp	Yes
Tong et al., 2014	2014	China, Liaoning Province	CC-H	Sp[j]	Yes
Li et al., 2015	2015	China, Guangdong Province	CC-H	Co, Wk, Aa,*	Yes
Wada et al., 2015	2015	Japan, Takayama City	P(16)	Sp	Yes

[a]For each study the main publication is shown first in the list of sources. Studies are in chronological order of the main publication.
[b]Year of main publication.
[c]Design *P*(*n*) prospective study with *n* years of follow-up. CC: case-control study; controls indicated by: -B: benign breast disease; -F: friends of cases; -G: same general practitioner; -H: hospital patients without cancer; -P: population sample; NCC: case-control study nested within a prospective study.
[d]ETS sources for which results are available: Sp: spouse (or partner); Aa: any adult exposure; Co: cohabitant; Ch: childhood exposure; Oc: other cohabitants (not spouse); To: total lifetime exposure (childhood and adulthood); Wk: workplace. An asterisk (*) indicates that the study reported asking separately about childhood, adult at home, and other adult exposure, so is classified as collecting detailed exposure data.
[e]Subgroup analysis. Yes: results are reported that relate ETS to breast cancer separately by levels of exposure for at least one exposure index. See Table 10 and Supplementary item 2 for details.
[f]Questions were asked about exposures from age 10.
[g]Also District of Columbia and Puerto Rico.
[h]Combines data from study by Anderson et al. (2012) plus another study although different exposure considered. Not included in principal meta-analysis.
[i]Active smoking appears to have been ignored in this study, although another source is quoted stating that only 0.6% of Sri Lankan women smoke.
[j]Women who lived with two or more smokers were excluded from the study.

Table 2. RR of breast cancer in lifelong nonsmoking women according to ETS exposure from the spouse.

Study[a]	Study location	Study type[b]	Source of exposure (timing)[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
Wells, 1998 reporting the Sandler et al., 1985 study[g,h]	USA	CC	Spouse (ever)	32	1.62 (0.76–3.44)	–	am
Wells, 1998 reporting the Hirayama, 1987 study[h]	Japan	P	Spouse (ever)	115	1.32 (0.83–2.09)	No	c(1)m
Smith et al., 1994	UK	CC	Spouse/partner (adulthood)	94	1.58 (0.81–3.10)	–	ac(9)m
Morabia et al., 1996	Switzerland	CC	Spouse (ever)[i]	90	3.1 (1.6–6.1)	No	ac(9)m
Jee et al., 1999	Korea	P	Spouse (ever)	138	1.27 (0.91–1.77)	–	ac(5)em
Wartenberg et al., 2000[h]	USA	P	Spouse (ever)	669	1.00 (0.84–1.19)	No	ac(16)em
			Spouse (current)	439	1.0 (0.8–1.2)	–	ac(16)
			Spouse (former)	503	1.0 (0.8–1.2)	–	ac(16)
Nishino et al., 2001	Japan	P	Spouse (current)	67	0.58 (0.32–1.10)	–	ac(8)m
Alberg et al., 2004[g,h]	USA	NCC	Spouse (ever)	62	1.20 (0.59–2.40)	–	ac(4)m
Shrubsole et al., 2004[g]	China	CC	Spouse (ever)	813	1.0 (0.8–1.2)	No	ac(10)m
Roddam et al., 2007[g,h]	UK	CC	Spouse/partner (ever)	297	0.89 (0.64–1.25)	No	ac(9)m
Pirie et al., 2008	UK	P	Spouse/partner (current)	1915	1.02 (0.89–1.16)	–	ac(10)m
Nishino et al., 2014[g,h]	Japan	CC	Spouse (ever)	773	1.09 (0.91–1.31)	–	ac(15)em
Tong et al., 2014[h]	China	CC	Spouse (ever)	312	1.46 (1.05–2.03)	d1	ac(6)m
Wada et al., 2015[g,h]	Japan	P	Spouse (ever)	107	1.58 (0.89–2.83)	No	ac(9)em

[a]Studies are in chronological order of the main publication.
[b]Study type: P: prospective; CC: case-control; NCC: nested case control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes.
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported.
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed groups, otherwise: d1: RRs are 1.21, 1.99 for 1–5, >5 cigarettes smoked per day by the spouse (trend $p < 0.05$). No significant trend for years smoking by the spouse, or for pack-years of smoking by the spouse.
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number of variables adjusted for is shown in brackets; e: estimated from data reported; m: included in principal meta-analyses (see Table 9).
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]Reference group is less than 1 h/day ETS exposure from any source for 12 consecutive months during life.

CI 1.00–1.16), which is marginally significant. There is significant heterogeneity, mainly due to the RRs of 3.1 for Morabia et al. (1996) and 0.58 for Nishino et al. (2001). Random-effect meta-analysis increases the estimate to 1.14 and it remains marginally significant (95% CI 1.00–1.28).

Table 3 presents RRs for ETS exposure at home, other than spouse-only exposure, from 23 studies. Taking results from either Table 2 or Table 3 and preferring the more inclusive estimate for those three studies which provided results for both tables, statistically significantly increased RRs and/or dose-related trends are seen in six studies (Lash & Aschengrau, 1999; Li et al., 2015; Liu et al., 2000; Morabia et al., 1996; Tang et al., 2013; Tong et al., 2014) but many studies show no increase, and Lin et al. (2008) reported a significantly reduced risk for past exposure to cohabitant's smoking. The fixed-effect estimate for ETS exposure at home, based on 34 studies, is 1.05 (95% CI 1.02–1.09) while the random-effects estimate is 1.09 (1.03–1.16). Again, Morabia et al. (1996) makes a large contribution to the significant ($p < 0.001$) heterogeneity.

The results shown in Table 4 are for workplace (or not-home) exposure. Three studies (Li et al., 2015; Liu et al., 2000; Shrubsole et al., 2004) show significant positive RRs or trends, while Xue et al. (2011) reported a significantly negative dose–response. The RRs are significantly heterogeneous, with estimates varying from 0.80 for Wartenberg et al. (2000), Bonner et al. (2005) and Rollison et al. (2008) to about 1.50 for Smith et al. (1994) and Liu et al. (2000). No significant overall effect is evident (see Table 8).

Table 5 shows results for overall ETS exposure in adulthood. Fourteen studies give estimates either for any adult exposure or for home and/or workplace exposure. Based on the first estimate cited in Table 5 for studies giving multiple estimates, significantly increased RRs are seen in four studies (Johnson et al., 2000; Kropp & Chang-Claude, 2002; Li et al., 2015; Tang et al., 2013) and, overall, a significant elevation is seen, based on fixed-effect (1.09, 95% CI 1.04–1.14) or random-effects (1.13, 1.04–1.22) analysis. Again, the RRs are heterogeneous ($p < 0.01$).

The results for childhood exposure (Table 6) are from 18 studies. Most RRs are close to 1.0 and none are significantly increased, although Liu et al. (2000) reported a significant positive trend. Xue et al. (2011) reported a significantly negative association with exposure to smoking by the mother but not with exposure to the father. Based on the first RR given in Table 6 for studies with multiple RRs available, no significant overall effect is evident, with the fixed-effect (0.99, 0.95–1.03) and random-effects (1.00, 0.95–1.06) estimates both close to 1.

Twenty one studies give results (Table 7) for total lifetime exposure (studies considering exposure both during childhood and during adulthood). Significant increases and/or dose-related trends are seen in seven studies (Chilian-Herrera et al., 2010; De Silva et al., 2010; Dossus et al., 2014; Johnson et al., 2000; Kropp & Chang-Claude, 2002; Morabia et al., 1996; Zhu et al., 2006). One of these studies (Zhu et al., 2006), only reported as an abstract, found a dose-related positive trend but gave insufficient detail to allow derivation of an overall RR. Although the remaining 20 RR estimates are heterogeneous

Table 3. RR of breast cancer in lifelong nonsmoking women according to ETS exposure at home, other than spouse-only exposure.

Study[a]	Study location	Study type[b]	Source of exposure (timing)[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
*Smith et al., 1994	UK	CC	Cohabitant other than the spouse (adulthood)	94	1.36 (0.67–2.77)	No	ac(9)e
Lash & Aschengrau, 1999[g]	USA	CC	Cohabitant (ever)	120	2.0 (1.1–3.7)	No	ac(7)m
Delfino et al., 2000[g,h]	USA	CC	Cohabitant (ever)[i]	64	1.50 (0.79–2.87)	–	ac(2)m
Liu et al., 2000	China	CC	Cohabitant (adulthood)	186	1.49 (0.96–2.30)	d1	ac(2)em
*Wartenberg et al., 2000[g]	USA	P	Cohabitant (current)	669	1.1 (0.9–1.3)	–	ac(16)
Woo et al., 2000	USA	NCC	Cohabitant (current)	(706)	1.03 (0.81–1.31)	–	c(?)em
*Nishino et al., 2001	Japan	P	Cohabitant other than the spouse (current)	67	0.81 (0.44–1.50)	–	ac(8)
Lash & Aschengrau, 2002[h]	USA	CC	Cohabitant (ever)	305	0.85 (0.63–1.1)	No	ac(9)m
Gammon et al., 2004[g,h]	USA	CC	Cohabitant (ever)[j]	598	1.04 (0.81–1.35)	No	ac(7)m
Bonner et al., 2005[g]	USA	CC	Cohabitant (ever)	525	1.18 (0.86–1.63)	No	ac(11)em
Gram et al., 2005	Norway and Sweden	P	Cohabitant (ever)	(1130)	1.21 (0.98–1.50)	–	ac(8)m
Hanaoka et al., 2005[g]	Japan	P	Cohabitant (ever)[k]	154	1.0 (0.7–1.4)	–	ac(11)m
Lissowska et al., 2006	Poland	CC	Cohabitant (ever)	1034	0.92 (0.74–1.14)	–	ac(12)em
Mechanic et al., 2006[g,h]	USA	CC	Cohabitant (adulthood)	1211	1.10 (0.93–1.31)	–	ac(6)em
Lin et al., 2008	Japan	P	Cohabitant (past)	131	0.68 (0.47–0.97)	No	ac(10)em
Rollison et al., 2008	USA	CC	Cohabitant (adulthood)	124	0.98 (0.58–1.64)	–	ac(8)m
Reynolds et al., 2004[g]	USA	P	Cohabitant (adulthood)[l]	1150	0.97 (0.87–1.10)	–	ac(11)em
			Cohabitant (ever)	1164	0.94 (0.82–1.07)	–	ac(11)
Luo et al., 2011	USA	P	Cohabitant (adulthood)	1660	1.00 (0.91–1.11)	–	ac(10)em
Xue et al., 2011	USA	P	Cohabitant (adulthood)	2874	0.99 (0.92–1.07)	No	ac(15)em
Anderson et al., 2012[g]	Canada	CC	Cohabitant (adulthood)	918	1.08 (0.89–1.31)	No	ac(1)em
Tang et al., 2013	China	CC	Cohabitant (adulthood)	765	1.55 (1.23–1.96)	–	ac(9)m
Dossus et al., 2014	Europe	P	Cohabitant (current)	3286	1.03 (0.94–1.13)	–	ac(11)em
Li et al., 2015[g,h]	China	CC	Cohabitant (adulthood)	877	1.40 (1.15–1.71)	d2	ac(10)em

[a]Studies are in chronological order of the main publication. Studies marked * also provide estimates for ETS exposure from the spouse: see Table 2.
[b]Study type: P: prospective; CC: case-control; NCC: nested case control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes.
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported; where this is not known total number of cases in ever smokers is given in brackets.
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed groups, otherwise: d1: RRs are 0.47, 1.64, 2.14, 3.09 for light, medium, heavy, very heavy exposure from cohabitants (trend $p < 0.01$). No significant trend for number of smokers at home; d2: RRs are 1.06, 1.18, 1.66 for 1–15, 16–25, 26+ smoker-years exposure at home (trend $p < 0.05$). No significant trend for cigarettes per day smoked by the family at home, or for pack-years exposure at home.
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number of variables adjusted for is shown in brackets with ''?'' representing an unknown number of adjustment variables; e: estimated from data reported; m: included in principal meta-analyses (see Table 9).
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]Cohabitant(s) smoked in their home usually or some of the time.
[j]Results are also reported for spouse (ever) but have not been included in Table 2 as they appear to be based on ever smokers as well as never smokers.
[k]Reference group is never exposed at home during life and not exposed daily outside the home at baseline.
[l]Based on 6 years of follow-up only.

($p < 0.001$), 16 of these are above 1, and the overall estimate is significant, using either fixed-effect (1.09, 95% CI 1.04–1.14) or random-effects (1.22, 1.09–1.37) meta-analysis.

Total lifetime exposure was the only index of exposure considered in Table 8 for which evidence ($p < 0.001$) of an outlier was seen. This was for the study by Chilian-Herrera et al. (2010), where removing this high RR of 3.34 (95% CI 2.38–4.68) reduced the random-effects estimate from 1.22 (1.09–1.37) to 1.12 (1.03–1.22).

Some evidence of publication bias ($p < 0.05$) was seen for three of the six indices considered in Table 8. This was generally due to small studies tending to give above average RRs.

Table 8 also includes results of meta-analyses separately by study type. It is evident that there is much clearer evidence of an association from case-control studies where the random effects RRs always exceed those from the prospective (including nested case-control) studies. For workplace and childhood exposure no significant increase in risk is seen for case-control or prospective studies, while for spousal, home and adulthood exposure, a significant increase in risk is seen only for case-control studies. Only for total exposure is an increase seen for both study types, though that seen for prospective studies (RR 1.07, 95% CI 1.03–1.12) is quite weak, based on individual study estimates of 0.98, 1.09, 1.10, 1.10, 1.10 and 1.18. Heterogeneity between estimates is not significant for any index for prospective studies, but is significant for case-control studies for spousal, home, workplace and total exposure.

Principal meta-analysis

A principal meta-analysis was conducted using one RR from each study, for the exposure most equivalent to the classic

Table 4. RR of breast cancer in lifelong nonsmoking women according to ETS exposure in the workplace.

Study[a]	Study location	Study type[b]	Source of exposure (timing)[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
Smith et al., 1994	UK	CC	Workplace (NOS)	94	1.49 (0.76–2.92)	No	ac(9)e
Liu et al., 2000	China	CC	Workplace (NOS)	186	1.54 (1.02–2.32)	No	eu
Wartenberg et al., 2000	USA	P	Workplace (current)	669	0.8 (0.6–1.0)	–	ac(16)
Shrubsole et al., 2004[h]	China	CC	Workplace (last 5 years)[i]	864	1.1 (0.9–1.4)	d1	ac(10)
Bonner et al., 2005[g]	USA	CC	Workplace (ever)	522	0.80 (0.64–1.01)	No	ac(11)e
Hanaoka et al., 2005	Japan	P	Outside home, daily (current)[j]	77	1.3 (0.9–1.9)	–	ac(11)
Lissowska et al., 2006	Poland	CC	Workplace (ever)	1034	1.05 (0.88–1.27)	–	ac(12)e
Rollison et al., 2008	USA	CC	Workplace (ever)	124	0.80 (0.49–1.32)	No	ac(8)
Reynolds et al., 2009	USA	P	Workplace (ever)	1754	1.02 (0.93–1.13)	–	ac(10)
Luo et al., 2011	USA	P	Workplace (adulthood)	1660	1.08 (0.97–1.19)	–	ac(10)e
Xue et al., 2011	USA	P	Workplace (current)	2468	0.94 (0.86–1.04)	d2	ac(16)e
Anderson et al., 2012[g,h]	Canada	CC	Workplace (adulthood)	909	0.99 (0.82–1.20)	No	ac(1)e
Tang et al., 2013	China	CC	Workplace (adulthood)	586	1.23 (0.92–1.64)	–	ac(9)
			Workplace only (adulthood)	474	1.21 (0.84–1.74)	–	ac(9)
Dossus et al., 2014	Europe	P	Workplace (current)	3286	1.05 (0.98–1.13)	–	ac(11)e
			Workplace only (current)	1117	1.08 (0.95–1.23)		ac(11)
Li et al., 2015[g,h]	China	CC	Workplace (ever)	877	1.34 (1.01–1.77)	–	ac(10)e
			Workplace (ever) among those ever employed[k]	418	1.19 (0.80–1.78)	No	ac(10)

[a]Studies are in chronological order of the main publication.
[b]Study type: P: prospective; CC: case-control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes. NOS implies ever in adulthood.
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported.
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed groups, otherwise: d1: RRs are 0.9, 1.1, 1.1, 1.6 for 1–59, 60–179, 180–299, 300+ minutes of exposure per day (trend $p<0.05$); d2: RRs are 0.99, 0.87 for occasional, regular exposure at work (trend $p<0.05$).
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number adjusted for shown in brackets; e: estimated from data reported; u: unadjusted.
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]Analysis restricted to women who had worked during the 5 years prior to interview.
[j]Reference group is never exposed at home during life and not exposed daily outside the home at baseline.
[k]Reference group is never exposed at work or at home who had ever been employed.

index ''spouse ever smoked.'' The RRs used, 14 from Table 2, 20 from Table 3, four from Table 5 and seven from Table 7, are marked with an ''m'' in the notes column of these tables.

Overall, these studies give a fixed-effect estimate of 1.07 (95% CI 1.04–1.10). However, there is marked heterogeneity ($p<0.001$), mainly due to high RRs in three studies (Chilian-Herrera et al., 2010; Kropp & Chang-Claude, 2002; Morabia et al., 1996). Consequently, the random-effects estimate is higher (1.15, 1.07–1.23) (see Table 9 and Figure 1).

Chilian-Herrera et al. (2010) was again a significant ($p<0.001$) outlier, and as shown in Table 9, removing it from the meta-analysis reduced the random-effects estimate from 1.15 (95% CI 1.07–1.23) to 1.11 (1.05–1.17). This study was one of only two for which the available results came from an abstract. Also removing the other (Woo et al., 2000) had little further effect, the random-effects estimate becoming 1.11 (1.05–1.18).

There was some evidence of publication bias ($p<0.05$). This is illustrated in Figure 2, where the logarithm of the RR is plotted against the standard error of the RR estimate. The tendency for studies with high standard errors, which would be based on relatively few cases, to report high RRs, is evident, and is consistent with the idea that smaller studies may not report results unless they find a positive relationship.

To study further possible sources of heterogeneity, RRs were compared by various study characteristics.

Continent

Although there is some evidence of an effect for all three continents, with a significant increase seen in North America (random-effects estimate 1.12, 95% CI 1.02–1.23, based on $n=21$ estimates) and in Asia (1.21, 1.04–1.42, $n=13$), and an almost significant increase seen in Europe (1.12, 0.98–1.27, $n=11$), there is heterogeneity ($p<0.01$) between continents due to the higher estimate for Asia. There is significant ($p<0.01$) heterogeneity within each continent.

Study size

The results from the 19 studies involving over 500 cases show some evidence of heterogeneity ($p<0.05$) and increase in risk (random-effects RR 1.07, 95% CI 1.02–1.13). The 23 smaller studies also show significant ($p<0.001$) heterogeneity, and an increase in risk (random-effects RR 1.22, 1.04–1.43). Although estimates are higher for the smaller than the larger studies, this difference is not significant.

Adjustment for potential confounding variables

Studies were divided, approximately equally, into those that had adjusted for age and nine or more other potential confounding variables and those that had not adjusted for age or had adjusted for eight or fewer other variables. In both

Table 5. RR of breast cancer in lifelong nonsmoking women according to overall ETS exposure in adulthood.

Study[a]	Study location	Study type[b]	Source of exposure (timing)[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
Smith et al., 1994	UK	CC	Spouse/partner, work, other (adulthood)	94	2.49 (0.87–7.16)	No	ac(9)e
Johnson et al., 2000[g]	Canada	CC	Home or workplace (NOS)	606	1.47 (1.06–2.04)	–	ac(11)em
Wartenberg et al., 2000	USA	P	Any (current)	669	1.0 (0.8–1.2)	No	ac(16)e
			Places other than home or workplace (current)	669	0.9 (0.7–1.2)	–	ac(16)
Kropp & Chang-Claude, 2002	Germany	CC	Home or workplace (adulthood)	197	1.69 (1.16–2.45)	No	ac(6)em
Shrubsole et al., 2004	China	CC	Home (ever) or workplace (last 5 years)[i]	864	1.01 (0.79–1.28)	–	ac(10)e
Ahern et al., 2009	USA	CC	Any (adulthood)[j]	232	0.86 (0.57–1.31)	–	ac(5)em
Reynolds et al., 2009	USA	P	Any (adulthood)	1754	1.04 (0.91–1.19)	–	ac(10)
Luo et al., 2011	USA	P	Home or workplace (adulthood)	1660	1.01 (0.88–1.15)	–	ac(10)e
Xue et al., 2011[g]	USA	P	Home and work (adulthood)	2109	1.04 (0.94–1.16)	No	ac(15)e
Anderson et al., 2012[g]	Canada	CC	Any (adulthood)	916	1.09 (0.83–1.42)	No	ac(1)e
			Social situations (adulthood)	907	1.14 (0.95–1.38)	No	ac(1)e
Ilic et al., 2013	Serbia	CC	Home or work (NOS)	130	1.57 (0.81–3.03)	–	c(9)m
Tang et al., 2013[g,h]	China	CC	Home or workplace (adulthood)	765	1.47 (1.18–1.83)	–	ac(9)
			Home only (adulthood)	615	1.52 (1.17–1.97)	–	ac(9)
			Home and workplace (adulthood)	468	1.76 (1.16–2.69)	–	ac(9)
Dossus et al., 2014	Europe	P	Home or workplace (current)	3286	1.06 (0.99–1.15)	–	ac(11)e
			Home only (current)	844	1.30 (1.07–1.59)	–	ac(11)
			Home and workplace (current)	832	1.08 (0.87–1.32)	–	ac(11)
Li et al., 2015[g,h]	China	CC	Home or Work (adulthood)	877	1.35 (1.11–1.65)	–	ac(9)

[a]Studies are in chronological order of the main publication.
[b]Study type: P: prospective; CC: case-control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes. NOS: not otherwise specified; taken to imply ever in adulthood. Where more than one estimate is available, the estimate closest to overall exposure in adulthood is listed first and is included in the Adulthood meta-analysis (see Table 8).
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported.
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed groups.
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number adjusted for shown in brackets; e: estimated from data reported; m: included in principal meta-analysis (see Table 9).
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]Analysis restricted to women who had worked during the 5 years prior to interview.
[j]Reference group is never exposed in lifetime.

groups, there is significant heterogeneity. In the 21 studies that had adjusted for age and nine or more other potential confounding variables, there was no significant evidence of an association of ETS with breast cancer (random-effects RR 1.07, 95% CI 0.999–1.15) but, in the group that had not adjusted for age or had adjusted for eight or fewer other variables, there was a significant relationship, random-effects RR 1.19, 1.07–1.32). The difference in RR by number of confounding variables adjusted for was significant at $p < 0.05$.

We also investigated the effect of adjustment in specific studies, by comparing most-adjusted and least-adjusted RR estimates for the principal exposure index. In fact, only eight studies (De Silva et al., 2010; Hanaoka et al., 2005; Ilic et al., 2013; Lin et al., 2008; Luo et al., 2011; Smith et al., 1994; Wartenberg et al., 2000; Xue et al., 2011) presented results allowing such comparison. Effects of additional adjustment were generally minimal, with the overall most-adjusted/least-adjusted ratio estimated as 1.01 (95% CI 0.96–1.07).

Study type

There is a clear difference ($p < 0.001$) between the study types. Thus, the 16 prospective studies show no significant evidence of an effect or of heterogeneity (see Figure 3), with no evidence that RR estimates varied by length of follow-up. However, the 29 case-control studies do show an association (random-effects RR 1.26, 95% CI 1.13–1.41) and are significantly heterogeneous ($p < 0.001$) (see Figure 4). This is consistent with nearly all the significant ($p < 0.05$) positive associations shown in Tables 2–7, being in case-control studies. The estimate was very similar (1.25, 1.08–1.44) when attention was restricted to the 20 case-control studies using population controls.

Detailed questions

Of the 45 studies for which an RR estimate is available for spousal smoking or nearest equivalent, 24 were based on studies which asked detailed ETS exposure questions. As shown in Table 9, there was no evidence of any variation in risk whether or not detailed questions were asked. This was true when all studies were considered, and also in separate analyses by study type. It is notable that, in the eight studies which were both prospective in design and asked detailed questions, which might be regarded as providing the best evidence on effects of ETS, there was no evidence of heterogeneity or of an increased risk, with the meta-analysis estimate very close to 1. Six of these estimates came from

Table 6. RR of breast cancer in lifelong nonsmoking women according to ETS exposure in childhood.

Study[a]	Study location	Study type[b]	Source of exposure[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
Sandler et al., 1985	USA	CC	Mother	29	0.92 (0.26–3.34)	–	ue
			Father	28	0.91 (0.41–2.04)	–	ue
Smith et al., 1994	UK	CC	Any	94	1.18 (0.55–2.55)	No	ac(9)e
Lash & Aschengrau, 1999	USA	CC	At home	99	2.40 (0.78–7.40)[i]	–	ac(8)e
Johnson et al., 2000	Canada	CC	At home	606	1.24 (0.93–1.64)	–	ac(11)e
Liu et al., 2000	China	CC	At home	186	1.16 (0.73–1.84)[j]	d1	ac(2)e
Kropp & Chang-Claude, 2002	Germany	CC	At home	197	1.09 (0.77–1.55)	No	ac(6)e
Lash & Aschengrau, 2002	USA	CC	At home	224	1.12 (0.82–1.54)	–	ac(9)e
Bonner et al., 2005[g]	USA	CC	At home	525	1.24 (0.96–1.60)	No	ac(11)e
Lin et al., 2008	Japan	P	At home	178	1.24 (0.84–1.85)	–	ac(10)
Pirie et al., 2008	UK	P	Mother	2344	0.96 (0.88–1.05)	–	ac(11)
			Father	2344	1.03 (0.93–1.14)	–	ac(11)
Rollison et al., 2008	USA	CC	At home	123	0.81 (0.47–1.40)	No	ac(8)
Slattery et al., 2008	USA	CC	Any	1347	No association	–	–
Ahern et al., 2009	USA	CC	Any[k]	232	1.20 (0.78–1.84)	–	ac(5)e
Reynolds et al., 2004, 2009	USA	P	At home[l]	1150	0.95 (0.84–1.07)	–	ac(11)e
			Any at age <20	1313	1.06 (0.94–1.19)	–	ac(10)
Luo et al., 2011	USA	P	Any	1660	1.08 (0.98–1.19)	–	ac(10)e
Xue et al., 2011	USA	P	Mother	2883	0.88 (0.79–0.98)	–	ac(15)e
			Father	2883	1.00 (0.93–1.08)	–	ac(15)e
Anderson et al., 2012[g,h]	Canada	CC	At home[m]	912	0.91 (0.75–1.10)	No	ac(1)e
			Any[n]	912	0.91 (0.74–1.13)	No	ac(1)e
Chuang et al., 2011 reporting the Dossus et al., 2014 study	Europe	P	Parents[o]	3187	0.98 (0.91–1.06)	No	ac(14)

[a]Studies are in chronological order of the main publication.
[b]Study type: P: prospective; CC: case-control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source.
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported.
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed groups, otherwise: d1: RRs are 1.01, 2.50, 8.98 for 0, 1, 2, 3+ smokers at home (trend $p < 0.05$), and 0.69, 1.31, 1.64, 1.74 for light, medium, heavy, very heavy exposure at home (trend $p < 0.05$).
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number adjusted for shown in brackets; e: estimated from data reported; u: unadjusted.
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]For exposure at age < 12 years.
[j]For exposure at age 1–9 years. For exposure at age 10–16 RR (95% CI) is 1.06 (0.67–1.68) with no significant dose–response.
[k]Results were reported for parental, maternal and paternal smoking separately but are not included as based on ever smokers as well as never smokers.
[l]Based on 6 years of follow-up only.
[m]Exposure from others in household during ages 2–12 years only.
[n]Exposure from any source during ages 13–19 years only.
[o]Exposure from parents and other sources in childhood for two study centers only, based on only 10 years of follow-up.

studies published since our earlier review (Lee & Hamling, 2006).

RR estimates by menopausal status

Table 10 presents results by menopausal status for 25 studies. The Reynolds study presented results for ages <50 and 50+ at diagnosis and for menopausal status at baseline. As the follow-up was for 10 years, the first of these is used as the estimate of menopausal status at diagnosis. Four of these 25 studies (Hanaoka et al., 2005; Rosenberg et al., 2013; Wells, 1991; Woo et al., 2000) show significantly higher RRs in premenopausal women, with no increase seen for postmenopausal women. In three more studies (Alberg et al., 2004; Delfino et al., 2000; Johnson et al., 2000) the pattern is similar, but the variation is not significant. In Chilian-Herrera et al. (2010), the RRs for both pre- and postmenopausal women are significantly increased, but the RR in premenopausal women is much higher. In Pirie et al. (2008), the RR for premenopausal women is significantly decreased, while no association is seen for peri- or postmenopausal women. Li et al. (2015) reports a non-significantly increased risk for premenopausal women and a significantly increased RR for postmenopausal women. The remaining studies showed no evidence of variation in risk according to menopausal status.

As shown in Table 11, meta-analysis of the 23 studies providing RR estimates by menopausal status shows no effect of ETS in postmenopausal women. Exposure is, however, associated with a significant increase in premenopausal women. However, there is marked heterogeneity ($p < 0.001$) and the random-effects estimate (1.36, 95% CI 1.15–1.60) is considerably higher than the fixed-effects estimate (1.24, 1.14–1.35). Some evidence of a higher risk in premenopausal women is also seen when the ratio, for each study, of the premenopausal to postmenopausal RR was meta-analyzed. The random-effects estimate for premenopausal women is little changed, to 1.38 (1.18–1.61), if RRs for two additional case-control studies of young women (Kropp & Chang-Claude, 2002; Smith et al., 1994) are included, on the basis that all, or virtually all, of the women would have been

Table 7. RR of breast cancer in lifelong nonsmoking women according to total lifetime ETS exposure.

Study[a]	Study location	Study type[b]	Source of exposure[c]	Number of breast cancers[d]	RR (95% CI)	Dose response[e]	Notes[f]
Smith et al., 1994	UK	CC	Childhood, spouse/partner, work or other	94	2.58 (0.96–6.94)	No	ac(9)e
Morabia et al., 1996[g,h]	Switzerland	CC	All[i]	126	3.2 (1.7–5.9)	No	ac(9)
Johnson et al., 2000	Canada	CC	Childhood, home or work	606	1.49 (1.02–2.18)	d1	ac(11)e
Rookus et al., 2000[h]	Netherlands	CC	Home or work[j]	918	1.2 (0.8–1.7)[l]	–	c(?)m
Kropp & Chang-Claude, 2002[h]	Germany	CC	Childhood, home or work	197	1.59 (1.06–2.39)	No	ac(6)
Hanaoka et al., 2005	Japan	P	Childhood, home or outside home	162	1.1 (0.8–1.6)	–	ac(11)
Sillanpää et al., 2005[h]	Finland	CC	Home or work (ever, by years exposed)	363	0.85 (0.62–1.16)	–	ac(6)m
Lissowska et al., 2006[g,h]	Poland	CC	Home (at different times) or work (for each job)	1034	1.11 (0.85–1.46)	No	ac(12)
Zhu et al., 2006[g,h]	China	P	Lifetime (NOS)	390	Not available	d2	n
Pirie et al., 2008[g,h]	UK	P	Parents/spouse	2344	0.98 (0.88–1.09)	–	ac(11)
Rollison et al., 2008	USA	CC	Cohabitants (lifetime)	122	1.06 (0.56–2.02)	No	ac(8)
Slattery et al., 2008[g,h]	USA	CC	Childhood, home or outside home	1347	1.05 (0.88–1.27)	No	ac(9)[l]em
Ahern et al., 2009	USA	CC	Parents, home or work	232	0.91 (0.54–1.55)	–	ac(5)e
Reynolds et al., 2009	USA	P	Childhood, home, work or social	1754	1.10 (0.94–1.30)	No	ac(10)
Young et al., 2009[m]	Canada	CC	Childhood, home or work	2751	0.97 (0.88–1.08)	–	a
Chilian-Herrera et al., 2010[g]	Mexico	CC	Lifetime home or work	(504)	3.34 (2.38–4.68)[n]	d3	ac(?)m
Conlon et al., 2010[h]	Canada	CC	Lifetime home or work	129	1.15 (0.61–2.18)	No	emu
De Silva et al., 2010	Sri Lanka	CC	Any (NOS)	100	2.96 (1.53–5.75)[o]	–	ac(7)m
Luo et al., 2011[h]	USA	P	Childhood, home or work	1660	1.09 (0.92–1.29)	No	ac(10)
Rosenberg et al., 2013[g]	USA	P	Home (ages 0–30) or work (ages 21–30)	771	1.18 (0.98–1.42)	–	ac(13)m
Dossus et al., 2014	Europe	P	Childhood; home or work (at baseline)	3597	1.10 (1.01–1.20)	–	ac(11)

[a]Studies are in chronological order of the main publication.
[b]Study type: P: prospective; CC: case-control.
[c]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes.
[d]Number of breast cancers in lifelong nonsmokers in the analysis reported. Number in bracket: number of cases in the study, including ever-smokers (number in never-smokers unknown).
[e]Dose response: ''–'' indicates dose response not studied, ''No'' indicates dose–response studied but no significant trend seen within the exposed group, otherwise: d1: for premenopausal breast cancer RRs are 1.2, 1.8, 2.0, 3.3, 2.9 for 1–6, 7–16, 17–21, 22–35, 36+ combined years exposure at home and at work (trend $p<0.05$). No trend seen for postmenopausal breast cancer. d2: RRs are 1, 1.02, 1.42, 1.72 for never exposed, <2.0, 2.0 to <4.0, 4.0 + h/day average lifetime exposure (trend $p<0.0001$). Trend over the exposed categories probably also significant but data provided are insufficient to check. No information was given on numbers of unexposed subjects, so overall RR (CI) could not be estimated. d3: a significant positive trend was reported ($p<0.001$), but it was not stated whether this was within the exposed groups only.
[f]Notes: a: adjusted for age of subject; c: adjusted for other confounding variables (see Supplementary item 1) – number adjusted for is shown in brackets with ''?'' representing an unknown number of adjustment variables; e: estimated from data reported; m: included in principal meta-analysis (see Table 9); n: adjustment not specified; u: unadjusted.
[g]See Table 10 for pre/post menopausal results for this analysis.
[h]See Supplementary item 2 for other subgroup results for this analysis.
[i]Exposed for at least 1 h/day ETS exposure from any source for at least 12 consecutive months during life.
[j]Exposed daily to the smoke of home-smokers or colleagues during at least 20 years or if someone smoked daily in their bedroom during more than 1 year.
[k]RR was noted to be no greater for first exposure before first pregnancy.
[l]Adjusted for factors shown in Supplementary item 1 plus menopausal status and ethnicity during estimation of RR.
[m]Combines data from the study by Anderson et al. (2012) plus another study. Not included in principal meta-analysis.
[n]RR given for ''t3'' versus ''t1'', but no explanation of groupings given although it was stated that reference group consisted of never active smokers without history of passive smoking.
[o]An alternative result of 2.90 (1.49–5.63), adjusted for eight confounding variables, was also reported by this study.

premenopausal. We have not included results for age <50 years from two prospective studies (Hirayama, 1987; Wartenberg et al., 2000) as these relate to age at baseline, and many of the cases of breast cancer would have occurred in postmenopausal women.

Table 11 also includes separate results for prospective and case-control studies. In postmenopausal women, RRs are markedly higher in case-control studies than in prospective studies ($p<0.001$). Heterogeneity by study type is not evident in premenopausal women, where some evidence of an increased risk is seen for both study types, though significant only for case-control studies.

RR estimates by other factors

Supplementary item 2 presents RRs for various subgroups other than menopausal status which are available in the source papers. These include results by factors such as age, occupation, a range of genetic markers and aspects of the cancer, such as hormone receptor status.

Generally, these results provide little evidence of any significant variation in RR by genetic status (NAT1, NAT2, p53, SULT1A1, MnSOD, XRCC1, XPD, NER, IL6, ESR1, CYP2E1, UGT1A7, PARP1 and other unspecified genes), by age or by any other factor considered. Significant variation

Table 8. Meta-analyses of breast cancer risk for six indices of ETS exposure.

Index of exposure[a]	N[b]	Fixed-effect RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity			Egger p[d,e]
				Chi-squared	df[c]	p[d]	
All studies							
Spouse (2)[f]	14	1.08 (1.00–1.16)	1.14 (1.00–1.28)	25.69	13	<0.05	<0.1
Home (2 and 3)[g]	34	1.05 (1.02–1.09)	1.09 (1.03–1.16)	70.05	33	<0.001	<0.01
Workplace (4)[h,i]	15	1.03 (0.99–1.07)	1.03 (0.97–1.10)	25.87	14	<0.05	NS
Adulthood (5)[i,j]	14	1.09 (1.04–1.14)	1.13 (1.04–1.22)	28.96	13	<0.01	<0.05
Childhood (6)[i]	17	0.99 (0.95–1.03)	1.00 (0.95–1.06)	21.27	16	NS	<0.1
Total (7)	20	1.09 (1.04–1.14)	1.22 (1.09–1.37)	84.11	19	<0.001	<0.05
Excluding outlier[k]	19	1.07 (1.02–1.12)	1.12 (1.03–1.22)	41.32	18	<0.01	<0.01
Prospective studies[l]							
Spouse (2)[f]	7	1.04 (0.95–1.15)	1.07 (0.93–1.22)	8.28	6	NS	
Home (2 and 3)[g]	15	1.01 (0.97–1.06)	1.02 (0.97–1.07)	17.86	14	NS	
Workplace (4)[h,i]	6	1.02 (0.98–1.07)	1.01 (0.95–1.09)	9.77	5	<0.1	
Adulthood (5)[i,j]	5	1.04 (0.99–1.10)	1.04 (0.99–1.80)	0.57	4	NS	
Childhood (6)[i]	6	0.98 (0.94–1.02)	0.98 (0.92–1.04)	9.48	5	<0.1	
Total (7)	6	1.07 (1.02–1.13)	1.07 (1.02–1.12)	4.23	5	NS	
Case-control studies							
Spouse (2)[f]	7	1.13 (1.01–1.26)	1.24 (1.00–1.55)	16.39	6	<0.05	
Home (2 and 3)[g]	19	1.14 (1.07–1.22)	1.18 (1.06–1.31)	42.04	18	<0.01	
Workplace (4)[h,i]	9	1.06 (0.97–1.15)	1.08 (0.95–1.23)	15.55	8	<0.05	
Adulthood (5)[i,j]	9	1.28 (1.16–1.41)	1.28 (1.11–1.49)	15.10	8	<0.1	
Childhood (6)[i]	11	1.08 (0.97–1.20)	1.05 (0.97–1.15)	8.60	10	NS	
Total (7)	14	1.12 (1.05–1.21)	1.40 (1.12–1.75)	78.89	13	<0.001	
Excluding outlier[k]	13	1.07 (0.99–1.15)	1.24 (1.05–1.48)	37.07	12	<0.001	

[a]Source table shown in parentheses.
[b]N: number of studies in meta-analysis.
[c]df: degrees of freedom.
[d]p expressed as <0.001, <0.01, <0.05, <0.1 or NS ($p \geq 0.1$).
[e]Egger's test for publication bias.
[f]Index includes ''partner''. Where a study provides more than one estimate, the first RR cited is selected. This ensures that exposure to spouse (ever) is chosen for preference where multiple results are available.
[g]The Home meta-analysis selects estimates for cohabitant from Table 3 for studies for which they are available and spousal estimates from Table 2 where they were not. Thus for Wartenberg et al. (2000) the estimate cited in Table 3 has been selected rather than that cited in Table 2. For Smith et al. (1994) and Nishino et al. (2001), where the estimates in Table 3 were for cohabitant other than the spouse, the spousal estimate cited in Table 2 has been selected. Only the first estimates for a study given in Table 2 or Table 3 are considered for selection.
[h]Index includes ''not home'' exposure.
[i]First RR cited for each study in the table.
[j]Index includes ''home or workplace'' exposure.
[k]Excluding the estimate of 3.34 (95% CI 2.38–4.68) from Chilian-Herrera et al. (2010). Outliers were not found for other indices.
[l]Including nested case-control studies.

(at $p < 0.05$) was only noted in Wartenberg et al. (2000) by product smoked by the spouse among those whose spouse was a former smoker; in Lash & Aschengrau (2002) for first exposure being before or after first pregnancy, where first exposure before first pregnancy gave a significant reduction in estimated risk; in Gammon et al. (2004) by BMI, where the variation was not systematic and may well be due to chance; in Zhu et al. (2006) by use of oral contraceptives and by use of other female hormones; and in Anderson et al. (2012) by CYP2E1 genotype in postmenopausal women exposed to passive smoke as a teenager. Li et al. (2015) report a range of analyses by combinations of subgroups, among which the estimates for smoker-years exposure in postmenopausal women and for total smoker-years exposure when considering cases with hormone receptor status ER+/PR + show statistically significant heterogeneity (results not shown). Many of the subgroups were only investigated in a few studies, while in those that were studied more often no consistent patterns were evident. For example, six studies provided RRs for ETS exposure separately for NAT2 slow and fast acetylators. No significant differences were noted, with three studies giving higher RRs for slow acetylators and three giving higher RRs for fast acetylators.

Discussion

Comparison with our previous review

It is of interest to compare the results of this update, based on 47 studies, with those of our earlier review (Lee & Hamling, 2006) based on 22 studies. For the principal index of exposure, most closely equivalent to ''spouse ever smoked'', the existence of an association is confirmed, with the random-effects RR of 1.15 (95% CI 1.07–1.23) quite similar to the earlier estimate of 1.12 (1.02–1.24). For the associations with exposure from the spouse (or partner) and with at home exposure generally, non-significant associations previously evident have become marginally significant with the greater number of studies, with random-effects RRs now 1.14 (1.00–1.28) for spousal exposure and 1.09 (1.03–1.16) for at-home exposure. However, associations remain non-significant for workplace exposure (1.03, 0.97–1.03) and childhood exposure (1.00,

Table 9. Meta-analyses of breast cancer risk for principal index of ETS exposure (spouse ever smoked or nearest equivalent)[a].

Subgroup	N[c]	Fixed-effect RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity[b] Chi-squared	df[d]	p[e]	Egger pe,f
All studies							
All	45	1.07 (1.04–1.10)	1.15 (1.07–1.23)	139.64	44	<0.001	<0.05
Excluding outlier[g]	44	1.06 (1.03–1.09)	1.11 (1.05–1.17)	95.68	43	<0.001	<0.01
Excluding abstracts[h]	43	1.06 (1.03–1.09)	1.11 (1.05–1.18)	95.63	42	<0.001	
N.America[i]	21	1.04 (1.00–1.09)	1.12 (1.02–1.23)	66.89	20	<0.001	
Asia	13	1.20 (1.11–1.30)	1.21 (1.04–1.42)	37.56	12	<0.001	
Europe	11	1.06 (0.99–1.12)	1.12 (0.98–1.27)	25.77	10	<0.01	
			(Between continents	9.42	2	<0.01)	
>500 cases	19	1.04 (1.01–1.08)	1.07 (1.02–1.13)	33.17	18	<0.05	
<500 cases[j]	23	1.14 (1.04–1.25)	1.22 (1.04–1.43)	57.91	22	<0.001	
			(Between study sizes	3.02	1	NS)	
9+ confounders[k]	21	1.04 (1.00–1.07)	1.07 (1.00–1.15)	53.98	20	<0.001	
<9 confounders[l]	21	1.15 (1.07–1.23)	1.19 (1.07–1.32)	34.43	20	<0.05	
			(Between adjustments	6.80	1	<0.01)	
Prospective[m]	16	1.02 (0.98–1.06)	1.02 (0.97–1.08)	19.69	15	NS	
Case-control	29	1.18 (1.12–1.25)	1.26 (1.13–1.41)	100.78	28	<0.001	
			(Between study types	19.18	1	<0.001)	
Detailed questions[n]	24	1.05 (1.01–1.09)	1.14 (1.04–1.25)	95.21	23	<0.001	
Not detailed questions	21	1.12 (1.05–1.19)	1.16 (1.05–1.28)	41.37	20	<0.01	
			(Between detail levels	3.06	1	<0.1)	
Prospective studies[m]							
Detailed questions[n]	8	1.00 (0.96–1.05)	1.00 (0.96–1.05)	8.12	7	NS	
Not detailed questions	8	1.09 (0.99–1.19)	1.10 (0.98–1.25)	9.23	7	NS	
			(Between detail levels	2.33	1	NS)	
Follow-up ≤10 years	8	1.02 (0.96–1.08)	1.02 (0.95–1.10)	8.41	7	NS	
Follow-up 11+ years	8	1.02 (0.97–1.07)	1.03 (0.95–1.11)	11.27	7	NS	
			(Between length groups	0.00	1	NS)	
Case-control studies							
Detailed questions[n]	16	1.21 (1.13–1.31)	1.30 (1.09–1.54)	68.17	15	<0.001	
Not detailed questions	13	1.14 (1.06–1.24)	1.21 (1.05–1.39)	31.42	12	<0.01	
			(Between detail levels	1.19	1	NS)	
Population controls	20	1.13 (1.06–1.21)	1.25 (1.08–1.44)	83.13	19	<0.001	
Other types of controls	9	1.29 (1.17–1.43)	1.31 (1.14–1.51)	12.91	8	NS	
			(Between control types	4.75	1	<0.05	

[a]Based on RRs marked with an ''m'' in the notes column in Tables 2, 3, 5 and 7.
[b]Heterogeneity relates to variation between studies within subgroup, except for the results given in italics which relate to heterogeneity between subgroups.
[c]Nnumber of studies in meta-analysis.
[d]df: degrees of freedom.
[e]p expressed as <0.001, <0.01, <0.05, <0.1 or NS ($p \geq 0.1$).
[f]Egger's test for publication bias.
[g]Excluding the estimate of 3.34 (95% CI 2.38–4.68) from Chilian-Herrera etal. (2010).
[h]Also excluding the estimate of 1.03 (95% CI 0.81–1.31) from Woo etal. (2000).
[i]Includes one study in Mexico.
[j]The number of cases in nonsmokers was not known for three studies (see Tables 3 and 7).
[k]Analyses that adjusted for age and 9+ potential confounders. Three studies were excluded from this and from the <9 confounders analysis because the number of confounding variables adjusted for other than age was not clear (see Supplementary item 1).
[l]This analysis includes estimates that were adjusted for 9+ potential confounders but not for age.
[m]Including nested case-control studies.
[n]A study is categorized as asking detailed questions if it included questions on exposure in childhood, at home in adulthood (spousal or more general home exposure) and other adult exposure, such as workplace exposure. The studies are identified in Table 1 by having an asterisk against ETS sources.

0.95–1.06). As before, a significant association is seen with any adult exposure (1.13, 1.04–1.22) and also with total exposure, though the magnitude of this relationship has weakened, from 1.54 (1.17–2.04) based on six RR estimates, to 1.22 (1.09–1.37) based on 20. The strength of the association with menopausal status has also weakened, with the RR for the ratio of pre- to postmenopausal status reducing from 1.50 (1.12–2.00) based on 10 estimates, to a just non-significant 1.19 (1.00–1.42) based on 23. (Note that, in the above, and in the rest of this discussion, meta-analysis RRs cited are unless stated otherwise, always random-effects.)

As before, heterogeneity is clearly evident in nearly all of these associations. Some similarities and differences are again evident in the analyses based on the principal index investigating relationships with various study characteristics. While both now and earlier there was clear variation by continent, the pattern of results has changed. Earlier these were due to a high RR for Europe of 1.50 (95% CI 1.14–1.97) based on five estimates, but this has declined considerably to 1.12 (0.98–1.27), based on 11. In contrast, the estimate for Asia has increased, from 1.09 (0.90–1.33) based on six studies, to 1.21 (1.04–1.42), which is now higher than the estimates for North America and Europe. As before, there is a

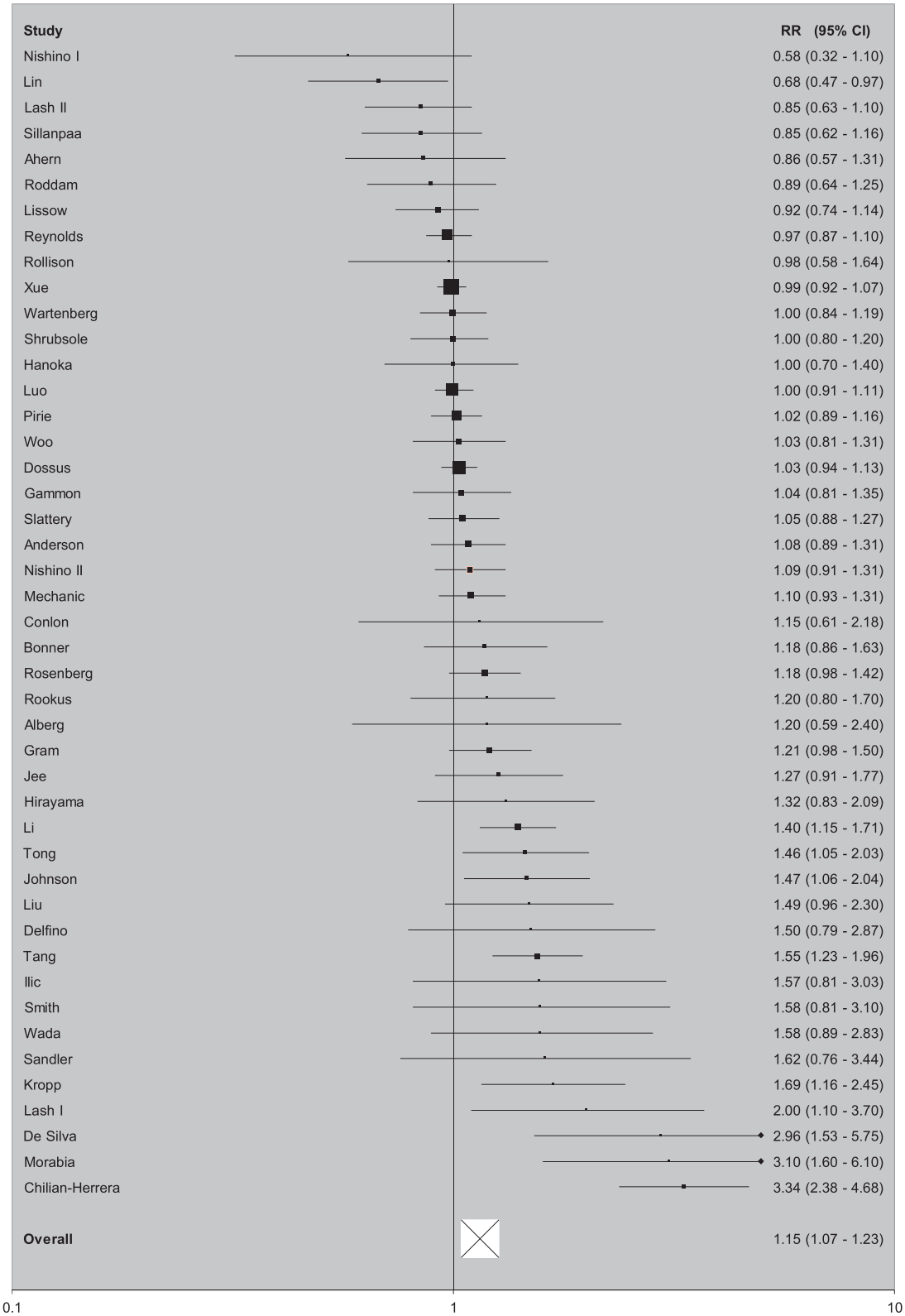

Figure 1. Forest plot of random-effects RRs and 95% CIs from the principal meta-analysis – all studies. Studies are shown in order of increasing RR estimate. Lines representing CIs that are marked ♦ have not been shown to their full length. See the CI values given.

tendency for estimates to be smaller for larger studies (based on at least 500 cases) and for studies adjusting for age and at least nine confounding variables.

A striking similarity between the two sets of analyses is the finding that there is essentially no association between ETS and breast cancer in prospective or nested case-control studies, where the exposure would have been determined prior to disease onset, the only exception being for total exposure where the RR was 1.07 (95% CI 1.02–1.12), based on six estimates. In our earlier analysis, the overall RR from nine prospective studies for the principal ETS exposure index was 1.02 (0.93–1.10) and there was concern that the great

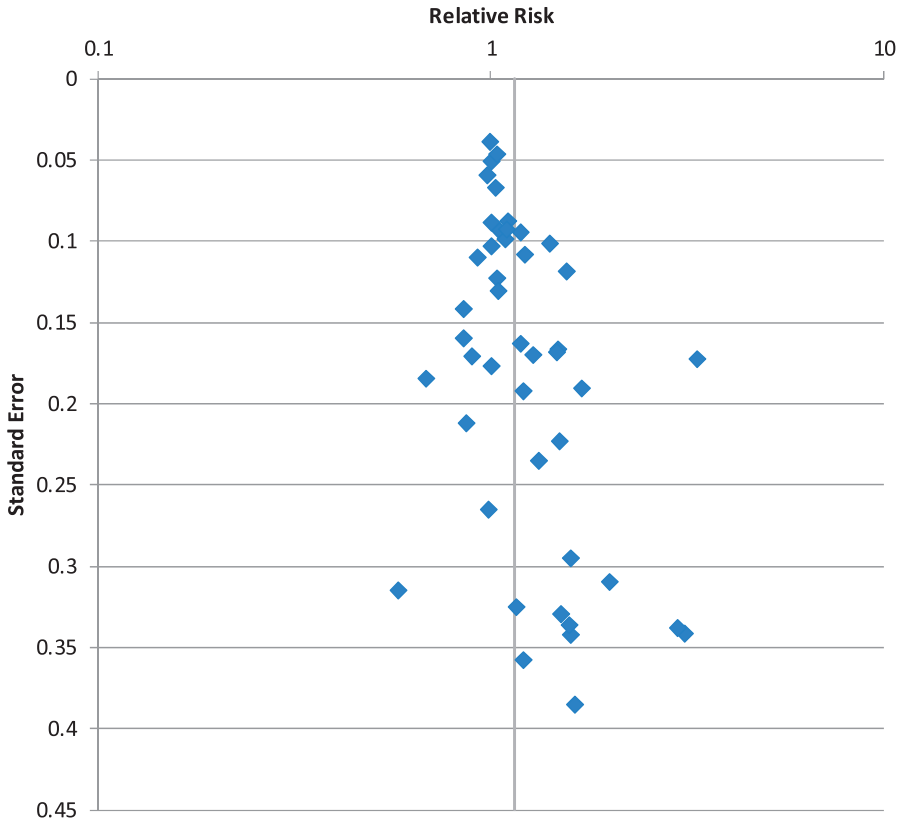

Figure 2. Funnel plot of each RR from the principal meta-analysis against its standard error. RRs are shown on a logarithmic scale. The vertical line at RR 1.15 represents the overall meta-analysis RR.

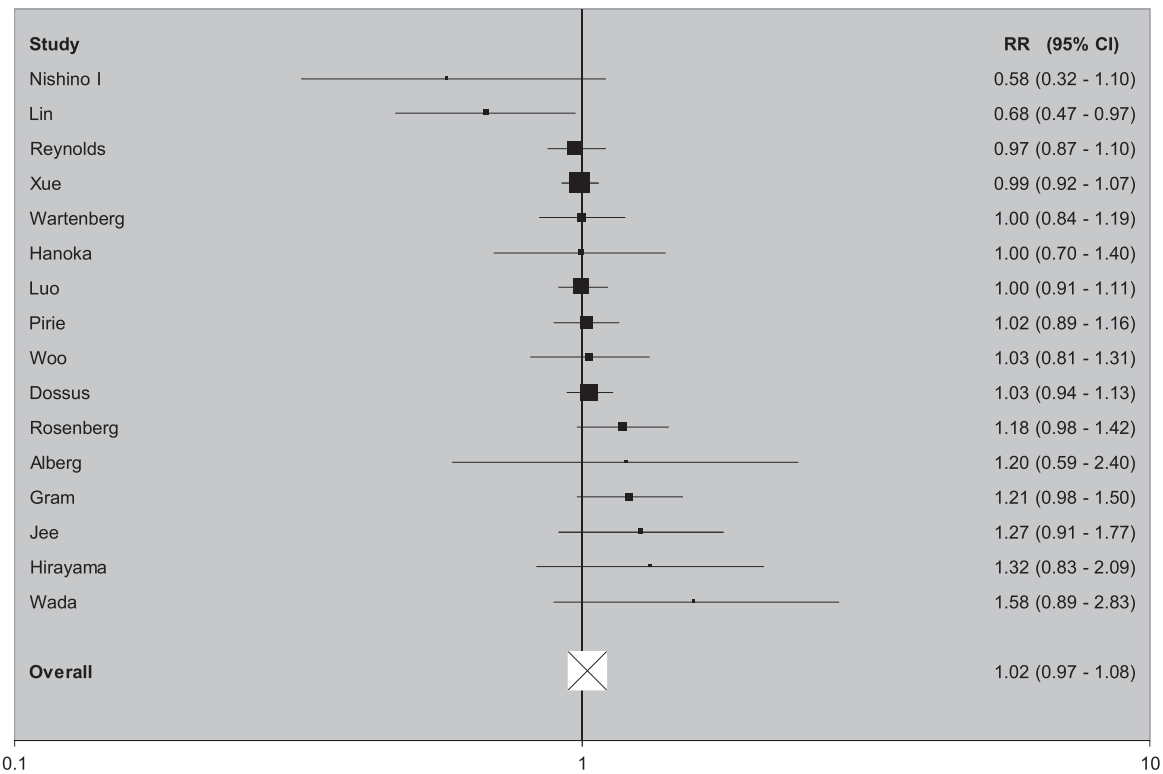

Figure 3. Forest plot of random-effects RRs and 95% CIs from the principal meta-analysis – prospective studies. Studies are shown in order of increasing RR estimate.

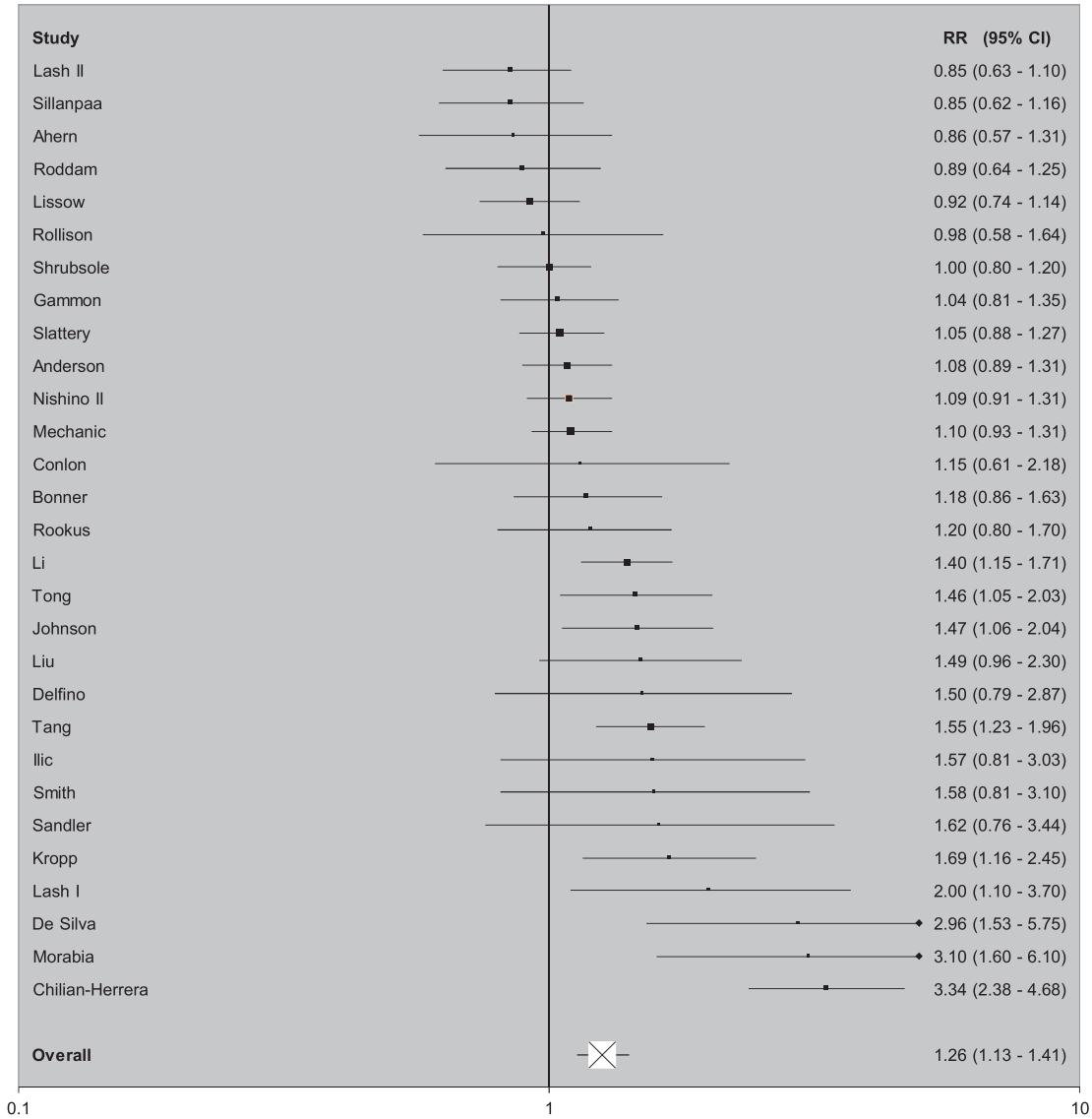

Figure 4. Forest plot of random-effects RRs and 95% CIs from the principal meta-analysis – case-control studies. *Note*: Studies are shown in order of increasing RR estimate. Lines representing CIs that are marked ♦ have not been shown to their full length. See the CI values given.

Table 10. RR of breast cancer in lifelong nonsmoking women according to ETS exposure; by menopausal status.

Study[a]	Exposure index (timing)[b]	Subgroup	RR (95% CI)	Heterogeneity[c]	Notes[d]
Wells, 1991 reporting the Sandler et al., 1985 study	Spouse (ever)	Premenopausal	7.11 (1.35–37.5)	4.62 (1), $p<0.05$	ue
		Postmenopausal	0.89 (0.36–2.22)		
Morabia et al., 1998	All (ever)[e]	Premenopausal	2.21 (1.03–4.75)	0.03 (1), NS	ae
		Postmenopausal	2.04 (1.19–3.48)		
Delfino et al., 2000	Cohabitant (ever)	Premenopausal	2.69 (0.91–8.00)	2.01 (1), NS	ac_1
		Postmenopausal	1.01 (0.45–2.27)		
Johnson et al., 2000	Home or work (ever)	Premenopausal	2.3 (1.2–4.6)	2.64 (1), NS	ac_2f
		Postmenopausal	1.2 (0.8–1.8)		
Woo et al., 2000	Cohabitant (current)	Premenopausal	2.78 (1.37–5.63)	8.50 (1), $p<0.01$	u
		Postmenopausal	0.91 (0.71–1.18)		
Alberg et al., 2004	Spouse (ever)	Premenopausal	1.83 (0.32–10.57)	0.37 (1), NS	ue
		Postmenopausal	1.01 (0.45–2.24)		
Gammon et al., 2004	Cohabitant (ever)	Premenopausal	1.21 (0.78–1.90)	0.89 (1), NS	ac_2
		Postmenopausal	0.93 (0.68–1.29)		
Shrubsole et al., 2004	Spouse (ever)	Premenopausal	1.0 (0.8–1.3)	0.24 (1), NS	ac_2g
		Postmenopausal	0.9 (0.6–1.2)		
Bonner et al., 2005	Cohabitant (ever)	Premenopausal	1.35 (0.78–2.33)	0.35 (1), NS	ac_2
		Postmenopausal	1.10 (0.74–1.64)		
	Workplace (ever)	Premenopausal	0.63 (0.41–0.96)	1.79 (1), NS	ac_2
		Postmenopausal	0.89 (0.68–1.18)		
	At home (childhood)	Premenopausal	1.35 (0.84–2.18)	0.17 (1), NS	ac_2
		Postmenopausal	1.20 (0.89–1.63)		
Hanaoka et al., 2005	Cohabitant (ever)[f]	Premenopausal	1.6 (0.9–2.7)	4.71 (1), $p<0.05$	ac_2h
		Postmenopausal	0.7 (0.4–1.1)		
Lissowska et al., 2007	Home or work (ever)	Premenopausal	1.55 (0.81–2.97)	1.61 (1), NS	ac_3ei
		Postmenopausal	0.97 (0.71–1.34)		

(*continued*)

Table 10. Continued

Study[a]	Exposure index (timing)[b]	Subgroup	RR (95% CI)	Heterogeneity[c]	Notes[d]
Millikan et al., 1998 reporting the Mechanic et al., 2006 study	Cohabitant (ever)[g]	Premenopausal	1.5 (0.8–2.8)	0.27 (1), NS	ac_4
		Postmenopausal	1.2 (0.7–2.2)		
Zhu et al., 2006	All (ever)	Premenopausal	Data not shown	NA	j
		Postmenopausal	Data not shown		
Roddam et al., 2007	Spouse (ever)	Premenopausal	0.83 (0.59–1.17)	0.31 (1), NS	ac_5
		Peri/postmenopausal	1.51 (0.19–12.2)		
Pirie et al., 2008	Parents (ever)/ spouse (current)	Premenopausal	0.54 (0.30–0.99)	3.80 (2), NS	ac_2
		Postmenopausal	0.98 (0.87–1.10)		
		Perimenopausal	1.03 (0.69–1.55)		
Slattery et al., 2008	Any (ever)	Pre/perimenopausal	1.13 (0.85–1.50)	0.42 (1), NS	ac_6e
		Postmenopausal	1.00 (0.79–1.27)		
Reynolds et al., 2006	Cohabitant (ever)	Age (at diagnosis/end of follow-up) <50	1.05 (0.76–1.45)	0.96 (1), NS	ac_3ef
		≥ 50	0.88 (0.76–1.01)		
Reynolds et al., 2004	Cohabitant (ever)	Pre/perimenopausal (at baseline)	0.93 (0.71–1.22)	0.01 (1), NS	ac_2f
		Postmenopausal (at baseline)	0.92 (0.78–1.08)		
Chilian-Herrera et al., 2010	Home or work (ever)	Premenopausal	4.75 (2.58–7.35)[h]	2.31 (1), NS	ac_3
		Postmenopausal	2.83 (1.87–4.28)[h]		
Egan et al., 2002, reporting the Xue et al., 2011 study	Home and work (adulthood)	Premenopausal	Data not shown	NS	ac_2
		Postmenopausal	Data not shown		
Anderson et al., 2012[i]	Cohabitant (adulthood)	Premenopausal	1.07 (0.78–1.47)	0.01 (1), NS	ac_3e
		Postmenopausal	1.09 (0.86–1.39)		
	Cohabitant (childhood)	Premenopausal	0.81 (0.58–1.12)	0.67 (1), NS	ac_3e
		Postmenopausal	0.96 (0.75–1.21)		
	Work (adulthood)	Premenopausal	0.98 (0.71–1.35)	0.01 (1), NS	ac_3e
		Postmenopausal	1.00 (0.79–1.27)		
	Social situations (adulthood)	Premenopausal	1.21 (0.88–1.66)	0.18 (1), NS	ac_3e
		Postmenopausal	1.11 (0.88–1.41)		
	Any (teenage)	Premenopausal	0.98 (0.69–1.39)	0.23 (1), NS	ac_3e
		Postmenopausal	0.88 (0.68–1.14)		
	Any (adulthood)	Premenopausal	1.18 (0.78–1.77)	0.28 (1), NS	ac_3e
		Postmenopausal	1.02 (0.71–1.45)		
Rosenberg et al., 2013	Childhood, home or workplace (ever)	Premenopausal	1.42 (1.09–1.85)	4.52 (1),	ac_3
		Postmenopausal	0.92 (0.68–1.24)	$p<0.05$	
Tang et al., 2013	Home or workplace (adulthood)	Premenopausal	1.54 (1.14–2.07)	0.02 (1), NS	ac_2
		Postmenopausal	1.49 (1.03–2.16)		
Nishino et al., 2014	Spouse (ever)	Premenopausal	0.88 (0.61–1.29)	2.03 (1), NS	ac_3
		Postmenopausal	1.22 (0.95–1.56)		
Li et al., 2015	Home or workplace (adulthood)	Premenopausal	1.18 (0.93–1.50)	4.11 (1), $p<0.05$	ac_3
		Postmenopausal	1.83 (1.29–2.60)		
	Home exposure (adulthood)	Premenopausal	1.10 (0.84–1.43)	4.45 (1), $p<0.05$	ac_7
		Postmenopausal	1.80 (1.24–2.61)		
	Workplace (ever)	Premenopausal	1.07 (0.67–1.70)	0.83 (1), NS	ac_8
		Postmenopausal	1.70 (0.70–4.08)		
Wada et al., 2015	Spousal (ever)	Premenopausal	1.32 (0.59–2.93)	0.27 (1), NS	ac_3e
		Postmenopausal	1.80 (0.77–4.21)		

[a]Studies are in chronological order of the main publication.
[b]Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes.
[c]The chi-squared statistic is shown with the degrees of freedom in brackets and then the *p*-value. NS=$p \geq 0.1$. NA = not available.
[d]Notes: a: adjusted for age; c: adjusted for other confounding variables as indicated below; c_1: family history of breast cancer; c_2: all variables listed in Supplementary item 1 except the subgroup variable; c_3: all variables listed in Supplementary item 1; c_4: race, age at menarche, age at first full-term pregnancy, parity, family history of breast cancer, benign breast biopsy, alcohol; c_5: region, parity and oral contraceptive use; c_6: all variables listed in Supplementary item 1, and ethnicity; c_7: all variables listed in Supplementary item 1 except residence and study stage, subjects exposed at work only excluded; c_8: all variables listed in Supplementary item 1 except residence and study stage, subjects exposed at home only excluded; u: unadjusted; e: estimated from data reported.
[f]RRs for adult and childhood exposure separately also did not vary significantly by menopausal status or age at diagnosis (data not shown).
[g]RRs for workplace exposure and for combined spousal and workplace exposure also did not vary significantly by menopausal status (data not shown).
[h]RRs for exposure other than at home and for any exposure were also both significantly higher for premenopausal than postmenopausal women. Non-home (2.3 versus 0.4, Heterogeneity $p<0.001$), Any (2.6 versus 0.7, Heterogeneity $p<0.01$).
[i]For each menopausal status, dose response analysis (<100, 101–200, >200 h/day-years) was non-significant (*p* value for trend 0.08 for premenopausal, 0.74 for postmenopausal).
[j]Results quoted only as ''The [hazard ratio] for [secondhand smoke] was higher among premenopausal than postmenopausal women.''
[e]Exposed for at least 1 h/day ETS exposure from any source for at least 12 consecutive months during life.
[f]Reference group is never exposed at home during life and not exposed daily outside the home at baseline.
[g]Based on subset of 352 cases.
[h]RR given for ''t3'' versus ''t1'' but no explanation of groupings given although it was stated that reference group consisted of never active smokers without history of passive smoking.
[i]An earlier abstract (Anderson et al., 2010) refers to having studied 11 candidate genes, including the five for which results were given in the later paper (Anderson et al., 2012) and shown above, concluding that the relationship between passive smoke exposure and breast cancer was found to be modified by certain genetic variants, but without giving any detailed results.

Table 11. Meta-analyses of breast cancer risk in relation to ETS exposure by menopausal status[a].

Study type	Menopausal status	N[b]	Fixed-effect RR (95% CI)	Random-effects RR (95% CI)	Heterogeneity			Egger p[d,e]
					Chi-squared	df[c]	p[d]	
All	Premenopausal	23	1.24 (1.14–1.35)	1.36 (1.15–1.60)	68.33	22	<0.001	<0.05
	Postmenopausal	23	1.04 (0.98–1.10)	1.12 (1.00–1.25)	58.28	22	<0.001	<0.1
	Ratio pre/post	23	1.14 (1.01–1.28)	1.19 (1.00–1.42)	40.28	22	<0.05	NS
Prospective[f]	Premenopausal	7	1.27 (1.07–1.50)	1.28 (0.92–1.77)	15.48	6	<0.05	
	Postmenopausal	7	0.93 (0.86–1.01)	0.95 (0.90–1.00)	4.95	6	NS	
	Ratio pre/post	7	1.32 (1.06–1.63)	1.35 (0.89–2.05)	16.77	6	<0.05	
Case-control	Premenopausal	16	1.23 (1.12–1.36)	1.40 (1.14–1.71)	52.77	15	<0.001	
	Postmenopausal	16	1.19 (1.09–1.30)	1.23 (1.06–1.44)	37.64	15	<0.01	
	Ratio pre/post	16	1.07 (0.93–1.23)	1.11 (0.92–1.33)	21.03	15	NS	
Heterogeneity by study type	Premenopausal				0.08	1	NS	
	Postmenopausal				15.69	1	<0.001	
	Ratio pre/post				2.48	1	NS	

[a]Based on data in Table 10.
[b]N: number of studies in meta-analysis.
[c]df: degrees of freedom.
[d]p expressed as <0.001, <0.01, <0.05, <0.1 or NS ($p \geq 0.1$).
[e]Egger's test for publication bias.
[f]Including nested case-control studies.

majority of these came from studies which had not determined detailed exposure histories. In the present analysis, which includes results from many more studies with detailed histories, no association is again seen, with the RR again 1.02, though with somewhat narrower 95% CI of 0.97–1.08. In the present analyses, we defined a study as having a detailed exposure history if it asked about childhood ETS exposure as well as about exposure in adulthood both in the home and outside. No significant differences were seen between studies with or without detailed questions on exposure, and it was notable that the combined results from the eight prospective studies that did ask detailed questions gave a RR estimate for the principal index of 1.003 (0.96–1.05), not suggestive of any relationship.

Conclusions from other reviews

As noted in the introduction, various reviews of the evidence have been conducted in the last 10 years or so. These include the California EPA (California Environmental Protection Agency, 2005; Johnson, 2005; Miller et al., 2007), the Canadian Expert Group (Collishaw et al., 2009; Johnson et al., 2011), the IARC (International Agency for Research on Cancer, 2012; Secretan et al., 2009), the Oxford Group (Pirie et al., 2008) and the 2014 report of the US Surgeon General (2014). There is broad agreement between these reviews and ours in various aspects of the evidence. These include the following: the associations of ETS exposure and of active smoking with breast cancer are both weak; there is little or no evidence of any association with ETS exposure in prospective studies; there is no evidence of an association with childhood ETS exposure; there is considerable evidence of heterogeneity; and associations are much more clearly evident for premenopausal women than for postmenopausal women. Despite this there is marked variation between the reviews in how the results are to be interpreted. At one extreme, the California EPA and the Canadian Expert Group argue that the data show a causal relationship in premenopausal women, while at the other the Oxford Group argue that the evidence is consistent with ETS exposure having no effect on breast cancer risk. Intermediate positions are occupied by the IARC, who do not include breast cancer in the cancers for which sufficient evidence of an effect of ETS exposure has been demonstrated, and by the US Surgeon General. In their report (US Surgeon General, 2014), they regarded the evidence as ''suggestive but not sufficient to infer a causal relationship'' of breast cancer with tobacco smoke, active smoking and exposure to secondhand smoke.

In assessing the results in terms of a causal relationship, various issues have to be taken into account. These are outlined in the sections that follow, in which we refer, where appropriate, to the views expressed in the various reviews.

Selection of studies for inclusion

We have restricted attention to studies of lifelong nonsmokers, an approach which is traditional in studies of ETS, and is the one also generally used in published reviews.

Study weaknesses

None of the studies had serious weaknesses, as defined in Lee (1993). However, many studies had less serious weaknesses. These include the following:

(i) Small number of cases, with some of the RRs being based on less than 100 cases, with consequent variability of the estimate.
(ii) Prospective studies of some years duration determining ETS exposure and other risk factors only at baseline, so not allowing for possible changes in exposure. As shown in Table 1, there were 12 prospective studies involving nine years of follow-up or more, and in none of them were repeat interviews carried out.
(iii) Use of control groups with diseases that may be associated with ETS exposure. This will bias the RR for ETS and breast cancer downward where this association is positive, and upward where it is negative.

(iv) General reliance on ETS exposure reported by the subject (or, in Lash & Aschengrau, 1999, 2002, by the next-of-kin for some subjects), with no confirmation by cotinine or other biomarker, or by data reported by other individuals such as the spouse or coworker.

(v) Failure in many studies to restrict attention to married subjects when analyzing spousal exposure or to control for household size when analyzing household exposure. Thus, for example, for spousal smoking, comparing exposed women who by definition must be married, with unexposed women who may or may not be, leads to the possibility of confounding by variables that differ between married and unmarried women.

We did not exclude any of the studies from analysis due to these weaknesses because their assessment is subjective and therefore open to criticism, although in some analyses we demonstrated the effect of excluding results which were clear outliers on statistical grounds. This was only relevant to the study by Chilian-Herrera et al. (2010), where excluding its high RR reduced the overall estimates for total ETS exposure and for the principal meta-analysis, though not affecting the significance of these associations.

While most reviews use data from all available studies, some meta-analyses have been reported restricted to ''better'' studies. Thus, the California Environmental Protection Agency (2005) limited some analyses to ''Most informative studies'' which restricted attention to those studies that included a historical determination of lifetime exposure to tobacco smoke, used a referent population that was unexposed to the multiple sources of exposure considered, and which considered exposures at different ''windows of susceptibility''. Essentially, this implies preference for estimates of lifetime total exposure over individual source estimates.

Also, the 2014 report by the US Surgeon General (2014) reported some results for the ''most comprehensive measure of secondhand smoke ... excluding studies with design or analysis issues''. It was notable that, while the California EPA's exclusions tended to increase the observed association of ETS with breast cancer, the US Surgeon General's tended to reduce it. It is likely that neither set of exclusions were derived blind of the results.

Plausibility

While the 2014 report by the US Surgeon General (2014) regards the evidence as ''sufficient to identify mechanisms by which cigarette smoking may cause breast cancer'', they do not regard the evidence that active smoking increases breast cancer risk as more than suggestive. Though the California Environmental Protection Agency (2005) regards the evidence on active smoking as demonstrating a causal relationship, there still remains the problem of understanding how the claimed increases in risk from active smoking and ETS exposure might be so similar.

One possible reason given by the Canadian Expert Panel (Collishaw et al., 2009) for the similarity in risks was the relative difference in anti-estrogenic effects between the two sources of tobacco exposure, whereby the anti-estrogenic effects associated with active smoking might depress the level of breast cancer risk related to tobacco smoke in active smokers, but not be strong enough in women exposed to ETS to depress their tobacco-related risk. Another explanation put forward was the existence of a low threshold effect where pathways become saturated at a relatively low level of exposure to tobacco smoke, in the range normally associated with ETS exposure, with further exposure not resulting in further risk. As pointed out by the IARC (International Agency for Research on Cancer, 2012), the theory that ''active smoking may have counterbalancing protective and differential effects on breast cancer risk that in combination, produced little or no association, whereas secondhand tobacco smoking may only have an adverse effect on risk'' suffers from the weakness of a ''lack of direct evidence identifying the mechanism by which active smoking may cause the proposed [protective] antiestrogenic effect''.

In contrast, some reviews have not concluded that there is a demonstrated effect of active smoking or ETS exposure on breast cancer risk. Thus, the IARC (International Agency for Research on Cancer, 2004) concluded that there is evidence suggesting a lack of carcinogenicity of tobacco smoking for female breast cancer, noting a combined analysis from 53 studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002) which showed that a weak association can be explained by confounding by alcohol consumption and in the same year, the US Surgeon General (2004) also concluded that the evidence is ''suggestive of no causal relationship.'' Although, in 2014, the US Surgeon General (2014) referred to ''multiple lines of evidence'' supporting ''biologic plausibility'', and that the evidence of a causal relationship was ''suggestive'' for both active smoking and ETS exposure, they still regarded it as ''not sufficient to infer a causal relationship''.

If indeed active smoking has little or no effect on breast cancer risk, is it plausible that ETS exposure might have a true effect on the risk? In our earlier review (Lee & Hamling, 2006) we pointed out that the denominators are not the same in the two RR calculations, with the risk in smokers generally compared to that in all nonsmokers, whether ETS exposed or not. We went on to present calculations showing that the observation that risks are similar in smokers and nonsmokers, but higher in ETS exposed than in ETS unexposed nonsmokers, implies that the increase in risk relative to the totally unexposed group is greater as a result of ETS exposure than as a result of active smoking.

It has been argued that, as the mix of carcinogens in sidestream tobacco smoke is different from the mix in mainstream smoke inhaled during active smoking, it is not essential for the causality decision on ETS that active smoking causes breast cancer (Anderson et al., 2012; Miller, 2008). However, it still seems implausible that ETS exposure might have a greater effect on risk than active smoking. One reason is that exposure to smoke constituents is in general very much higher from smoking than from ETS. Another is that smokers are exposed to higher levels of ETS exposure than are nonsmokers, partly as they are more likely to mix with other smokers, and partly as they are exposed to ETS from their own cigarettes. To fit the observations one would have to argue that ETS exposure is carcinogenic to the breast, but smoking is anti-carcinogenic. *A priori* it seems more plausible to us that no true effects of smoking or ETS

exposure exist, with observed increases in risk associated with ETS seen in some analyses resulting from one or more of the biases possible in epidemiological studies.

While genetic differences in susceptibility to tobacco-induced cancers have been put forward as a possible reason for the observed results (Alberg et al., 2004; Anderson et al., 2012; Chuang et al., 2011; Conlon et al., 2010; Dossus et al., 2014; Johnson & Glantz, 2008; Luo et al., 2011; Mechanic et al., 2006; Sillanpää et al., 2005; Tang et al., 2013), we are unaware of any consistent evidence of an increased risk of ETS associated breast cancer in relation to any gene.

Consistency

The 45 estimates for the principal exposure index are significantly ($p < 0.001$) heterogeneous. Study type is a major source of the heterogeneity, with the RR for prospective studies not significantly elevated at 1.02 (95% CI 0.97–1.08) but clearly raised for case-control studies at 1.26 (1.13–1.41), the difference by study type being highly significant ($p < 0.001$). While heterogeneity for the case-control study RRs ($p < 0.001$) still remains, it is interesting to note that it is not evident for the prospective study RRs. Other sources of heterogeneity observed are by continent ($p < 0.01$) with RRs higher for Asia (1.21, 1.04–1.42) than for Europe (1.12, 0.98–1.27) or North America (1.12, 1.02–1.23), and by extent of adjustment for potential confounding variables ($p < 0.01$), with the RR higher for studies adjusting for fewer variables (1.19, 1.07–1.32) than for studies adjusting for more (1.07, 1.00–1.15).

As noted earlier, there is also inconsistency between results for different ETS exposure indices, with no evidence of an association for childhood or for workplace ETS exposure, but more evidence for ETS exposure indices involving multiple sources of exposure.

The US Surgeon General (2014) noted that, while the evidence ''is relatively consistent for a real effect of active smoking on risk for breast cancer'', it is ''less consistent for passive exposure to smoking, with marked differences between case-control and cohort studies and greater sensitivity to exclusions for design and analysis issues, sample size and extreme estimates''.

Assessment of ETS exposure and recall bias

In our previous review (Lee & Hamling, 2006), we noted that a number of case-control studies which asked very detailed lifetime ETS exposure histories had reported high RRs, and we suggested that these may be unusually open to recall bias. We noted that it seemed ''unlikely that anyone will actually have had no ETS exposure in their life, and because memory of low exposures is difficult and subjective, there must be concern about the accuracy of RR estimates that depend greatly on which subjects happen to be classified in this 'unexposed' reference group. If a relatively low level of actual ETS exposure is more likely to be reported by cases, perhaps in an effort to explain their disease, than by controls, such differential recall may cause substantial bias to the estimated effects of ETS.''

At that time there were hardly any prospective studies which collected detailed ETS exposure histories, but that is not the situation now. Interestingly, the analyses shown in Table 9 indicate that there is no material difference between RRs for studies using detailed ETS questions and for those that did not, and that this is so when prospective and case-control studies are considered separately.

While results from case-control studies which asked detailed exposure questions have been regarded by some (e.g. California Environmental Protection Agency, 2005; Johnson, 2005) as contributing greatly to the evidence, it is interesting to note the complete lack of association for prospective studies which asked detailed questions (RR 1.00, 95% CI 0.96–1.05).

As noted by Reynolds (2013), ''measurement error is a problem in all studies, and is likely a larger problem for secondhand smoking than for active smoking''. In this context it is worth pointing out that it is questionable whether in fact detailed questions which are reliant on accuracy of recall of lifetime exposure histories actually give more reliable answers than do simple questions likely to be quite accurately answered, though not incorporating all sources of exposure. While there is abundant evidence that asking whether the spouse smokes is associated with clearly elevated cotinine levels (e.g. Lee, 1999), such objective validation of exposure is not available for more complex measures.

Crucial to the opinions of the reviews is their opinion on the relevance of recall bias. It is clear that the authors of the California EPA and the Canadian Expert Group do not regard the elevated risks seen in case-control studies as materially affected by recall bias. Thus, Johnson (2005) notes that reviews of recall bias in studies of ETS and lung cancer, and ETS and heart disease ''have concluded that recall bias is unlikely to have had an important effect on those observed relationships'' and the California Environmental Protection Agency (2005) regard such bias as unlikely ''since a possible link of smoking or ETS to breast cancer is not commonly known to the public nor previously accepted by the scientific community''.

In contrast, other reviewers clearly regard recall bias as highly relevant. Thus, the US Surgeon General (2014) noted in 2014 that ''cohort studies are generally regarded as providing stronger evidence then case-control studies for causality because they satisfy the temporality criterion that the measurement of exposure precede the ascertainment of the outcome'', while the Oxford Group (Pirie et al., 2008) is more emphatic about the importance of recall bias. As noted in the introduction, they emphasize the lack of effect seen in prospective studies and consider that the results from the case-control studies may have been ''distorted'' by recall bias. They noted that the evidence for breast cancer following ETS exposure is similar to that for breast cancer following induced abortion, where no increased risk is seen when the data on induced abortion are collected before the cancer, but an increase is seen when they are collected afterwards. It is also interesting to note that the IARC (International Agency for Research on Cancer, 2012) included a discussion on recall bias giving reasons why case-control studies with the most complete information on lifetime exposure to ETS may be most susceptible to recall bias, pointing out that ''it is easier to report smoking by a parent or spouse than it is to remember exposure from other sources that possibly occurred many years ago in daily life''.

Can this discrepancy of views be resolved? Some of the individual publications have attempted to obtain information on the magnitude of recall bias. Two studies (Conlon et al., 2010; Morabia et al., 1996) have asked questions concerning worry about ETS exposure, but similarity of response in cases and controls does not exclude the possibility that, regardless of worry, the cases were readier to give full details of their ETS exposure, as the study may have been more important to them than to the controls.

The evidence of Johnson et al. (2000) relating to recall bias derives from the observation that ''when lung cancer risk was assessed using the same target control group, observed lung cancer risks associated with passive smoking were consistent with those in the lung cancer-passive smoking literature''. But the lung cancer RR of 1.2 had a very large variability, with a 95% CI of 0.7–2.1, and furthermore related to an exposure index ''6 or more years of adult residential exposure to passive smoking'' that did not involve all the recorded sources of ETS exposure.

Delfino et al. (2000) avoided recall bias by recruiting cases and controls from those with suspicious breast masses, and collecting questionnaire data prior to biopsy diagnosis. Although this approach excluded recall bias, and the study found no association of ETS with breast cancer, it is doubtful whether the controls are representative of the population at large.

Considered together, this evidence adds little to the debate about recall bias.

Dose–response relationship

Assessment of the existence of a dose–response relationship is made difficult by the lack of data from a number of studies, and by the heterogeneous nature of the results that are available. Corresponding to the 45 estimates for the principal ETS exposure index, dose–response data within ETS exposed subjects were available for only 20 studies. Three studies showed a statistically significant positive trend (Li et al., 2015; Liu et al., 2000; Tong et al., 2014). The study by Chilian-Herrera et al. (2010) reported a significant positive trend, but gave no further details, not making it clear if the trend had been calculated within the exposed groups only. No significant trend was seen in the remaining 16 studies. Among the 15 which provided RRs by level of exposure, the RRs tended to increase with increasing exposure in nine, to decrease in five, and to show no relationship in one.

There appears to be more evidence of a dose response for total exposure. However, some trends reported as significant in the source publications (e.g. Morabia et al., 1996; Reynolds et al., 2009) are based on data including the unexposed group, with RRs similar in the ETS exposed groups. Our Table 7 identifies only three studies as reporting a significant dose response within the exposed groups. One is Chilian-Herrera et al. (2010), as noted above, and another is Johnson et al. (2000), which found a trend only in premenopausal women. The third is Zhu et al. (2006), which actually provided insufficient data to formally calculate the trend within the exposed groups,

Overall, it is not apparent that consideration of dose–response data, which the 2014 report by the US Surgeon General (2014) regards as ''not definitive'', adds to the case for or against ETS exposure as a possible cause of breast cancer.

Misclassification of the subject's smoking status

Misclassification of the subject's smoking may be a relevant biasing factor in studies of ETS and lung cancer (Lee et al., 2001) because lung cancer risk is markedly increased in smokers. However, inclusion in ETS and breast cancer studies of a few true smokers with a possibly slightly increased risk of breast cancer should have little or no biasing effect. This is not mentioned as a relevant issue in any of the reviews.

Confounding

Although (see supplementary item 1) the majority of studies have adjusted for an extensive list of potential confounding variables, not all did so. We therefore investigated confounding by comparing RR estimates for the principal index of ETS exposure in studies which had adjusted for an above average and below average number of variables. This showed weaker evidence of an association ($p < 0.01$) in studies that adjusted for age plus nine variables or more (RR 1.07, 95% CI 1.00–1.15), than for studies that adjusted for eight variables or fewer (1.19, 1.07–1.32). Although this may suggest that the association may have arisen partly due to limited attention to confounding in some studies, this inference is not straightforward. The studies that adjusted for nine variables or more included all the six large prospective studies (Dossus et al., 2014; Luo et al., 2011; Pirie et al., 2008; Reynolds et al., 2009; Wartenberg et al., 2000; Xue et al., 2011) that found no association of ETS exposure with breast cancer risk, and which together contributed over 60% of the total weight (inverse variance) of the meta-analysis.

We also investigated the effect of adjustment in specific studies, by comparing most- and least-adjusted RR estimates for the principal exposure index, with the estimated ratio indicating no significant systematic difference. However this was based on pairs of estimates from only eight studies.

Overall, the evidence does not suggest any very important role of uncontrolled confounding, and none of the reviews refer to this as a major issue.

Publication bias

We investigated publication bias formally by a standard test (Egger et al., 1997). The results showed some evidence of such bias, consistent with smaller studies finding no association of ETS with breast cancer being less likely to publish their findings. The effect that this would have on the overall association is difficult to assess reliably. Among other things, one should realize that there exist some large prospective studies (e.g. Cancer Prevention Study I) which have reported results relating ETS to other diseases (e.g. Garfinkel, 1981) but not for breast cancer risk.

Risk by menopausal status

Of the 23 studies allowing comparison of risks associated with ETS exposure in premenopausal and postmenopausal women, 16 were case-control studies, five were prospective studies and two were case-control studies nested in

prospective studies. In the case-control studies menopausal status was as at time of interview, following the diagnosis of the cases, whilst in the prospective studies it was generally at the time of the baseline interview, before follow-up for cancer. In one of the nested studies, Alberg et al. (2004), appears to relate menopausal status to the time of diagnosis of breast cancer. The abstract by Woo et al. (2000) does not make the position clear for the other nested study. Given the length of follow-up was 10 years or more in three prospective studies (Hanaoka et al., 2005; Rosenberg et al., 2013; Wada et al., 2015), some of the women would have reached the menopause between interview and breast cancer diagnosis, so the results from the two types of study are not completely comparable. This problem is less so for Pirie et al. (2008), where follow-up was only for 3.5 years. For the other prospective study we preferred to use the results reported by age at diagnosis (<50, ≥50 years) published by Reynolds et al. (2006), rather than other results (Reynolds et al., 2004, 2009) based on menopausal status at baseline.

Many of the women who were postmenopausal at the time of cancer onset would have been exposed premenopausally to ETS. Given the latent period of cancer, it seems difficult to explain why, if there indeed is a true effect premenopausally, there would not be some corresponding effect postmenopausally. It remains unclear why (see Table 10) some studies, but not others, should report an increased risk of breast cancer in premenopausal but not postmenopausal women, and how, if there is indeed a true effect, this relates to time of exposure and time of onset. Any proposed relationship needs to fit in with the observed lack of association of breast cancer with ETS exposure in childhood.

Discussing the evidence, the US Surgeon General (2014) noted in 2014 that recent studies have reduced the estimated strength of the relationship of ETS exposure to breast cancer risk in premenopausal women, but ''nonetheless, the difference in risk between premenopausal and postmenopausal women remains''. They remarked that ''it is difficult to ascertain'' why the association with passive smoking in premenopausal women should be greater than that for active smoking. They also pointed out that the results from cohort studies do not show an association with passive smoking, and that results ''do not support the hypothesis'' that passive exposure has ''greater carcinogenic effects during periods when breast tissues are less differentiated and more susceptible'', noting that ''results for exposure to passive smoking during childhood were generally null, regardless of study design''.

Commenting on the results of their meta-analyses by menopausal status, Pirie et al. (2008) noted that ''The fact that active smoking has little effect on either pre- or post-menopausal women ..... makes it implausible that pre-menopausal women would be especially sensitive to passive exposure'', and that, while the finding of an apparent protective effect of passive smoking in premenopausal women in the Million Women study ''does not provide good evidence of a real protective effect, it does provide prospective evidence against the view that passive smoking increases the risk of breast cancer in pre-menopausal women and, perhaps more importantly, it illustrates the statistical unreliability of such subgroup analyses''. Presumably, this conclusion was reached because of the marginally significant nature of the RR of 0.54 (95% CI 0.30–0.99) and the number of subgroup analyses considered.

Conclusions

Given the weak association of active smoking with breast cancer, and the considerably lower exposure to smoke constituents provided by ETS exposure, and given the general problems in detecting small effects in epidemiological studies, it is clearly extremely difficult to reliably determine any true effect of ETS exposure on risk of breast cancer. While the overall evidence suggests an association with some indices of ETS exposure, particularly in premenopausal women, the fact that this association is mainly only seen in case-control studies suggests that recall bias is likely to have been an important contributor to the association. In prospective studies, there is no evidence of an increased risk associated with our principal index ''spouse ever smoked or nearest equivalent'', regardless of whether detailed questions were asked on ETS exposure. Nor was there any significant association, in prospective studies, with other indices, including spousal, at home, workplace or childhood ETS exposure, or in postmenopausal women. A weak, but significant, association with overall ETS exposure was seen.

Overall, we consider that the available evidence that ETS exposure can cause breast cancer, though to some extent suggestive, is clearly not definitive. In particular, the evidence of an association seen in case-control studies is subject to criticism regarding possible recall bias. Additional evidence is required, particularly from large prospective studies with data on ETS exposure collected at regular intervals, and validated by objective markers (such as cotinine) and by informants other than the subject.

Post script

At a late stage, one of the reviewers cited a recent abstract White et al. (2016) which described the results of a prospective study reporting an increased RR of 1.18 (95% CI 1.02–1.38) in nonsmoking women exposed to ETS throughout their childhood, relative to those without any childhood ETS. Though we have not attempted to update our original searches (conducted up to June 2015) to include this and any other very recent studies, we do note that adding in this result to the meta-analyses of childhood exposure in Table 8 would have had very little effect, increasing the random-effects RR for all studies from 1.00 (0.95–1.06) to 1.01 (0.96–1.06), and that for prospective studies from 0.98 (0.92–1.04) to 0.99 (0.93–1.05).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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