EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND BREAST CANCER

A Review With Meta-Analyses

Executive Summary

Results of 41 studies relating breast cancer in women to ETS exposure in nonsmokers have been published. This document presents a comprehensive review of the evidence, with meta-analysis.

The studies varied in design and in the ETS exposure indices used. Based on a single estimate from each of the 39 studies that provided relative risk estimates for exposure compared with no or little exposure, and selecting the index of exposure most nearly equivalent to ever smoking by the spouse or partner, random-effects meta-analysis gave an overall estimate of 1.13 (95% CI 1.05-1.21). However, the 39 estimates were significantly ($p<0.001$) heterogeneous, with estimates close to 1.00 for prospective studies, larger studies (>500 cases) and studies taking more confounding variables than average into account, significantly elevated in case-control studies (1.26, 1.11-1.44), in those studies that had taken fewer confounding variables than average into account (1.16, 1.04-1.30) and in North American studies (1.12, 1.02-1.23), and non-significantly raised in European studies (1.11, 0.97-1.26), Asian studies (1.16, 0.92-1.47) and in smaller studies (1.19, 0.998-1.41). In those studies providing relevant data, there was no evidence of an association in postmenopausal women, but some increase in premenopausal women (1.43, 1.17-1.75).

Evidence of a dose-response relationship was similarly heterogeneous, with significant trends reported in a few studies contrasting with a lack of relationship reported in other studies.

There was no evidence of an association at all for childhood ETS exposure, and the increased relative risk estimate was not significant using indices based specifically on exposure from the spouse, in the workplace or from the spouse or

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other cohabitant. However for those 19 studies that provided estimates relating to total exposure, based on a detailed questionnaire that asked (at least) about at-home exposure in childhood and in adulthood and about workplace exposure, it was notable that the relative risk estimate was slightly higher (1.15, 1.06-1.24).

Detailed examination of the evidence suggested that where associations were seen, the elevated risk estimate derived mainly from those case-control studies that asked very detailed questions about ETS exposure and depend heavily on the accuracy of the reported answers. Estimates expressed relative to a totally unexposed baseline are highly dependent on which subjects happen to get classified in the baseline group, and may well be unusually subject to recall bias. Results from more large prospective studies involving very detailed ETS exposure indices would aid interpretation.

Also relevant to interpretation of the data are weaknesses inherent in a number of studies and the possibilities of publication bias and uncontrolled confounding.

Overall, in view of the inherent implausibility that ETS exposure might cause breast cancer, given the virtually identical risks in smokers and nonsmokers, and the doubts about the reliability of estimates from case-control studies involving extremely detailed questionnaires on ETS exposure, one cannot conclude that ETS exposure has actually been shown to increase the risk of breast cancer in nonsmokers.

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1. Introduction

A collaborative re-analysis by the Oxford Group[1] of individual data on alcohol, tobacco and breast cancer from 53 epidemiological studies concluded that smoking has little or no independent effect on the risk of developing breast cancer. Paradoxically, in view of this conclusion, a number of epidemiological studies have suggested a possible increase in risk in lifelong nonsmokers associated with exposure to environmental tobacco smoke [ETS] exposure[2,3], though this seems to have been contradicted by large US prospective studies[4-6] showing little or no relationship.

This review, which is an update to reviews conducted in 2005[7], 2006[8], 2008[9], 2010[10] and 2012[11], attempts to assess the available evidence to date. We restrict attention to epidemiological studies of breast cancer in which the relationship of mortality or incidence to one or more indices of ETS exposure has been studied in lifelong nonsmokers. This requirement means that some studies which might at first have seemed relevant[12-21] have been excluded from consideration.

We also comment briefly on similar reviews by Johnson[22], the California EPA[23], the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk[24] and the US Surgeon General[25].

2. Methods

In April 2014, publications describing the results of epidemiological studies relating the risk of breast cancer in nonsmoking women to ETS exposure, that were not included in our previous reviews[7-11], were sought from MEDLINE searches (using search terms "cancer", "passive smoking", "environmental tobacco smoke" and "involuntary smoking" and the date range 2011 to April 2014), from the extensive files on smoking and health accumulated by P N Lee Statistics Computing Ltd (PNLSC), and from reference lists of papers retrieved. Studies with serious weaknesses[26] would have been excluded, but none were found.

From these publications, details were extracted of the study location and design and of the potential confounding variables considered. Where available, estimates of the relative risk (RR)[*], together with their associated 95% confidence interval (CI), were obtained relating to ETS exposure at home, at work, in adulthood, in childhood and in life. For a given exposure, the RR adjusted for the greatest number of potential confounding variables was selected for analysis. Where RRs were only presented by subgroup (e.g. premenopausal and postmenopausal women), estimates for the total population were combined by fixed-effect meta-analysis[27], though the results for the subgroups were also considered. Where adjusted results were given only by level of exposure, RRs and CIs for overall exposure were estimated[28,29] (if enough details were given of the study to make this possible), because differences in the metrics used in different studies made dose-response data not readily combinable over study. For a given source of exposure, RRs were obtained, where possible, comparing women exposed and unexposed to that source. Exceptions to this, where the reference group may include women with a low exposure to the source, are noted in the tables. RRs were also extracted by subgroup, where available.

Fixed-effect and random-effects meta-analyses were conducted using standard methods[27]. For a "principal" meta-analysis, one result was selected from each study for which an estimate of risk of exposure (versus no or minimal exposure from that

[*] Note that in this review, the term "relative risk" is taken to include not only direct estimates of the RR from prospective studies, but also indirect estimates (odds ratios) from cross-sectional studies.

source) was provided or could be estimated. The selection was based firstly on source of exposure (spouse highest preference, then partner, cohabitant, home or work) and secondly on time of exposure (for spouse or partner preferring ever to current, and, for other types of exposures, adulthood to ever in life). This was intended to produce an index that was most closely equivalent to "spouse ever smoked". Spousal smoking is the index traditionally used for studying effects of ETS exposure, for example for lung cancer[30,31], as it has been clearly demonstrated that women married to a smoker have a markedly higher ETS exposure, as judged by cotinine, than women married to a nonsmoker[32]. Other endpoints used in meta-analyses are discussed later. One study[33], reported only as an abstract, could not be included in the principal meta-analysis because too little detail is given to allow the results (given by hours per day of exposure) to be combined into an estimate for overall exposure.

3. Results

3.1. The studies

The studies are identified by the first author of the principal publication, with the two studies by Lash and Aschengrau[34,35] identified as Lash I and Lash II. As shown in Table 1, two of the studies were published in the 1980s, four in the 1990s, 27 between the years 2000 and 2009, and eight since then. This reflects a massive upsurge of interest in studying the possibility that ETS might cause breast cancer. Four studies[33,36-38] were published only as abstracts. One "study"[39] is actually a combination of the results of two studies conducted in Canada, one of which has already been reported extensively elsewhere[40], although based on differing exposure indices, while the other has not been previously reported. Due to the overlap, and the more appropriate exposure index already reported, its results were not included in the principal meta-analysis, although it is included in Table 1 and referred to in relevant results tables.

Of the 41 studies, 21 have been conducted in North or Central America (16 in the USA, four in Canada, one in Mexico), 10 in Asia (four each in Japan and China, one in Korea and one in Sri Lanka) and 10 in Europe (three in the UK, one each in Switzerland, the Netherlands, Germany, Norway/Sweden, Finland and Poland and one in 10 European countries).

Thirteen of the studies were of prospective design, with follow-up varying from 3.5 to 24 years. The majority of these studies were of breast cancer onset, but the Hirayama and Wartenberg studies[4,41] were of breast cancer mortality, based on death certificates. The Woo and Alberg studies[37,42] were case-control studies nested within prospective studies of incident breast cancer. The remaining 26 studies were of case-control design, mainly using population controls. However, the Sandler study[43] used friends of cases or controls, which are not necessarily representative of the population, and three used hospital-based controls, the Delfino study[44] using benign breast disease patients, and the Liu and Tang studies[45,46] patients without cancer. Most of the case-control studies collected the information directly from the subject herself, but the Lash I and Lash II studies[34,35] used proxy interviews for deceased cases and their matched controls. The Smith study[47] had an upper age limit

of 36 years for cases, and the Roddam study[48] an upper age limit of 45. Two studies[49,50] had an age limit of 50 years and two[36,45] had a limit of 54 or 55 years. The remaining case-control studies included older women.

A variety of ETS exposure indices were studied. In the Hirayama and Jee studies[41,51], both conducted in Asia, in the Alberg study[42] in the US, and in the Roddam study[48] in the UK only exposure from the spouse/partner was studied. An additional 10 studies[34,35,37,43,44,50,52-55] restricted attention to at-home exposure. The other 27 studies collected information on more extensive sources of exposure, individually and/or totally.

Results were mainly reported for all breast cancer cases combined, but three studies[53,56,57] reported some results by hormone receptor status of the cases. One of these[53] also reported results separately for *in situ* and invasive cases, while another[57] presented results separated by histological subtype.

Twenty-eight of the 41 studies presented results not only for the whole population of nonsmokers studied, but also for subgroups of the population. Most commonly (21 studies), this was for subgroups defined by menopausal status, but seven studies gave results by age (or age of husband) and 13 studies gave results by genetic status.

While many studies presented results comparing women exposed or unexposed to the source of interest, some studies required a minimum level of exposure to count as exposure. For example, in three studies[49,56,58] exposure had to be for at least 1 hour/day for a year, and in another study[46] subjects had to be exposed to passive smoking for at least 15 minutes/day for a year, while in the Young study[39] exposure had to be for at least 2 hours/day. In the Johnson study[59] the women had to be in the presence, specifically, of regular smokers. The Rookus study[36] defined exposure as "exposed daily to the smoke of home-mates or colleagues during at least 20 years or if someone smoked daily in their bedroom during more than one year." The Chilian-Herrera study[38] presented results for "t3 vs. t1", without giving any further explanation of the groupings used although it was stated that the reference group consisted of never active smokers with no history of passive smoke exposure.

Table 2 lists the potential confounding variables adjusted for in analysis. The studies by Rookus, Woo, Zhu and Chilian-Herrera[33,36-38] published only as abstracts did not make it particularly clear which variables had been adjusted for. In one study[60] the only usable results presented were not adjusted for any potential confounders. Of the other 32 studies, all had adjusted for age, except for the Hirayama study[41], which adjusted for age of the husband, and the De Silva study[61]. The Hirayama, Sandler and Young studies[39,41,43] adjusted for no other variables, but the rest adjusted for between two and 16 variables. Apart from age, there were a number of variables that were adjusted for in at least 10 studies, including 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 (BMI, or other similar indices of obesity), physical activity, education (or socio-economic status) and hormone use. These are all well known risk factors for breast cancer[62,63]. Other less commonly considered variables included aspects of diet and breastfeeding.

3.2. Relative risk estimates and meta-analyses

Tables 3-6 give RRs (with CIs) for, in turn, ETS exposure from the spouse or at home; other sources of ETS exposure in adulthood; ETS exposure in childhood; and total lifetime ETS exposure. Table 7 gives results by subgroups of the data. Table 8 gives the results of various meta-analyses.

The results for indices of ETS exposure at home, shown in Table 3, are based on 30 studies. Statistically significantly increased ($p<0.05$) RRs and/or dose-related trends were seen in four studies[34,45,46,56]. In one study[64], a significantly reduced risk of breast cancer was reported in association with past exposure to cohabitant's smoking.

Eleven of these studies presented results specifically for exposure from the spouse (or partner in the Smith[47], Roddam[48] and Pirie[55] studies). Combining these estimates (and selecting the result for spouse ever smoked for the Wartenberg study[4]) gives, as shown in Table 8, a fixed-effect meta-analysis estimate of 1.05 (0.97-1.14), which is not statistically significant ($p\geq0.05$). There is some evidence of heterogeneity ($p<0.05$), due mainly to the high RR estimate of 3.1 in the Morabia

study[56] and the low RR estimate of 0.58 in the Nishino study[52]. When random-effects meta-analysis is carried out, the RR estimate is slightly increased, to 1.10, but remains non-significant (95% CI 0.95-1.27).

Based on the first RR cited in Table 3 for those studies where multiple estimates are available, the fixed-effect meta-analysis estimate for exposure at home is 1.03 (0.995-1.07) while the random-effects estimate is 1.06 (0.998-1.12). Again, the high estimate from the Morabia study[56] is the largest contributor to the significant ($p<0.01$) heterogeneity.

The results shown in Table 4 for other sources of ETS exposure in adulthood are based on 18 studies. Fifteen studies gave results for workplace exposure (or not-home exposure), with the Liu and Shrubsole studies[45,65] showing significant RRs and/or trends. In addition, the Xue study[66] reported a significantly negative dose-response. The 14 estimates for workplace exposure are heterogeneous ($p<0.05$), with the low estimates of 0.8 (0.6-1.0) from the Wartenberg study[4], 0.80 (0.64-1.01) from the Bonner study[67] and 0.80 (0.49-1.32) from the Rollison study[68] contrasting with estimates around or above 1.0 from the other studies. No significant overall effect is seen, whether fixed-effect or random-effects meta-analysis is used (see Table 8).

Table 4 also gives RRs from 12 studies for either any adult exposure or for home or workplace exposure. Significantly increased RRs are seen in the Johnson, Kropp and Tang studies[46,49,59], and the overall estimates of risk are also elevated, with both the fixed-effect estimate (1.07, 1.02-1.12) and the random-effects estimate (1.10, 1.02-1.18) reaching statistical significance. There was significant heterogeneity between the results ($p<0.01$), which ranged from 0.86 (0.57-1.31) in the Ahern study[69] to 2.52 (0.87-7.31) in the Smith study[47].

The results for childhood exposure shown in Table 5 are from 18 studies. Most of the RRs are quite close to 1.00 and none are significantly increased, although the Liu study[45] did report a significant positive trend. However, the Xue study[66] reported a significantly negative association with exposure to smoking by the mother, but not the father. Based on the first RR cited in Table 5 for those studies where multiple estimates are available, the estimates show no significant heterogeneity and

give a fixed-effects estimate of 0.99 (0.96-1.03) and a random-effects estimate of 1.00 (0.95-1.06).

Table 6 presents results from 20 studies for an index of total lifetime exposure, nine[36,38,49,55,58-60,68,70] based on questions restricted to home and work, and 11[33,39,47,56,57,61,69,71-74] based on a wider definition. Significant increases and/or dose-related positive trends were seen in the Morabia, Johnson, Kropp, Reynolds, Chilian-Herrera, De Silva and Dossus studies[38,49,56,59,61,73,74]. One study reported only as an abstract[33] found a dose-related positive trend but gives insufficient detail to quote an overall relative risk. Though the 19 RR estimates in Table 6 were significantly ($p<0.001$) heterogeneous, 15 of the estimates were above 1, and significant overall estimates were seen using either fixed-effect (1.09, 1.04-1.14) or random-effects (1.15, 1.06-1.24) meta-analysis.

For some studies, the footnotes of Tables 3, 5 and 6 summarize additional results by time of exposure, by type of case or by product smoked. Generally, there was no evidence of significant variation by any of these factors. The only exception was in Table 3 for the Lash II study[35], where a significant variation in risk according to whether time of first exposure was before or after first pregnancy was due to a reduced RR in the latter group.

Table 7 presents RRs by subgroup. Of the 21 studies that reported results separately for premenopausal and postmenopausal women, the studies by Sandler, Woo and Hanaoka[37,71,75] reported RRs that were significantly higher in premenopausal than postmenopausal women, indeed finding no increase at all for postmenopausal women. In the Delfino, Johnson and Alberg studies[42,44,59] a similar pattern was seen, but the variation by menopausal status was not significant. In the study by Chilian-Herrera[38] the relative risks for both pre and postmenopausal women were significantly increased, but the risk in premenopausal women was much higher. In the study by Pirie[55], the RR for premenopausal women was significantly decreased, while no association was seen for peri- or postmenopausal women. The remaining studies showed no evidence of variation in risk according to menopausal status.

As shown in Table 8, the 19 studies that presented actual RR estimates by menopausal status provided no real indication of an effect of ETS on breast cancer risk in postmenopausal women. ETS exposure was, however, associated with a significant increase in risk in premenopausal women. There was significant heterogeneity ($p<0.001$) and the random-effects estimate (1.43, 1.17-1.75) was higher than the fixed-effect estimate (1.25, 1.13-1.39). The evidence for an increase in premenopausal, but not postmenopausal, women was supported by a significant elevation in the pre/post ratio of RRs, with the random-effects estimate 1.27 (1.06-1.52). The random-effects estimate for premenopausal women was little changed, to 1.45 (1.20-1.76), if RRs for two additional case-control studies of young women[47,49] were included, on the basis that all, or virtually all, of the women would have been premenopausal. (We have not included results for age <50 years from two prospective studies[4,41] as these relate to age at baseline and many of the cases of breast cancer would have occurred in postmenopausal women.)

Generally, the results in Table 7 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 subgroup other than menopausal status. Significant variation (at $p<0.05$) was only noted in the Zhu study[33] by use of oral contraceptives and by use of other female hormones, and in the Gammon study[53] by BMI, where the variation was not systematic and may well be due to chance, and in the Anderson study[40] for the CYP2E1 genotype in postmenopausal women exposed to passive smoke as a teenager.

3.3. Principal meta-analysis

As described in the methods section, a principal meta-analysis was carried out using one estimate from each of the 39 studies that provided relative risk estimates for exposure compared with no or little exposure from that source, choosing the estimate which was most equivalent to the classic exposure index of "spouse ever smoked". The estimates used included all 30 RRs considered in the meta-analysis of spouse or cohabitant exposure (Table 3), together with the RRs from the Johnson study[59], the Kropp study[49] and the Ahern study[69] shown in Table 4, and from the Rookus study[36], the Sillanpaa study[70], the Slattery study[72], the Chilian-Herrera study[38], the Conlon

study[60] and the De Silva study[61] shown in Table 6. They are marked with an "m" in the notes column of these three tables.

Overall, these 39 studies give a fixed-effect estimate of 1.05 (1.02-1.09) which just reaches statistical significance. There is highly significant ($p<0.001$) heterogeneity, the largest contributions being from the high RRs in the Morabia study[56], the Kropp study[49], the De Silva study[61], the Tang study[46], and particularly the Chilian-Herrera study[38]. As a result, the random-effects estimate is slightly higher (1.13, 1.05-1.21), and is also statistically significant.

In an attempt to study possible sources of heterogeneity, risks were compared by four factors: study type, continent, study size and degree of adjustment for confounding.

Study type : The 14 prospective studies provide no evidence of an effect, with no significant heterogeneity, and individual estimates varying from 0.58 to 1.32. In contrast, the 25 case-control studies do show an association, with both the fixed-effect estimate (1.16, 1.09-1.23) and the random-effects estimate (1.26, 1.11-1.44) being statistically significant. The estimates for the case-control studies are significantly heterogeneous ($p<0.001$).

Continent : The results from the 20 North American studies (including the Mexican study by Chilian-Herrera[38] as this was conducted in US border states) show significant heterogeneity ($p <0.001$) with the fixed-effect estimate (1.04, 0.995-1.08) being close to 1, while the random-effects estimate (1.12, 1.02-1.23) is higher and statistically significant. The results from the 10 European studies show a similar pattern, with the fixed-effect estimate being close to 1 (1.05, 0.99-1.12), and the random-effects model being higher (1.11, 0.97-1.26). Again, there is significant heterogeneity between the estimates ($p<0.01$). The estimates from the nine Asian studies are also significantly heterogeneous ($p<0.001$), but show no increase in risk for the random-effects model compared to the fixed-effect estimate (fixed-effect: 1.15, 1.03-1.29, random-effects: 1.16, 0.92-1.47). The heterogeneity between continents is not statistically significant.

Study size : The results from the 16 largest studies, involving over 500 cases, show no evidence of heterogeneity and combined risk estimates of 1.03 (0.99-1.07) for the fixed-effect estimate and 1.04 (0.99-1.09) for the random effects estimate. In contrast, the 20 smaller studies show significant ($p<0.001$) heterogeneity and an increase which just fails to reach statistical significance, whether fixed-effect (1.10, 0.995-1.21) or random-effects (1.19, 0.998-1.41) estimates are considered.

Adjustment for confounding : Studies were divided, approximately equally, into those that had adjusted for nine or more potential confounding variables other than age and those that had adjusted for eight or fewer. In both groups, there is significant heterogeneity. In the 17 studies that had adjusted for nine or more potential confounding variables, there was no significant evidence of an association of ETS with breast cancer (fixed-effect 1.01, 0.98-1.05, random-effects 1.03, 0.96-1.11) but, in the group that had adjusted for eight or fewer, there was a significant relationship (fixed-effect 1.13, 1.05-1.22, random-effects 1.16, 1.04-1.30). The lack of significant association in the studies that adjusted for a greater number of potential confounding variables remained evident when alternative cut points of 5 or more, 7 or more or 11 or more were used rather than 9 or more (data not shown).

4. Discussion

Based on 39 estimates of the risk of breast cancer associated with ever having a husband who smoked, or the nearest equivalent ETS exposure index available, random-effects meta-analysis gave a significantly increased RR estimate of 1.13 (1.05-1.21). In assessing this association in terms of a causal relationship, various issues have to be taken into account, which are discussed in the sections that follow.

4.1. Selection of studies for inclusion

Attention has been restricted to studies of lifelong nonsmokers, which is traditional in studies of ETS[23,76]. This is because it is likely to be extremely difficult to detect reliably any ETS effect on a smoking-associated disease in the presence of a history of smoking, partly since the total extent of a smoker's exposure to smoke constituents will be dominated by his own smoking habits, and partly since any errors in assessing active smoking history are likely to cause a residual confounding effect substantially larger than any possible effect of ETS.

None of the studies had serious weaknesses, as defined by Lee[26]. However, as discussed later, many of the studies had less serious weaknesses. As is usual in such meta-analyses, we did not attempt to exclude any of the studies on this basis because the assessment of such weaknesses is subjective and therefore open to criticism.

4.2. Plausibility

In a review by the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk[24], it was concluded that "the relationships between active smoking and both pre- and post-menopausal breast cancer are consistent with causality", as is the relationship between ETS and breast cancer in younger, primarily premenopausal women. One possible reason given for the similarity in risks associated with active smoking and ETS exposure was the relative difference in anti-oestrogenic effects between the two sources of tobacco exposure, whereby the anti-oestrogenic 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. Elsewhere, genetic differences in susceptibility to tobacco-induced cancers have been put forward as a possible reason for the observed results[40,42,46,54,57,60,70,74,77,78].

In contrast, some authoritative reviews have failed to conclude that there is a demonstrated effect of active smoking or ETS exposure on breast cancer risk. Thus, in 2004, IARC[76] concluded that there is evidence suggesting a lack of carcinogenicity of tobacco smoking for female breast cancer[76], noting a combined analysis[1] from 53 studies which showed that a weak association can be explained by confounding by alcohol consumption. And the same year the US Surgeon General[79] also concluded that the evidence is "suggestive of no causal relationship," despite referring to studies indicating that mutagenic tobacco smoke components reach breast tissue and that DNA adducts characteristic of cigarette smoke can be detected in breast tumours from women who smoke. Though, in 2014, the US Surgeon General[25] 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 no effect on breast cancer risk, is it plausible that ETS exposure might have a true effect on the risk? In considering this question, one must realise that the denominators are not the same in the two relative risk calculations, with the risk in smokers compared to that in all nonsmokers, whether ETS exposed or not. To see what effect this might have, assume that among the nonsmokers a proportion p are unexposed to ETS and have a risk of 1 unit, while a proportion $1-p$ are exposed and have a risk of E units. The nonsmokers as a whole, therefore, have an average risk of $p + (1-p)E$ units. Let us also suppose that smokers, relative to the totally unexposed group, have a true risk of S units. The observation that the risk is the same in smokers as in all nonsmokers therefore implies that $S = p + (1-p)E$, and hence that the risk from smoking is less than that from ETS exposure, with approximate equality being obtained only if p is small. Thus 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 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[40,80]. However, there are two main reasons why it seems implausible that ETS exposure might have a greater effect on risk than active smoking. One is that exposure to smoke constituents is in general very much higher from smoking than from ETS. For example, cotinine levels are typically some hundreds of times higher in active smokers[32]. Even though, for some smoke constituents, concentrations in sidestream smoke substantially exceed concentrations in mainstream smoke, nonsmokers are not exposed to neat sidestream, but to smoke that has been considerably diluted and has aged. The second main reason is that smokers are exposed to higher levels of ETS exposure than are nonsmokers, not only because they are more likely to mix with other smokers, but also because 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 that smoking is anti-carcinogenic. While one can speculate that protective anti-oestrogenic effects operate only in smokers, it seems implausible that positive and negative effects of smoking should neatly balance out to end up with smoker/nonsmoker relative risks so close to 1. *A priori* it seems more plausible that no true effects of smoking or ETS exposure exist, with observed increases in risk associated with ETS in some analyses due to one or more of the biases possible in epidemiological studies.

4.3. Consistency

The 39 estimates are significantly ($p<0.001$) heterogeneous. Risk estimates (random-effects) are close to 1.00 for prospective studies, for larger studies (>500 cases) and for studies that had taken more confounding variables than average into account. Conversely, risk estimates are significantly elevated in case-control studies (random-effects RR 1.26, 1.11-1.44), in studies that had taken fewer confounding variables than average into account (1.16, 1.04-1.30), and in North American studies (1.12, 1.02-1.23), and are non-significantly raised in European studies (1.11, 0.97-1.26), in Asian studies (1.16, 0.92-1.47) and in smaller studies (1.19, 0.998-1.41).

It is also notable that in those 19 studies which provided separate estimates, there is evidence of an association in premenopausal women (1.43, 1.17-1.75) but not in postmenopausal women.

Although there is no evidence of any association for childhood or for workplace ETS exposure, there is more evidence of an association for ETS exposure indices involving multiple sources of exposure. Indeed 19 studies provided estimates relating to total exposure based on a questionnaire that asked (at least) about at-home exposure in childhood and in adulthood and about workplace exposure, and these studies produce a relatively high random-effects estimate of 1.15 (1.06-1.24). Also, as shown by additional analysis, there was a relatively high random-effects estimate of 1.18 (1.06-1.33) when the principal meta-analysis was restricted to those 20 studies that had collected information on ETS exposure from multiple sources (home, work and childhood).

4.4. Assessment of ETS exposure

All these variabilities are clearly not independent, and it appears that many arise because of relatively high RR estimates in some case-control studies which asked very detailed lifetime ETS exposure histories[36,38,47,49,56,59,61].

The question arises as to whether one should draw inferences based on analyses involving single sources of ETS exposure (such as the spouse or the workplace) or on analyses involving overall exposure from multiple sources. The arguments for and against are not straightforward. Asking a subject whether their spouse smoked during their marriage has the advantage of being easy to understand, and quite likely to be answered accurately. This is supported by substantial evidence that marriage to a smoker (and working with a smoker) are associated with increased overall ETS exposure, as judged by levels of cotinine in blood, urine or saliva[32]. Marriage to a smoker has also had a long history of use in studies of ETS and other diseases, notably lung cancer (e.g.[81]). However, it is in theory possible that studies based on a limited assessment of ETS may lack the power to detect any true effect that studies based on a more detailed assessment would have. This may be particularly true for childhood exposure where comparing subjects who were and

were not exposed in childhood includes those with varying amounts of adult ETS exposure in both numerator and denominator.

In principle, analyses based on a more complete assessment of ETS should have higher power to detect any true effect than do studies based on a less complete assessment, and for this reason use of an index based on total ETS exposure seems attractive. However, the advantage of such an index would depend on its validity as a marker. Some case-control studies have asked very detailed questions about multiple sources of ETS over the whole of the subject's lifetime, and analyses have been conducted using those with no reported exposure at all or with exposure above some low cut-off point as the comparison group. Because it seems 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. It is notable that of those studies that report risk estimates relating to a total estimate of ETS exposure (in Table 6), it was only the case-control studies that showed evidence of an increase.

4.5. 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 39 estimates for the principal ETS exposure index, dose-response data were available for only 18 studies. No significant trend was seen in 15 of these, with estimates close to unity for all levels of the dose-response metrics considered in seven of them: the Wartenberg, Lash II, Gammon, Shrubsole, Roddam, Chuang and Xue studies[4,35,48,53,65,66,78]. Only three studies showed a statistically significant trend (all calculated including the unexposed group). Of these Liu[45] showed a response that clearly increased within the exposed groups, but the Morabia study[56] did not, the relative risk estimates being similar, 3.1 and 3.2, for 1-50 and >50 hours/day-years ETS exposure from the spouse, the trend being significant because the risk in the exposed group as a whole was elevated. In the

Chilian-Herrera study[38] no explanation of the groupings used was given, nor were all of the risk estimates, although a significantly positive trend was reported. It is clear that a dose-response relationship has not been demonstrated for this exposure index.

There seems rather more evidence of a dose-response for total exposure (see Table 6), with significant positive trends reported in the Morabia, Johnson, Kropp, Zhu, and Reynolds studies[33,49,59,73,82], in addition to the Chilian-Herrera study[38] discussed above. However, the first three of these are the same studies that report a significantly increased RR and the same reservations about recall bias apply, and the Zhu study[33] is reported only as an abstract so no detailed comment can be made. Finally, in the Reynolds study[73], although the trends are reported as being positive, in reality all of the risk estimates are very similar for the different exposure groups considered.

Overall, it is not apparent that consideration of dose-response data adds to the case against ETS exposure as a possible cause of breast cancer.

We now consider potential sources of bias other than recall bias:

4.6. Misclassification of the subject's smoking status

Misclassification of the subject's smoking status may be a relevant biasing factor in studies of ETS and lung cancer[83], as lung cancer risk is very much higher in smokers than nonsmokers. Here it is doubtful whether breast cancer risk is increased by smoking at all[1] and, even if it is, the inclusion, in the self-reported nonsmokers, of a few true smokers with a slightly increased risk of breast cancer will have little or no biasing effect.

4.7. Confounding

Although, as shown in Table 2, the majority of studies have taken into account quite an extensive list of potential confounding variables, not all did so. An attempt was therefore made to investigate the role of 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 no evidence of an association in studies that adjusted for nine variables or more, but a significant

increase in studies that adjusted for eight variables or fewer. Although at first glance this may suggest that the overall association may have arisen because of 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 (Wartenberg, Pirie, Reynolds, Luo, Xue, Dossus[4,55,57,66,73,74]) 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.

Another approach is to look at the effect of adjustment in specific studies, by comparing RR estimates adjusted only for age with those adjusted for age and additional potential confounders. In fact, only the Smith, Wartenberg, Hanaoka, Lin, Luo and Xue studies[4,47,57,64,66,71] presented both sets of results, and these found the two sets of estimates to be very similar.

Overall, the evidence does not demonstrate any important role of uncontrolled confounding.

4.8. Publication bias

That authors are more likely to submit, and editors more likely to accept, papers showing an association is well documented[84]. It is notable that although results from American Cancer Society Cancer Prevention Study II have been published by Wartenberg *et al*[4], results from the earlier large Cancer Prevention Study I have only been reported for some other diseases[85,86] and not for ETS and breast cancer risk. Such an analysis would have materially contributed to the overall literature. Whether there are other large studies that could have provided data, but have not done so, is unclear.

4.9. Study weaknesses

There are a number of weaknesses that are common to many or a number of the studies:

(i) small number of cases, with some of the analyses in Tables 3-6 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 10 prospective studies involving nine years of follow-up or more, and in none of them were repeat interviews carried out;

(iii) general reliance on ETS exposure reported by the subject (or, in the Lash I and Lash II studies[34,35], by the next-of-kin for some subjects) with no confirmation by cotinine or by other sources of information; and

(iv) failure in many studies to restrict attention to married subjects when analysing spousal exposure or to control for household size when analysing household exposure.

Other issues relating to specific studies are commented on in the Appendix. Of the 39 estimates included in the principal meta-analysis, 21 relate to studies cited in the Appendix. Regarding these as being of poorer quality, it is of some interest that there is little evidence of an increase in the better studies (random-effects RR 1.02, 95% CI 0.95-1.08) but a significantly increased risk in the poorer studies (random-effects RR 1.28, 95% CI 1.11-1.47). Such a division is to some extent subjective and open to criticism but the results may be indicative.

4.10. Risk by time of menopause

Of the 19 studies that allowed comparison of the risks associated with ETS exposure in premenopausal and postmenopausal women, 12 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 at the time of the baseline interview, before follow-up for cancer. In one of the nested studies, the Alberg study[42], menopausal status appears to be related to the time of diagnosis of breast cancer. The abstract[37] does not make the position clear for the other nested study by Woo. Given the length of follow-up in the prospective Hanaoka study[71], from 1990 to 1999, it is likely that some of the women would have reached the menopause between interview and breast cancer diagnosis, so that the results from the two types of study are not completely comparable. This problem is less for the prospective Pirie study[55] where follow-up was only for 3.5 years. The follow-up in the prospective study by Reynolds[73] was from 1997 to 2007, and used menopausal status at baseline, but the smoking categories did not correspond with those used in

other studies, so these results were not used in this review. The original report of this study[6], based on follow-up from 1995 to 2000, also used menopausal status at baseline interview, but an additional analysis of the study by age at diagnosis (<50, ≥50 years) has been published[87] and these are the results used in our analyses by menopausal status.

It should also be noted that 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 7) 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.

4.11. Other reviews of ETS and breast cancer risk

The parallel reviews of the evidence on breast cancer by Johnson[22] and the California EPA[23] consider a data set very similar to that in the review we published in 2006[8] though of course they do not consider the more recent studies. There are some differences. They omit the Rookus and Woo studies reported only as abstracts[36,37], omit giving any results from the study with apparently unreliable adjusted estimates[45] and include results from a study by Zhao *et al*[15] where the report in the literature does not present results specifically for lifelong nonsmokers. They also use somewhat different relative risks in their principal meta-analyses, not concentrating on the nearest equivalent to ever exposure from the spouse. Some other inappropriate estimates may also have been used. For example, for the Mechanic study, they use an estimate from one source[88] when there is a later estimate from another source[89] that is based on considerably more cases. Also, for the Smith study[47] they apparently combine relative risk estimates from 1-200 and 200+ cigarette-years exposure as if they are independent, when they are not, being expressed relative to the same unexposed group.

However the broad findings from their meta-analyses are very similar to those in our previous reviews and those reached here. In particular, both sets of meta-analysis find an increased risk in case-control but not prospective studies, and in premenopausal but not postmenopausal women, and evidence of an increase that is concentrated in those studies that collect detailed exposure data, particularly when risks are expressed relating to total exposure versus complete nonexposure.

Although Johnson[22] appropriately points to the need for "cohort studies with thorough positive smoking assessment," he takes the view that recall bias is probably unlikely to explain the associations observed in the case-control studies with very detailed assessment of ETS. One reason for his belief is that two of the studies with detailed exposure assessment[56,59] assessed recall bias and did not find any clear evidence of its existence.

In fact, neither study provided particularly convincing evidence of a lack of important recall bias. For the Morabia study[56] the evidence concerned results from questions asking cases and controls whether or not they were worried about passive smoking, the proportion reporting that they were worried being only slightly, and nonsignificantly, greater in nonsmoking cases (55%) than in nonsmoking controls (50%). Though nonsignificant, the calculated odds ratio of 1.20 (95% CI 0.81-1.76) does not exclude the possibility that cases were actually substantially more likely to be worried. Furthermore, it could also well be that, regardless of worry, 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.

For the Johnson study[59] the evidence relating to potential recall bias derived from their 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 relative risk, of 1.2, has a very large variability with a 95% CI of 0.7-2.1, and furthermore relates 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.

The California EPA[23] interprets the findings as "consistent with a causal association" between ETS exposure and breast cancer for younger, primarily premenopausal women, but "inconclusive" for older/postmenopausal women. A more recent review by the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk[24], which included all of the studies in the California EPA review, plus those by Bonner[67], Lissowska[90], Roddam[48] and Pirie[55], concurred with this interpretation of the results, although they do not appear to have carried out a meta-analysis of their results. In support of these conclusions, it was argued that an association is plausible on biological grounds[22-24], and suggested that the findings for ETS and active smoking can be reconciled if in fact risks are similar for the two exposures and a large percentage of the nonsmoker reference group has ETS exposure. It was also stated that the lack of association seen in three large US prospective studies[4-6] was because the reference group in all their ETS analyses could have included many women exposed from sources not investigated or at times not studied.

There are a number of difficulties with these arguments. In the first place the precise dose-response model proposed is unclear. A "step" model in which risk of breast cancer is increased by an exposure (to ETS or active smoking) above some defined minimum, but in which the risk increase is not otherwise related to dose, could explain the similar risks in smokers and nonsmokers, if the great majority of nonsmokers are exposed above this minimum. It could also explain the lack of association of risk of breast cancer among nonsmokers with indices of ETS exposure based on a single source (such as the husband), where the comparison group includes a very high proportion of nonsmokers exposed above the minimum from other sources. However, this "step" model would not predict the dose-relationship seen in a number of studies, particularly those using detailed ETS exposure histories. Such a model does not, in any case, seem particularly attractive on biological grounds, and is not clearly defined because the critical minimum exposure is not known.

An alternative model in which risk is increased above some defined minimum exposure, and is then related to dose of ETS, would be more consistent with the dose-response results, but would not seem to fit in with the complete lack of effect of ETS seen in the three large US prospective studies[4,6,66]. As shown in Table 3, these studies

all reported RRs for exposure from the spouse or cohabitant that were not elevated at all, and it is well documented[32] that cotinine levels in women living with a smoker are substantially higher, by a factor of about three, than cotinine levels in women living with a nonsmoker. The Wartenberg study[4] also reported no association (RR 1.0, 95% CI 0.8-1.2) of breast cancer with any current exposure in adulthood, whether at home, at work or in other places, again apparently inconsistent with any true marked relationship of ETS to breast cancer risk.

If indeed there is a relationship of risk to dose of ETS, it is also unclear why risks in smokers and nonsmokers should be the same. Given the equality, such a model would imply that the risk for heavily ETS exposed nonsmoking women is higher than the risk for the average smoker, which seems implausible.

The most recent review, by the US Surgeon General[25], concluded that "the evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer" and that "there is insufficient evidence to conclude that the risk for breast cancer is modified by timing, source, location of exposure, estrogen receptor status, or genetic susceptibility". Results were given for eight measures of exposure and are similar to those given in our review. The studies on which these results are based are also similar, although it is notable that several studies in which some subjects were active smokers were included. In addition, only studies published before 2012 were included. For the "most comprehensive" index an overall estimate of 1.14 (1.06-1.23) was reported, with no increase being seen in prospective studies. The risk estimate was reduced to a non-significant 1.04 (0.99-1.09) when studies were excluded due to inclusion of active smokers among subjects, design weaknesses including failure to adequately control for confounding, small size and outlying results. The exclusions also reduced the association seen in premenopausal women, but did not completely remove it. As with our review, no association was seen with childhood ETS exposure.

Compared to the evidence for active smoking, which the US Surgeon General[25] also considered to be insufficient to infer causality, it was noted that "the evidence is less consistent for passive 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", along with the weak association between breast cancer and ETS, and the mixed evidence on a dose-response relationship.

Generally, the reviews by Johnson[22], the California EPA[23], the Canadian Expert Panel[24] and the US Surgeon General[25] do not provide convincing evidence of a true relationship of ETS exposure to breast cancer risk.

5. Summary and conclusions

Results of 41 studies relating breast cancer in women to ETS exposure in nonsmokers have been published. This document presents a comprehensive review of the evidence, with meta-analysis.

The studies varied in design and in the ETS exposure indices used. Based on a single estimate from each of the 39 studies that provided relative risk estimates for exposure compared with no or little exposure, and selecting the index of exposure most nearly equivalent to ever smoking by the spouse or partner, random-effects meta-analysis gave an overall estimate of 1.13 (95% CI 1.05-1.21). However, the 39 estimates were significantly ($p<0.001$) heterogeneous, with estimates close to 1.00 for prospective studies, larger studies (>500 cases) and studies taking more confounding variables than average into account, significantly elevated in case-control studies (1.26, 1.11-1.44), in those studies that had taken fewer confounding variables than average into account (1.16, 1.04-1.30) and in North American studies (1.12, 1.02-1.23), and non-significantly raised in European studies (1.11, 0.97-1.26), in Asian studies (1.16, 0.92-1.47) and in smaller studies (1.19, 0.998-1.41). In those studies providing relevant data, there was no evidence of an association in postmenopausal women, but some increase in premenopausal women (1.43, 1.17-1.75).

Evidence of a dose-response relationship was similarly heterogeneous, with significant trends reported in a few studies contrasting with a complete lack of relationship reported in other studies.

There was no evidence of an association at all for childhood ETS exposure, and the increased relative risk estimate was not significant using indices based specifically on exposure from the spouse, in the workplace or from the spouse or other cohabitant. However, it was notable that from those 19 studies that provided estimates relating to total exposure, based on a detailed questionnaire that asked (at least) about at-home exposure in childhood and in adulthood and about workplace exposure, the relative risk estimate was slightly higher (1.15, 1.06-1.24).

Detailed examination of the evidence suggested that where associations were seen, the elevated risk estimate derived mainly from those case-control studies that asked very detailed questions about ETS exposure and depend heavily on the accuracy of the reported answers. Expressing estimates relative to a totally unexposed baseline produces estimates that are highly dependent on which subjects happen to get classified in the baseline group and may well be unusually subject to recall bias. Results from more large prospective studies involving very detailed ETS exposure indices would aid interpretation.

Also relevant to interpretation of the data are weaknesses inherent in a number of studies and the possibilities of publication bias and uncontrolled confounding.

Overall, in view of the inherent implausibility that ETS exposure might cause breast cancer, given the virtually identical risks in smokers and nonsmokers, and the doubts about the reliability of estimates from case-control studies involving extremely detailed questionnaires on ETS exposure, one cannot conclude that ETS exposure has actually been shown to increase the risk of breast cancer in nonsmokers.

6. Tables

TABLE 1 – Studies providing data on ETS and breast cancer

Study author [ref][a]	Year[b]	Location	Design[c]	ETS sources studied[d]	Subgroup analyses[e]
Sandler[43,75,91]	1985	USA, N Carolina	CC-F	Sp, Ma, Pa	Age, menopause
Hirayama[41,75,91]	1987	Japan, 6 prefectures	P(16)	Sp	Age of husband
Smith[47]	1994	UK, 11 regions	CC-P	Sp, Oc, Wk, Oa, Ch	-
Morabia[56,92,93]	1996	Switzerland, Geneva	CC-P	Sp, Wk, Oa[f]	Menopause, NAT2 acetylation genotype
Jee[51]	1999	Korea, nationwide	P(6)	Sp	-
Lash I[34]	1999	USA, Massachusetts	CC-P	Co	-
Delfino[44]	2000	USA, California	CC-B	Co	Menopause, NAT2 acetylation genotype
Johnson[59]	2000	Canada, 8 provinces	CC-P	Co, Wk, Ch	Menopause
Liu[45]	2000	China, Chongqing	CC-H	Co, Wk, Ch	-
Rookus[36]	2000	Netherlands, Amsterdam	CC-P	Co, Wk, Ch	p53 expression
Wartenberg[4]	2000	USA, 50 states[g]	P(12)	Sp, Oc, Wk, Oa	Age, age at marriage
Woo[37]	2000	USA, Maryland	NCC	Co	Menopause
Nishino[52]	2001	Japan, Miyagi	P(9)	Sp, Oc	-
Kropp[49,94,95]	2002	Germany, 2 regions	CC-P	Co, Wk, Ch	NAT2 acetylation genotype, SULT1A1 genotype
Lash II[35]	2002	USA, Massachusetts	CC-P	Co	-
Alberg[42]	2004	USA, Washington County	NCC	Sp	NAT2 acetylation genotype, menopause
Gammon[53,96,97]	2004	USA, New York	CC-P	Co, Oc	Age, menopause, HRT use, BMI, alcohol, use of oral contraceptives, family history of breast cancer, MnSOD genotype
Shrubsole[65]	2004	China, Shanghai	CC-P	Sp, Wk	Menopause, most recent job
Bonner[67]	2005	USA, New York state	CC-P	Co, Wk, Ch	Menopause
Gram[50]	2005	Norway and Sweden	P(10)	Co	-
Hanaoka[71]	2005	Japan, 14 districts	P(10)	Co, Ob	Menopause
Sillanpaa[70,98]	2005	Finland, Kuopio	CC-P	Co, Wk	NAT2 acetylation,XRCC1 and XPD genotypes
Lissowska[58,90]	2006	Poland, Warsaw and Łódź	CC-P	Co, Wk	Age, menopause
Mechanic[54,88,89]	2006	USA, N Carolina	CC-P	Co	Race, NER genotypes, menopause, p53 expression NAT1 and NAT2 acetylation genotypes
Zhu[33]	2006	China, Shanghai	P(7)	To	Menopause, oral contraceptives, other female hormone use

continued

TABLE 1 – Studies providing data on ETS and breast cancer (continued)

Study author [ref][a]	Year[b]	Location	Design[c]	ETS sources studied[d]	Subgroup analyses[e]
Roddam[48]	2007	UK, 3 regions	CC-G	Sp	Menopause, alcohol, use of oral contraceptives, family history of breast cancer, parity with age of giving birth, socioeconomic status, BMI, age at menarche
Lin[64]	2008	Japan, nationwide	P(13)	Co, Ob, Ch	-
Pirie[55]	2008	UK, nationwide	P(3.5)	Sp, Ma, Pa	Age, employment status, age at menarche, menopausal status, parity, age at first birth, alcohol, oral contraceptives, HRT use, BMI, physical activity, living with partner
Rollison[68]	2008	USA, Delaware	CC-P	Co, Ch, Wk, To	-
Slattery[72]	2008	USA, 4 states	CC-P	To	Menopausal status, race, IL6 genotype, ESR1 genotype
Ahern[69]	2009	USA, Massachusetts	CC-P	Co, Wk, Ma, Pa, To	-
Reynolds[6,73,87]	2009	USA, California	P(10)	Co,Wk, Ch, To	Age at diagnosis, menopause at baseline
Young[39]	2009	Canada, Ontario[h]	CC-P	Co, Wk, Ch	-
Chilian-Herrera[38]	2010	Mexico, US border states	CC-P	Co, Wk	Menopausal status, age
Conlon[60]	2010	Canada, Ontario	CC-P	Co, Wk	Acetylation genotype
De Silva[61]	2010	Sri Lanka, Western province	CC-P	To[i]	-
Luo[57]	2011	USA, nationwide	P(10)	Ch, Co, Wk	Histology, hormone receptors
Xue[5,66]	2011	USA, 11 states	P(24)	Ch, Co, Ma, Pa, Wk	Menopause
Anderson[40,99]	2012	Canada, Ontario	CC-P	Ch, Co, Ob, Te, To, Wk,	Menopause, 11 candidate genes[j]
Tang[46]	2013	China, Guangzhou	CC-H	Co, Wk	Menopause, PARP1 and ESR1 genotypes
Dossus[74,78]	2014	Europe, 10 countries	P(18)	Ch, Co, Wk	-

See next page for notes.

[a] Studies are identified by the first author of the principal publication

[b] Year of first 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 asked about (though results are not necessarily available for all of these)

Ch	childhood (separately)	Pa	father (in childhood)
Co	cohabitant	Sp	spouse (or partner)
Ma	mother (in childhood)	Te	teenage years (separately)
Oa	other exposure in adulthood (not home or work)	To	total lifetime (not otherwise specified)
Ob	other exposure in adulthood (not home)	Wk	workplace
Oc	other cohabitants (not spouse)		

[e] Subgroup analyses Results (for at least some exposure indices) are reported that relate ETS to breast cancer separately by levels of the variables listed

[f] Questions were asked about exposures from age 10

[g] Also District of Columbia and Puerto Rico

[h] Combines data from study by [40] 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] Analysis of 5 genotypes from reference[40], analysis of 6 further genotypes from reference[99]

TABLE 2 – Potential confounding variables adjusted for in results cited in Tables 3-6

Study author [ref][a]	Year[b]	Potential confounding variables adjusted for
Sandler[43,75,91]	1985	Age (only in spousal analyses)
Hirayama[41,75,91]	1987	Age of husband
Smith[47]	1994	Age, region, age at menarche, nulliparity, age at first full-term pregnancy, breast feeding, oral contraceptive use, family history of breast cancer, biopsy for benign breast disease, alcohol
Morabia[56,92,93]	1996	Age, education, BMI, age at menarche, age at first live birth, oral contraception, family history of breast cancer, history of breast biopsy in all analyses. Also saturated fat, alcohol in first relative risk cited in Tables 3 and 6
Jee[51]	1999	Age, socioeconomic status, residency, husband's age, husband's vegetable consumption, husband's occupation
Lash I[34]	1999	Age, BMI, parity, history of radiation therapy, family history of breast cancer, history of breast cancer, history of benign breast disease in all analyses. Also alcohol in first relative risk cited in Table 3, and duration of passive smoking in relative risk cited in Table 5
Delfino[44]	2000	Age, menopausal status, family history of breast cancer
Johnson[59]	2000	Age, province, education, BMI, alcohol, physical activity, age at menarche, age at end of first pregnancy, number of live births, months of breastfeeding, height, menopausal status
Liu[45]	2000	Age at diagnosis, date of diagnosis, marital status, age at menarche, low body weight in childhood, overweight in adulthood, low family economic situation in youth, history of hospitalised diseases, history of benign breast disease, history of life-stress[c]
Rookus[36]	2000	Lifetime physical activity, other (unspecified) confounders
Wartenberg[4]	2000	Age, race, education, family history of breast cancer, age at first live birth, age at menarche, age at menopause, number of spontaneous abortions, oral contraceptive use, oestrogen replacement therapy use, BMI, history of breast cysts, alcohol, dietary fat, dietary vegetable, occupation of woman, occupation of spouse
Woo[37]	2000	Menopausal status and possibly other confounders
Nishino[52]	2001	Age, study area, alcohol, green and yellow vegetable intake, fruit intake, age at first birth, number of live births, age at menarche, BMI

continued

TABLE 2 – Potential confounding variables adjusted for in results cited in Tables 3-6 (continued/1)

Study author [ref][a]	Year[b]	Potential confounding variables adjusted for
Kropp[49,94,95]	2002	Age, alcohol, breastfeeding, education, family history of breast cancer, menopausal status, BMI
Lash II[35]	2002	Age, vital status, history of radiation therapy, BMI, family history of breast cancer, history of breast cancer, history of benign breast disease, alcohol, parity, age at first birth
Alberg[42]	2004	Age, race, menopausal status, day of menstrual cycle (premenopausal women only), date of blood donation
Gammon[53]	2004	Age, history of benign breast disease, BMI at age 20, family history of breast cancer, fertility problems, number of pregnancies, menopausal status, weight in year before reference date
Shrubsole[65]	2004	Age, education, family history of breast cancer, history of fibroadenoma, age at menarche, parity, age at first birth, menopausal status, age at menopause, physical activity, waist-to-hip ratio
Bonner[67]	2005	Age, education, race, previous benign breast disease, parity, age at menarche, BMI, age at first birth, family history of breast cancer, alcohol, age at menopause, menopausal status
Gram[50]	2005	Age, age at menarche, age at first birth, number of children, menopausal status, family history of breast cancer, hormonal contraceptive use, alcohol, BMI
Hanaoka[71]	2005	Age, public health centre, employment, education, BMI, family history of breast cancer, history of benign breast disease, age at menarche, number of births, menopausal status, hormone use, alcohol
Sillanpaa[70,98]	2005	Age, age at menarche, age at first full-term pregnancy, number of pregnancies, family history of breast cancer, history of benign breast diseases, alcohol
Lissowska[58,90]	2006	Age, site, education, age at menarche, number of full-term births, age at first full-term birth, age at menopause, BMI, family history of breast cancer, history of benign breast biopsy, previous screening mammography, oral contraceptive use, hormone replacement therapy use
Mechanic[54,88,89]	2006	Age, race, offsets[d], age at menarche[d], age at first full-term pregnancy/parity composite[d], family history[d], alcoho1[d], sampling fraction[e], p53 expression[e]
Zhu[33]	2006	Not specified
Roddam[48]	2007	Age, region, socioeconomic status, alcohol, BMI, parity, use of oral contraceptives, family history of breast cancer, age at menarche, menopausal status
Lin[64]	2008	Age, area, BMI, family history of breast cancer, alcohol, daily walking, age at menarche, age at birth of first child, menopausal status at baseline, number of births, use of sex hormones

continued

TABLE 2 – Potential confounding variables adjusted for in results cited in Tables 3-6 (continued/2)

Study author [ref][a]	Year[b]	Potential confounding variables adjusted for
Pirie[55]	2008	Age, region of residence, socioeconomic status, age at menarche, parity, age at first birth, menopausal status, BMI, physical activity, alcohol consumption, HRT use, living with partner
Rollison[68]	2008	Age, menopausal status, BMI, age at menarche, age at first live birth, oral contraceptive use, other hormone use, family history of breast cancer, alcohol
Slattery[72]	2008	Age, centre, BMI, aspirin/NSAID use, parity, alcohol, physical activity, recent hormone use (postmenopausal women only)
Ahern[69]	2009	Age, menopausal status, BMI, parity, alcohol, family history of breast cancer
Reynolds[6,73,87]	2009	Age, race, family history of breast cancer, age at menarche, parity, age at first pregnancy, physical activity, alcohol, BMI, menopausal status[f], BMI and menopausal status interaction[f], HRT use[f], menopausal status with HRT use interaction[g], lifetime duration of breast feeding[g]
Young[39]	2009	Age
Chilian-Herrera[38]	2010	"Known reproductive breast cancer risk factors"
Conlon[60]	2010	None[h]
De Silva[61]	2010	Lifetime duration of breastfeeding, age at first pregnancy, menopausal status, previous abortions, education, employment status, family history of breast cancer
Luo[57]	2011	Age at enrolment, ethnicity, education, BMI, physical activity, alcohol intake, parity, family history of breast cancer, hormone therapy use, age at menarche, age at first live birth
Xue[5,66]	2011	Age, family history of breast cancer, history of benign breast disease, BMI[i], BMI at age 18, height, alcohol intake, age at menarche, parity, age at first birth, physical activity[i], oral contraceptive use[i], menopausal status, postmenopausal hormone use, age at menopause, adult weight change[j], carotenoid intake[j], passive smoking at times other than that under investigation[i]
Anderson[40,99]	2012	Age, physical activity[k]
Tang[46]	2013	Age, marital status, physical activity, alcohol, age at menarche, menopausal status, BMI, parity, education, family history of breast cancer
Dossus[74,78]	2014	Age, study centre, BMI, education, use of oral contraceptives, use of HRT[l], menopausal status, parity, age at first full-term pregnancy[l], age at menarche, alcohol, physical activity, vegetable intake[m], fruit intake[m], non-alcoholic energy intake[m], adulthood passive smoking[m]

See next page for notes

[a] Studies are identified by the first author of the principal publication
[b] Year of first publication
[c] The first three variables were matching variables. Results of conditional logistic regression analyses adjusting for all the variables were reported, but only in models which simultaneously considered ETS exposure from three different sources, making the findings not logically comparable to those presented elsewhere. Furthermore, the results are expressed only as an odds ratio per unit of a passive smoking index, and give totally implausible results – for example someone having heavy exposure in adulthood from 3 smokers would have an index value of 9 and an estimated increase in risk by a factor of $4.07^9 = 306443$! Because of this only unadjusted results and those adjusted only for matching variables are included in Tables 3, 4 and 5
[d] Analyses from reference[54] only
[e] Analyses from reference[89] only
[f] Analyses from references[6] and[87] only
[g] Analyses from reference[73] only
[h] Results available adjusted by age, but using lowest level of exposure as reference group
[i] Analyses from reference[66] only
[j] Analyses from reference[5] only
[k] Analyses of premenopausal women only
[l] Analyses from reference[74] only
[m] Analyses from reference[78] only

TABLE 3 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure from spouse or at home

Study			Source of exposure (timing)[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Author [ref][a]	Location	Type[b]					
Sandler[91]	USA	CC	Spouse (ever)	32	1.62 (0.76-3.44)	-	am
Hirayama[91]	Japan	P	Spouse (ever)	115	1.32 (0.83-2.09)	No	c(1)m
Smith[47]	UK	CC	Spouse/partner (adulthood) Other cohabitant (adulthood)	94 94	1.58 (0.81-3.10) 1.36 (0.67-2.77)	- No	ac(9)m ac(9)e
Morabia[56]	Switzerland	CC	Spouse (ever)[g]	90	3.1 (1.6-6.1)	d1	ac(9)m
Jee[51]	Korea	P	Spouse (ever)	138	1.27 (0.91-1.77)	-	ac(5)em
Lash I[34]	USA	CC	Cohabitant (ever)	120	2.0 (1.1-3.7)[h]	No	ac(7)m
Delfino[44]	USA	CC	Cohabitant (ever)[i]	64	1.50 (0.79-2.87)	-	ac(2)m
Liu[45]	China	CC	Cohabitant (adulthood)	186	1.49 (0.96-2.30)	d2	ac(2)em
Wartenberg[4j]	USA	P	Spouse (ever) Spouse (current) Spouse (former) Cohabitant (current)	669 439 503 669	1.00 (0.84-1.19) 1.0 (0.8-1.2) 1.0 (0.8-1.2) 1.1 (0.9-1.3)	No - - -	ac(16)em ac(16) ac(16) ac(16)
Woo[37]	USA	NCC	Cohabitant (current)	(706)	1.03 (0.81-1.31)	-	c(1?)em
Nishino[52]	Japan	P	Spouse (current) Other cohabitant (current)	67 67	0.58 (0.32-1.10) 0.81 (0.44-1.50)	- -	ac(8)m ac(8)
Lash II[35]	USA	CC	Cohabitant (ever)	305	0.85 (0.63-1.1)[k]	No	ac(9)m
Alberg[42]	USA	NCC	Spouse (ever)	62	1.20 (0.59-2.40)	-	ac(4)m
Gammon[53]	USA	CC	Cohabitant (ever)[l]	598	1.04 (0.81-1.35)[m]	No	ac(7)m
Shrubsole[65]	China	CC	Spouse (ever)	813	1.0 (0.8-1.2)	No	ac(10)m
Bonner[67]	USA	CC	Cohabitant (ever)	525	1.18 (0.86-1.63)	No	ac(11)em
Gram[50]	Norway and Sweden	P	Cohabitant (ever)	(1130)	1.21 (0.98-1.50)	-	ac(8)m
Hanaoka[71]	Japan	P	Cohabitant (ever)[n]	154	1.0 (0.7-1.4)	-	ac(11)m
Lissowska[58]	Poland	CC	Cohabitant (ever)	1034	0.92 (0.74-1.14)	-	ac(12)em
Mechanic[54]	USA	CC	Cohabitant (adulthood)	1211	1.10 (0.93-1.31)	-	ac(6)em
Roddam[48]	UK	CC	Spouse/partner (ever)	297	0.89 (0.64-1.25)	No	ac(9)m
Lin[64]	Japan	P	Cohabitant (past)	131	0.68 (0.47-0.97)	No	ac(10)em
Pirie[55]	UK	P	Spouse/partner (current)	1915	1.02 (0.89-1.16)	-	ac(10)m
Rollison[68]	USA	CC	Cohabitant (ever)	124	0.98 (0.58-1.64)	-	ac(8)m
Reynolds[6]	USA	P	Cohabitant (adulthood)[o] Cohabitant (ever)	1150 1164	0.97 (0.87-1.10) 0.94 (0.82-1.07)	- 	ac(11)em ac(11)
Luo[57]	USA	P	Cohabitant (adulthood)	1660	1.00 (0.91-1.11)	-	ac(10)em
Xue[66]	USA	P	Cohabitant (adulthood) Cohabitant (current)	2874 2497	0.99 (0.92-1.07) 1.05 (0.96-1.14)	No No	ac(15)em ac(16)e
Anderson[40]	Canada	CC	Cohabitant (adulthood)	918	1.08 (0.89-1.31)	No	ac(1)em

continued

TABLE 3 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure from spouse or at home (continued)

Tang[46]	China	CC	Cohabitant (adulthood)	765	1.55 (1.23-1.96)	-	ac(9)m
Dossus[74]	Europe	P	Cohabitant (current)	3286	1.03 (0.94-1.13)	-	ac(11)em

[a] Studies are identified by the first author of the principal publication
[b] Study type P = prospective C = 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, "d1", "d2" indicates dose-response studied, significant trend, with more detailed data as follows:
  d1 relative risks are 1.0, 3.1, 3.2 for 0, 1-50, >50 hours/day-years ETS exposure from spouse (trend $p<0.05$)
  d2 relative risks are 1.00, 0.47, 1.64, 2.14, 3.09 for 0, light, medium, heavy, very heavy exposure from cohabitants (trend $p<0.01$). No significant trend for number of smokers at home.
[f] Notes:
  a adjusted for age of subject
  c adjusted for other confounding variables (see Table 2) – number of variables adjusted for is shown in brackets
  e estimated from data reported
  m included in principal meta-analyses
  u unadjusted for any confounding variable
[g] Reference group is less than 1 hour/day ETS exposure from any source for 12 consecutive months during life
[h] Relative risks are 4.5, 3.8 and 2.4 for, respectively, first exposure <12, 12-20 and 21+ years (heterogeneity not significant)
[i] Cohabitant(s) smoked in their home usually or some of the time
[j] Relative risks are also shown by type of product smoked by spouse (cigarette only, cigar/pipe only, mixed) which respectively are 1.0, 0.8, 1.1 for spouse current smoker and 0.9, 1.3, 1.2 for spouse former smoker – all non-significant
[k] Relative risks are 0.99, 0.84 and 0.79 for, respectively, first exposure <12, 12-20 and 21+ years (heterogeneity not significant), and are 0.94 for first exposed before first pregnancy and 0.55 for first exposed after first pregnancy (heterogeneity significant at $p<0.05$)
[l] Results are reported for spouse (ever) but have not been included as they appear to be based on ever smokers as well as never smokers
[m] Relative risks are 0.92 for *in situ* cases and 1.07 for invasive cases (heterogeneity not significant) and are 1.15, 0.80, 1.17 and 1.05 for, respectively, ER^+PR^+, ER^+PR^-, ER^-PR^+ and ER^-PR^- cases (heterogeneity not significant)
[n] Reference group is never exposed at home during life and not exposed daily outside the home at baseline
[o] From reference[6], based on 6 years of follow-up only

TABLE 4 - Relative risk of breast cancer in lifelong nonsmoking women according to other sources of ETS exposure in adulthood

Study			Source of exposure (timing)[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Author [ref][a]	Location	Type[b]					
Smith[47]	UK	CC	Workplace (NOS)	94	1.49 (0.76-2.92)	No	ac(9)e
			Any (NOS)	94	2.52 (0.87-7.31)	No	ac(9)e
Johnson[59]	Canada	CC	Home or workplace (NOS)	606	1.47 (1.06-2.04)	-	ac(11)em
Liu[45]	China	CC	Workplace (NOS)	186	1.54 (1.02-2.32)	d1	ue
Wartenberg[4]	USA	P	Workplace (current)	669	0.8 (0.6-1.0)	-	ac(16)
			Places other than home or workplace (current)	669	0.9 (0.7-1.2)	-	ac(16)
			Any (current)	669	1.0 (0.8-1.2)	No	ac(16)e
Kropp[49]	Germany	CC	Home or workplace (NOS)	197	1.69 (1.16-2.45)	No	ac(6)em
Shrubsole[65]	China	CC	Workplace (last 5 years)[g]	864	1.1 (0.9-1.4)	d2	ac(10)
			Home (ever) or workplace (last 5 years)[g]	864	1.01 (0.79-1.28)	-	ac(10)e
Bonner[67]	USA	CC	Workplace (ever)	522	0.80 (0.64-1.01)	No	ac(11)e
Hanaoka[71]	Japan	P	Outside home, daily (current)[h]	77	1.3 (0.9-1.9)	.	ac(11)
Lissowska[58]	Poland	CC	Workplace (ever)	1034	1.05 (0.88-1.27)	-	ac(12)e
Lin[64]	Japan	P	Public spaces (past)	140	0.79 (0.56-1.13)	No	ac(10)e
Rollison[68]	USA	CC	Workplace (ever)	124	0.80 (0.49-1.32)	No	ac(8)
Ahern[69]	USA	CC	Any (ever)[j]	232	0.86 (0.57-1.31)	-	a(5)em
Reynolds[73]	USA	P	Any (ever)	1754	1.04 (0.91-1.19)	-	ac(10)
			Workplace (ever)	1754	1.02 (0.93-1.13)	-	ac(10)
Luo[57]	USA	P	Workplace (adulthood)	1660	1.08 (0.97-1.19)	-	ac(10)e
			Any (adulthood)	1660	1.01 (0.88-1.15)	-	ac(10)e
Xue[66]	USA	P	Work (current)	2468	0.94 (0.86-1.04)	d3	ac(16)e
			Home and work (adulthood)	2109	1.04 (0.94-1.16)	No	ac(15)e
Anderson[40]	Canada	CC	Workplace (adulthood)	909	0.99 (0.82-1.20)	No[k]	ac(1)e
			Social situations (adulthood)	907	1.14 (0.95-1.38)	No	ac(1)e
			Any (adulthood)	916	1.09 (0.83-1.42)	No	ac(1)e
Tang[46]	China	CC	Home only (adulthood)	615	1.52 (1.17-1.97)	-	ac(9)
			Workplace (adulthood)	586	1.23 (0.92-1.64)	-	ac(9)
			Workplace only (adulthood)	474	1.21 (0.84-1.74)	-	ac(9)
			Home or workplace (adulthood)	765	1.47 (1.18-1.83)	-	ac(9)
			Home and workplace (adulthood)	468	1.76 (1.16-2.69)	-	ac(9)
Dossus[74]	Europe	P	Home only (current)	844	1.30 (1.07-1.59)	-	ac(11)
			Workplace (current)	3286	1.05 (0.98-1.13)	-	ac(11)e
			Workplace only (current)	1117	1.08 (0.95-1.23)	-	ac(11)
			Home or workplace (current)	3286	1.06 (0.99-1.15)	-	ac(11)e
			Home and workplace (current)	832	1.08 (0.87-1.32)	-	ac(11)

See next page for notes

[a] Studies are identified by the first author of the principal publication
[b] Study type P = prospective C = 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, "d1", "d2" etc indicates dose-response studied, significant trend, with more detailed data as follows:
- d1 relative risks are 1.0, 1.56, 0.77, 2.94 for 0, 1-4, 5-9, 10+ smokers at work (trend $p<0.05$)
- d2 relative risks are 1.0, 0.9, 1.1, 1.1, 1.6 for 0, 1-59, 60-179, 180-299, 300+ minutes of exposure per day (trend $p=0.02$)
- d3 relative risks are 1.0, 0.99, 0.87 for never, occasional, regular exposure at work

[f] Notes:
- a adjusted for age of subject
- c adjusted for other confounding variables (see Table 2) – number adjusted for shown in brackets
- e estimated from data reported
- m included in principal meta-analysis
- u unadjusted

[g] Analysis restricted to women who had worked during the five years prior to interview
[h] Reference group is never exposed at home during life and not exposed daily outside the home at baseline
[i] Results were reported for adult exposure at home but were not included as based on ever smokers and never smokers
[j] Reference group is never exposed in lifetime
[k] Reference[99] reports relative risk of 2.27 (1.19-4.31) for 19-40 years of exposure versus none; relative risk not given for <19 years of exposure

TABLE 5 – Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure in childhood

Study			Source of exposure[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Author [ref][a]	Location	Type[b]					
Sandler[43]	USA	CC	Mother	29	0.92 (0.26-3.34)	-	ue
			Father	28	0.91 (0.41-2.04)	-	ue
Smith[47]	UK	CC	Any	94	1.19 (0.55-2.55)	No	ac(9)e
Lash I[34]	USA	CC	At home	99	2.40 (0.78-7.40)[g]	-	ac(8)e
Johnson[59]	Canada	CC	At home	606	1.24 (0.93-1.64)	-	ac(11)e
Liu[45]	China	CC	At home	186	1.16 (0.73-1.84)[h]	d1	ac(2)e
Kropp[49]	Germany	CC	At home	197	1.09 (0.77-1.55)	No	ac(6)e
Lash II[35]	USA	CC	At home	224	1.12 (0.82-1.54)	-	ac(9)e
Bonner[67]	USA	CC	At home	525	1.24 (0.96-1.60)	No	ac(11)e
Lin[64]	Japan	P	At home	178	1.24 (0.84-1.85)	-	ac(10)
Pirie[55]	UK	P	Mother	2344	0.96 (0.88-1.05)	-	ac(11)
			Father	2344	1.03 (0.93-1.14)	-	ac(11)
Rollison[68]	USA	CC	At home	123	0.81 (0.47-1.40)	No	ac(8)
Slattery[72]	USA	CC	Any	1347	No association	-	-
Ahern[69]	USA	CC	Any[i]	232	1.20 (0.78-1.84)	-	ac(5)e
Reynolds[6,73]	USA	P	At home[j]	1150	0.95 (0.84-1.07)	-	ac(11)e
			Any	1754	1.06 (0.94-1.19)	-	ac(10)
Luo[57]	USA	P	Any	1660	1.08 (0.98-1.19)	-	ac(10)e
Xue[66]	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[40]	Canada	CC	At home[k]	912	0.91 (0.75-1.10)	d2	ac(1)e
			Any[l]	912	0.91 (0.74-1.13)	No	ac(1)e
Dossus[78]	Europe	P	Parents[m]	3187	0.98 (0.91-1.06)	No	ac(14)

[a] Studies are identified by the first author of the principal publication
[b] Study type P = prospective C = 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, "d1", "d2" etc indicates dose-response studied, significant trend, with more detailed data as follows:
d1 relative risks of 1.00, 1.01, 2.50, 8.98 for 0, 1, 2, 3+ smokers at home (trend $p<0.05$), and 1.00, 0.69, 1.31, 1.64, 1.74 for 0, light, medium, heavy, very heavy exposure at home (trend $p<0.05$)
d2 relative risks of 1.00, 0.98, 0.85, 0.85 for 0, 183-3653, 3654-16436, 16437-25568 hours exposure
[f] Notes:
a adjusted for age of subject
c adjusted for other confounding variables (see Table 2) – number adjusted for shown in brackets
e estimated from data reported
u unadjusted
[g] For exposure at age <12 years
[h] For exposure at age 1-9 years. For exposure at age 10-16 relative risk (95% CI) is 1.06 (0.67-1.68) with no significant dose-response
[i] Results were reported for parental, maternal and paternal smoking separately but are not included as based on ever smokers as well as never smokers
[j] From reference[6], based on 6 years of follow-up only
[k] Exposure from others in household during ages 2-12 years only
[l] Exposure from any source during ages 13-19 years only
[m] From reference[78], exposure from parents and other sources in childhood for two study centres only, based on only 10 years of follow-up

TABLE 6 – Relative risk of breast cancer in lifelong nonsmoking women according to total lifetime ETS exposure

Study			Source of exposure[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Author [ref][a]	Location	Type[b]					
Smith[47]	UK	CC	All	94	2.58 (0.96-6.94)	No	ac(9)e
Morabia[56]	Switzerland	CC	All[g]	126	3.2 (1.7-5.9)[h]	d1	ac(9)
Johnson[59]	Canada	CC	Home or work	606	1.49 (1.02-2.18)	d2	ac(11)e
Rookus[36]	Netherlands	CC	Home or work[i]	918	1.2 (0.8-1.7)[j]	-	c(?)m
Kropp[49]	Germany	CC	Home or work	197	1.59 (1.06-2.39)[k]	d3	ac(6)
Hanaoka[71]	Japan	P	All	162	1.1 (0.8-1.6)	-	ac(11)
Sillanpaa[70]	Finland	CC	Home or work	363	0.85 (0.62-1.16)	-	ac(6)m
Lissowska[58,90]	Poland	CC	Home or work	1034	1.11 (0.85-1.46)	No	ac(12)
Zhu[33]	China	P	All	390	Not available	d4	n
Pirie[55]	UK	P	Parents/spouse	2344	0.98 (0.88-1.09)	-	ac(11)
Rollison[68]	USA	CC	Cohabitants	122	1.06 (0.56-2.02)	No	ac(8)
Slattery[72]	USA	CC	Any (ever)	1347	1.05 (0.88-1.27)	No	ac(9)[l]em
Ahern[69]	USA	CC	Any (ever)	232	0.91 (0.54-1.55)	-	ac(5)e
Reynolds[73]	USA	P	All	1754	1.10 (0.94-1.30)	d5,d6,d7	ac(10)
Young[39m]	Canada	CC	Home or work	2751	0.97 (0.88-1.08)	-	a
Chilian-Herrera[38]	Mexico	CC	Home or work	(504)	3.34 (2.38-4.68)[n]	d8	ac(?)m
Conlon[60]	Canada	CC	Home or work	129	1.15 (0.61-2.18)	No	emu
De Silva[61]	Sri Lanka	CC	Any (ever)	100	2.96 (1.53-5.75)[o]	-	ac(7)m
Luo[57]	USA	P	Any (ever)	1660	1.09 (0.92-1.29)	No	ac(10)
Dossus[74]	Europe	P	Childhood, home or work (current)	3597	1.10 (1.01-1.20)	-	ac(11)

See next page for notes.

[a] Studies are identified by the first author of the principal publication

[b] Study type P = prospective C = 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, "d1", "d2" etc indicates dose-response studied, significant trend, with more detailed data as follows:

- d1 relative risks are 1.0, 3.1, 3.2 for 0, 1-50, >50 hours/day-years ETS exposure ever (trend $p<0.05$)
- d2 relative risks are 1.0, 1.2, 1.8, 2.0, 3.3, 2.9 for 0, 1-6, 7-16, 17-21, 22-35, 36+ combined years exposure at home and at work (trend $p<0.001$) – data for premenopausal breast cancer; no trend seen for postmenopausal breast cancer
- d3 relative risks are 1.00, 1.42, 1.83 for 0, 1-50, 51+ hours/day-years exposure in lifetime (trend $p=0.009$)
- d4 relative risks are 1, 1.02, 1.42, 1.72 for never exposed, <2.0, 2.0-<4.0, ≥4.0 hours/day average lifetime exposure (trend $p<0.0001$). No information was given on numbers of unexposed subjects, so overall RR (CI) could not be estimated.
- d5 relative risks are 1.10, 1.10, 1.12 for ≤15, 15.1-30.0, and >30.0 years of exposure
- d6 relative risks are 1.09, 1.08, 1.14 for intensity of exposure of ≤2.0, 2.1-3.0, >3.0
- d7 relative risks are 1.10, 1.10, 1.11 for ≤17.5, 17.6-42.0, >42.0 intensity-years of exposure
- d8 a significant trend was reported ($p<0.001$), but no explanation of groupings was given

[f] Notes:

- a adjusted for age of subject
- c adjusted for other confounding variables (see Table 2) – number adjusted for shown in brackets
- e estimated from data reported
- m included in principal meta-analysis
- n adjustment not specified
- u unadjusted

[g] Exposed for at least 1 hour/day ETS exposure from any source for at least 12 consecutive months during life

[h] Relative risks are 2.4 for first exposed before pregnancy and 2.1 for first exposed after first pregnancy (heterogeneity not significant), and are 3.8 for oestrogen receptor negative and 1.8 for oestrogen receptor positive (heterogeneity not significant)

[i] 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 one year

[j] Relative risk was noted to be no greater for first exposure before first pregnancy

[k] Relative risks are 1.42 for first exposed before pregnancy and 2.13 for first exposed after first pregnancy (heterogeneity not significant), and are 1.55 for exposure not in previous year and 1.67 for current exposure (heterogeneity not significant)

[l] Adjusted for factors shown in Table 2 plus menopausal status and ethnicity during estimation of relative risk

[m] Combines data from study by[40] plus another study. Not included in principal meta-analysis

[n] Relative risk given for "t3" vs "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 8 confounding variables, was also reported by this study

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses

Study author [ref][a]	Exposure index (timing)[b]	Subgroup	Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Sandler[75]	Spouse (ever)	Age - <40	4.42 (0.76-25.8)	3.98 (2), NS	ue
		40-49	2.85 (0.73-11.1)		
		50+	0.67 (0.20-2.22)		
		Premenopausal	7.11 (1.35-37.5)	4.62 (1), p<0.05	ue
		Postmenopausal	0.89 (0.36-2.22)		
Hirayama[75]	Spouse (ever)	Husband's age - 40-49	1.45 (0.50-4.17)	0.96 (3), NS	ue
		50-59	1.64 (0.77-3.50)		
		60-69	1.02 (0.47-2.21)		
		70-79	0.88 (0.15-5.24)		
Morabia[92]	All (ever)[e]	Premenopausal	2.21 (1.03-4.75)	0.03 (1), NS	ae
		Postmenopausal	2.04 (1.19-3.48)		
Morabia[93]	All (ever)[e]	NAT2 slow acetylator	1.9 (0.7-4.6)	2.40 (1), NS	ac_1
		NAT2 fast acetylator	5.9 (2.0-17.4)		
Delfino[44]	Cohabitant (ever)	Premenopausal	2.69 (0.91-8.00)	2.01 (1), NS	ac_2
		Postmenopausal	1.01 (0.45-2.27)		
		NAT2 slow acetylator	Data not shown	NS	ac_3
		NAT2 fast acetylator	Data not shown		
Johnson[59]	Home or work (ever)	Premenopausal	2.3 (1.2-4.6)	2.64 (1), NS	ac_4f
		Postmenopausal	1.2 (0.8-1.8)		
Rookus[36]	Home or work (ever)	p53 normal	Data not shown	NS	c_5
		p53 overexpressed	Data not shown		
Wartenberg[4]	Spouse (ever)	Age at baseline - <50	1.14 (0.81-1.59)	0.65 (3), NS	ac_6eg
		50-59	0.96 (0.73-1.26)		
		60-69	1.00 (0.74-1.36)		
		70+	1.06 (0.65-1.75)		
		Age at marriage - <20	1.04 (0.73-1.48)	0.04 (1), NS	ac_6eg
		20+	1.00 (0.84-1.19)		
Woo[37]	Cohabitant (current)	Premenopausal	2.78 (1.37-5.63)	8.50 (1), p<0.01	u
		Postmenopausal	0.91 (0.71-1.18)		
Kropp[94]	Home or work (lifetime)	NAT2 slow acetylator	1.16 (0.66-2.04)	1.30 (1), NS	ac_6h
		NAT2 fast acetylator	1.98 (0.96-4.09)		
Kropp[95]	Home or work (lifetime)	SULT1A1*1/*1 genotype	1.69 (0.89-3.21)	0.17 (1), NS	ac_6i
		SULT1A1*2 allele carrier	1.40 (0.74-2.64)		
Alberg[42]	Spouse (ever)	NAT2 slow acetylator	1.80 (0.60-5.20)	1.40 (1), NS	ac_7
		NAT2 fast acetylator	0.74 (0.27-2.0)		
		Premenopausal	1.83 (0.32-10.57)	0.37 (1), NS	ue
		Postmenopausal	1.01 (0.45-2.24)		

continued

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/1)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Gammon[53]	Cohabitant (ever)	Premenopausal		1.21 (0.78-1.90)	0.89 (1), NS	ac_4
		Postmenopausal		0.93 (0.68-1.29)		
		BMI	<22.3	1.70 (1.00-2.90)	10.31 (3), p<0.05	ac_4
			22.3-25.0	0.49 (0.28-0.86)		
			25.1-29.2	1.05 (0.65-1.70)		
			>29.2	1.16 (0.66-2.03)		
		Alcohol	- never	0.99 (0.69-1.41)	0.25 (1), NS	ac_4
			- ever	1.13 (0.78-1.64)		
		Use of hormone replacement therapy	- never	1.03 (0.78-1.37)	0.09 (1), NS	ac_4
			- ever	1.14 (0.61-2.12)		
		Use of oral contraceptives				
			- never	1.03 (0.74-1.42)	0.01 (1), NS	ac_4
			- ever	1.05 (0.69-1.59)		
		Family history of breast cancer	- no	0.98 (0.74-1.30)	1.39 (1), NS	ac_4
			- yes	1.49 (0.79-2.82)		
		Age	<65	1.09 (0.79-1.51)	0.43 (1), NS	ac_4
			65+	0.91 (0.59-1.41)		
Gammon[96]	Cohabitant (ever)	MnSOD genotype				
		Val/Val		1.78 (0.93-3.42)	3.15 (1), p<0.1	a
		Ala/Val or Ala/Ala		0.91 (0.64-1.30)		
Gammon[97]	Cohabitant(ever)	P53 genotype				
		- positive		0.94 (0.52-1.68)	1.25 (1), NS	ac_8
		- negative		1.38 (0.99-1.91)		
Shrubsole[65]	Spouse (ever)	Premenopausal		1.0 (0.8-1.3)	0.24 (1), NS	ac_4j
		Postmenopausal		0.9 (0.6-1.2)		
	Workplace (last 5 years)	Most recent job				
		- trade		0.96 (0.58-1.58)	2.38 (3), NS	ac_9e
		- service		1.29 (0.41-4.09)		
		- clerical		0.77 (0.40-1.49)		
		- professional actuarial		1.38 (0.87-2.21)		
Bonner[67]	Cohabitant (ever)	Premenopausal		1.35 (0.78-2.33)	0.35 (1), NS	ac_4
		Postmenopausal		1.10 (0.74-1.64)		
	Workplace (ever)	Premenopausal		0.63(0.41-0.96)	1.79 (1), NS	ac_4
		Postmenopausal		0.89 (0.68-1.18)		
	At home (childhood)	Premenopausal		1.35 (0.84-2.18)	0.17 (1), NS	ac_4
		Postmenopausal		1.20 (0.89-1.63)		
Hanaoka[71]	Cohabitant (ever)[f]	Premenopausal		1.6 (0.9-2.7)	4.71 (1), p<0.05	ac_4k
		Postmenopausal		0.7 (0.4-1.1)		
Sillanpaa[70]	Home or work (ever)	NAT2 slow acetylator		0.69 (0.46-1.03)	0.83 (1), NS	ue
		NAT2 fast acetylator		0.91 (0.59-1.42)		

continued

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/2)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup	Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Sillanpaa[98] (continued)	Home or work (ever)	XRCC1-280 genotype:			
		Arg/Arg	0.75 (0.54-1.03)	0.54 (1), NS	ue
		Arg/His + His/His	1.00 (0.49-2.07)		
		XRCC1-399 genotype:			
		Arg/Arg	0.60 (0.39-0.90)	3.84 (2), NS	ue
		Arg/Gln	1.02 (0.64-1.62)		
		Gln/Gln	1.36 (0.46-4.04)		
		XPD-751 genotype:			
		Lys/Lys	0.63 (0.37-1.07)	1.08 (2), NS	ue
		Lys/Gln	0.90 (0.59-1.37)		
		Gln/Gln	0.80 (0.40-1.60)		
Lissowska[58,90]	Home or work (ever)	Age <45	1.28 (0.52-3.11)	0.50 (2), NS	ac_6n
		45-55	1.27 (0.76-2.11)		
		>55	1.04 (0.74-1.46)		
		Premenopausal	1.55 (0.81-2.97)	1.61 (1), NS	ac_6ep
		Postmenopausal	0.97 (0.71-1.34)		
Mechanic[54]	Cohabitant (adulthood)	African Americans	1.40 (1.00-1.90)	3.02 (1), NS	ac_4
		Whites	1.00 (0.80-1.20)		
		NER 'at risk' genotypes			
		0-1	0.64 (0.39-1.06)	5.81 (2), NS	ac_6e
		2-3	1.16 (0.88-1.52)		
		≥4	1.37 (0.92-2.05)		
Mechanic[88]	Cohabitant (ever)[g]	Premenopausal	1.5 (0.8-2.8)	0.27 (1), NS	ac_{10}
		Postmenopausal	1.2 (0.7-2.2)		
		NAT1 * 10	1.38 (0.78-2.44)	0.02 (1), NS	$ac_{11}e$
		NAT1 – non * 10	1.30 (0.66-2.56)		
		NAT2 slow acetylator	1.46 (0.76-2.80)	0.21 (1), NS	$ac_{11}e$
		NAT2 fast acetylator	1.19 (0.66-2.16)		
Mechanic[89]	Cohabitant (ever)[g]	p53-	0.8 (0.5-1.3)	0.00 (1), NS	ac_{12}
		p53+	0.8 (0.5-1.2)		
Zhu[33]	All (ever)	Premenopausal	Data not shown	NA	q
		Postmenopausal	Data not shown		
		Oral contraceptive use			
		No	Data not shown	NA, p<0.05	r
		Yes	Data not shown		
		Use of other female hormones			
		No	Data not shown	NA, p<0.05	r
		Yes	Data not shown		

continued

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/3)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Roddam[48]	Spouse (ever)	Premenopausal		0.83 (0.59-1.17)	0.31 (1), NS	ac_{13}
		Peri/postmenopausal		1.51 (0.19-12.2)		
		Alcohol	Never drinker	0.93 (0.51-1.69)	0.04 (1), NS	ac_{13}
			Drinker	0.86 (0.56-1.30)		
		Oral contraceptive use				
		Never		0.68 (0.25-1.91)	4.91 (2), p<0.1	ac_{13}
		Within last 5 years		2.51 (0.90-6.99)		
		More than 5 years ago		0.74 (0.49-1.12)		
		Family history of breast cancer	No	0.89 (0.62-1.26)	0.07 (1), NS	ac_{13}
			Yes	1.12 (0.20-6.41)		
		Parity	Nulliparous	0.64 (0.21-1.91)	1.60 (2), NS	ac_{13}
			First birth at age <25	1.06 (0.63-1.78)		
			First birth at age 25+	0.68 (0.40-1.16)		
		Socioeconomic status				
		Professional		0.81 (0.40-1.63)	0.44 (2), NS	ac_{13}
		Non-manual		0.80 (0.45-1.43)		
		Manual/not employed		1.03 (0.58-1.85)		
		BMI	<25	0.72 (0.48-1.07)	0.95 (1), NS	ac_{13}
			25+	1.07 (0.54-2.14)		
		Age at menarche	<13	1.09 (0.66-1.79)	1.91 (1), NS	ac_{13}
			13+	0.67 (0.42-1.09)		
Pirie[55]	Parents (ever)/spouse (current)	Premenopausal		0.54 (0.30-0.99)	3.80 (2), NS	ac_4
		Perimenopausal		1.03 (0.69-1.55)		
		Postmenopausal		0.98 (0.87-1.10)		
		Age	<56	0.87 (0.73-1.04)	2.48 (1), NS	ac_4
			56+	1.04 (0.91-1.19)		
		Employed when passive exposure reported	Yes	0.94 (0.80-1.10)	0.31 (1), NS	ac_6
			No	1.00 (0.86-1.16)		
		Age at menarche	<13	0.97 (0.82-1.16)	0.01 (1), NS	ac_4
			13+	0.98 (0.86-1.13)		
		Parity	Nulliparous	0.97 (0.74-1.28)	0.01 (1), NS	ac_4
			Parous	0.98 (0.87-1.10)		
		Age at first birth	<21	1.09 (0.73-1.63)	0.35 (1), NS	ac_4
			21+	0.96 (0.85-1.09)		
		Alcohol	Non-drinker	1.04 (0.87-1.25)	1.54 (1), NS	ac_4
			Drinker	0.90 (0.78-1.03)		

continued

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/4)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Pirie[55] (continued)		Oral contraceptive use				
			Ever	0.96 (0.83-1.11)	0.08 (1), NS	ac_6
			Never	0.99 (0.84-1.16)		
		HRT use	Current user	1.08 (0.90-1.30)	2.16 (1), NS	ac_4
			Not current user	0.91 (0.80-1.05)		
		BMI	<25	1.01 (0.86-1.18)	0.30 (1), NS	ac_4
			25+	0.95 (0.82-1.11)		
		Strenuous physical activity				
			< Once/week	0.99 (0.85-1.14)	0.01 (1), NS	ac_4
			Once+/week	1.00 (0.85-1.18)		
		Living with partner	Yes	1.01 (0.90-1.13)	0.49 (1), NS	ac_4
			No	0.92 (0.73-1.17)		
Slattery[72]	Any (ever)	Pre/perimenopausal		1.13 (0.85-1.50)	0.42 (1), NS	ac_{14}e
		Postmenopausal		1.00 (0.79-1.27)		
		Non-Hispanic		1.07 (0.82-1.38)	0.02 (1), NS	ac_{15}e
		Hispanic/American Indian		1.04 (0.79-1.36)		
		IL6 genotype	GG	1.08 (0.81-1.44)	1.35 (1), NS	ue
			GA/AA	0.85 (0.64-1.13)		
		ESR1 genotype	xx	0.91 (0.68-1.22)	0.66 (1), NS	ue
			xX/XX	1.05 (0.80-1.38)		
Reynolds[6]	Cohabitant (ever)	Pre/perimenopausal (at baseline)		0.93 (0.71-1.22)	0.01 (1), NS	ac_4f
		Postmenopausal (at baseline)		0.92 (0.78-1.08)		
Reynolds[87]	Cohabitant (ever)	Age (at diagnosis/end of follow-up)	<50	1.05 (0.76-1.45)	0.96 (1), NS	ac_6ef
			≥50	0.88 (0.76-1.01)		
Chilian-Herrera[38]	Home or work (ever)	Premenopausal		4.75 (2.58-7.35)[h]	2.31 (1), NS	ac_6
		Postmenopausal		2.83 (1.87-4.28)[h]		
Conlon[60]	Home or work (ever)	NAT2 slow acetylator		1.55 (0.63-3.83)	0.93 (1), NS	ue
		NAT2 fast acetylator		0.78 (0.27-2.25)		
Luo[57]	Any (ever)	Histology	Ductal cancer	1.02 (0.83-1.26)	0.35 (1), NS	ac_6
			Lobular cancer	1.22 (0.70-2.11)		
		Hormone receptor	OR+PR+	1.04 (0.84-1.29)	0.14 (2), NS	ac_6
			OR+PR-	1.14 (0.70-1.86)		
			OR-PR-	1.10 (0.69-1.75)		
Xue[5]	Home and work (adulthood)	Premenopausal		Data not shown	NS	ac_4
		Postmenopausal		Data not shown		

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/5)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Anderson[40]	Cohabitant (childhood)	Premenopausal		0.81 (0.58-1.12)	0.67 (1), NS	ac_6e
		Postmenopausal		0.96 (0.75-1.21)		
	Cohabitant (adulthood)	Premenopausal		1.07 (0.78-1.47)	0.01 (1), NS	ac_6e
		Postmenopausal		1.09 (0.86-1.39)		
	Work (adulthood)	Premenopausal		0.98 (0.71-1.35)	0.01 (1), NS	ac_6e
		Postmenopausal		1.00 (0.79-1.27)		
	Social situations (adulthood)	Premenopausal		1.21 (0.88-1.66)	0.18 (1), NS	ac_6e
		Postmenopausal		1.11 (0.88-1.41)		
	Any (teenage)	Premenopausal		0.98 (0.69-1.39)	0.23 (1), NS	ac_6e
		Postmenopausal		0.88 (0.68-1.14)		
	Any (adulthood)	Premenopausal		1.18 (0.78-1.77)	0.28 (1), NS	ac_6e
		Postmenopausal		1.02 (0.71-1.45)		
	Any (teenage)	CYP2E1 genotype:				
		Premenopausal	CC	1.15 (0.72-1.81)	1.29 (1), NS	ac_6e
			TC/TT	0.77 (0.46-1.29)		
		Postmenopausal	CC	1.18 (0.84-1.68)	6.13 (1), $p < 0.05$	ac_6e
			TC/TT	0.59 (0.38-0.89)		
		NAT2 c341 genotype:				
		Premenopausal	TT	0.87 (0.50-1.52)	0.1 (2), NS	ac_6e
			CT	0.98 (0.59-1.62)		
			CC	0.94 (0.40-2.25)		
		Postmenopausal	TT	0.81 (0.50-1.31)	2.08 (2), NS	ac_6e
			CT	1.07 (0.72-1.59)		
			CC	0.65 (0.36-1.16)		
		NAT2 c.803 genotype:				
		Premenopausal	AA	0.88 (0.51-1.52)	0.21 (2), NS	ac_6e
			AG	0.95 (0.57-1.57)		
			GG	1.13 (0.45-2.85)		
		Postmenopausal	AA	0.88 (0.55-1.41)	1.28 (2), NS	ac_6e
			AG	1.00 (0.68-1.48)		
			GG	0.66 (0.36-1.21)		
		NAT2 c.-6-2933 genotype:				
		Premenopausal	TT	1.00 (0.61-1.63)	0.09 (2), NS	ac_6e
			CT	0.90 (0.51-1.58)		
			CC	0.90 (0.28-2.88)		
		Postmenopausal	TT	0.95 (0.65-1.38)	1.07 (2), NS	ac_6e
			CT	0.79 (0.51-1.22)		
			CC	1.41 (0.47-4.21)		
	Work (adulthood)	UGT1A7 genotype:				
		Premenopausal	GG	1.34 (0.79-2.28)	3.73 (2), NS	ac_6e
			GT	0.68 (0.43-1.07)		
			TT	0.78 (0.34-1.77)		
		Postmenopausal	GG	1.23 (0.83-1.81)	2.49 (2), NS	ac_6e
			GT	0.96 (0.67-1.37)		
			TT	0.69 (0.37-1.29)		
Anderson[99]	Childhood/adulthood	6 further candidate genes		Data not shown[i]	-	-

continued

TABLE 7 - Relative risk of breast cancer in lifelong nonsmoking women according to ETS exposure; subgroup analyses (continued/6)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Tang[46]	Home or workplace (adulthood)	Premenopausal		1.54 (1.14-2.07)	0.02 (1), NS	ac_4
		Postmenopausal		1.49 (1.03-2.16)		
		PARP1 genotype:	TT	1.40 (0.93-2.10)	0.23 (1), NS	ac_7
			TC + CC	1.58 (1.20-2.08)		
		ESR1 genotype:	TT	1.40 (0.97-2.04)	0.31 (1), NS	ac_7
			TC + CC	1.60 (1.20-2.13)		

[a] Studies are identified by the first author of the principal publication

[b] Reference group is all lifelong nonsmokers unexposed to the given source, except where indicated by a reference to other notes

[c] Heterogeneity The chisquared 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 education, family history of breast cancer
  - c_2 family history of breast cancer
  - c_3 family history of breast cancer, menopausal status
  - c_4 all variables listed in Table 2 except the subgroup variable
  - c_5 lifetime physical activity, other unspecified confounders
  - c_6 all variables listed in Table 2
  - c_7 menopausal status
  - c_8 income, daily alcohol intake, education
  - c_9 all variables listed in Table 2, and passive smoking from husband
  - c_{10} race, age at menarche, age at first full-term pregnancy, parity, family history of breast cancer, benign breast biopsy, alcohol
  - c_{11} as c_2 plus menopausal status
  - c_{12} race, sampling fraction
  - c_{13} region, parity and oral contraceptive use
  - c_{14} all variables listed in Table 2, and ethnicity
  - c_{15} all variables listed in Table 2, and menopausal status
- u unadjusted
- e estimated from data reported
- f relative risks for adult and childhood exposure separately also did not vary significantly by menopausal status or age at diagnosis (data not shown)
- g relative risks for spouse (current) and spouse (former) also did not vary significantly by age at baseline or by age at marriage (data not shown)
- h relative risks for adult and childhood exposure separately also did not vary significantly by NAT2 acetylation genotype (data not shown)
- i relative risks for adult exposure also did not vary significantly by SULT1A1 genotype (data not shown)
- j relative risks for workplace exposure and for combined spousal and workplace exposure also did not vary significantly by menopausal status (data not shown)
- k relative risks for exposure other than at home and for any exposure were also both significantly higher for premenopausal than postmenopausal women. Non-home (2.3 vs 0.4, Heterogeneity p<0.001), Any (2.6 vs 0.7, Heterogeneity p<0.01)
- n for each age group, dose response analysis (<100, 101-200, >200 hours/day-years) was non-significant (p-value for trend 0.93, 0.24, 0.35 for age groups <45, 45-55, >55 years respectively)
- p for each menopausal status, dose response analysis (<100, 101-200, >200 hours/day-years) was marginally or non-significant (p-value for trend 0.08 for premenopausal, 0.74 for postmenopausal)
- q results quoted only as "The [hazard ratio] for [secondhand smoke] was higher among premenopausal than postmenopausal women."
- r results quoted only as "The [hazard ratio] for [secondhand smoke] was synergistically increased by oral contraceptive (a p for interaction = 0.04) and other female hormone use (a p for interaction = 0.01)."

[e] Exposed for at least 1 hour/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] Relative risk given for "t3" vs "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[99] refers to having studied 11 candidate genes, including the 5 for which results were given in the later paper[40] 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 8– Meta-analyses of breast cancer risk in relation to ETS exposure

Index of exposure (Data source)	Subgroup	N[b]	Fixed-effect Relative risk (95% CI)	Random-effects Relative risk (95% CI)	Heterogeneity[a] Chisquared	DF[c]	p[d]
Spouse (Table 3)[e]	All	11	1.05 (0.97-1.14)	1.10 (0.95-1.27)	20.28	10	<0.05
Spouse or cohabitant (Table 3)[f]	All	30	1.03 (0.995-1.07)	1.06 (0.998-1.12)	55.00	29	<0.01
Workplace (Table 4)[g]	All	14	1.02 (0.98-1.06)	1.02 (0.96-1.09)	22.37	13	<0.05
Any adult (Table 4)[h]	All	12	1.07 (1.02-1.12)	1.10 (1.02-1.18)	25.46	11	<0.01
Child (Table 5)[i]	All	18	0.99 (0.96-1.03)	1.00 (0.95-1.06)	23.26	17	NS
Total (Table 6)	All	19	1.09 (1.04-1.14)	1.15 (1.06-1.24)	86.70	18	<0.001
Various (Table 7)[j]	Premenopausal	19	1.25 (1.13-1.39)	1.43 (1.17-1.75)	64.08	18	<0.001
	Postmenopausal	19	1.01 (0.95-1.08)	1.08 (0.96-1.22)	43.72	18	<0.001
	Ratio pre/post	19	1.22 (1.07-1.40)	1.27 (1.06-1.52)	25.56	18	NS
Principal[k]	All	39	1.05 (1.02-1.09)	1.13 (1.05-1.21)	123.99	38	<0.001
	Prospective	14	1.01(0.97-1.05)	1.01 (0.96-1.06)	14.78	13	NS
	Case-control	25	1.16 (1.09-1.23)	1.26 (1.11-1.44)	94.58	24	<0.001
				(Between study types)	*14.63*	*1*	*<0.001)*
	N.America[l]	20	1.04 (0.995-1.08)	1.12 (1.02-1.23)	65.14	19	<0.001
	Asia	9	1.15 (1.03-1.29)	1.16 (0.92-1.47)	31.43	8	<0.001
	Europe	10	1.05 (0.99-1.12)	1.11 (0.97-1.26)	24.37	9	<0.01
				(Between continents)	*3.05*	*2*	*NS)*
	>500 cases	16	1.03 (0.99-1.07)	1.04 (0.99-1.09)	22.18	15	NS
	<500 cases[m]	20	1.10 (0.995-1.21)	1.19 (0.998-1.41)	53.02	19	<0.001
				(Between study sizes)	*1.48*	*1*	*NS)*
	9+ confounders	17	1.01 (0.98-1.05)	1.03 (0.96-1.11)	39.70	16	<0.001
	<9 confounders[n]	19	1.13 (1.05-1.22)	1.16 (1.04-1.30)	31.40	18	<0.05
				(Between adjustments)	*7.02*	*1*	*<0.01)*

[a] Heterogeneity relates to variation between studies within subgroup, except for results given in italics which relate to heterogeneity between subgroups
[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≥0.1)
[e] Index includes "partner". Spouse (ever) is chosen for preference where multiple results are available
[f] First relative risk cited for each study in Table 3
[g] Index includes "not home"
[h] Index includes "home or workplace"
[i] First relative risk cited for each study in Table 5
[j] For the Reynolds study, results given by age at diagnosis (<50, ≥50) were used in preference to results by menopausal status at baseline
[k] Based on relative risks marked with an "m" in the notes column in Tables 3, 4 and 6
[l] Including one study in Mexico
[m] The number of cases in nonsmokers was not known for three studies (see Tables 3 and 6)
[n] Three studies were excluded as the number of confounding variables adjusted for other than age was not clear (see Table 2)

7. References

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8. Appendix

Weaknesses noted in individual studies are commented on below:

(i) In the Sandler study[43] friends of cases were used as controls, which seem unlikely to be representative. Also, the proportion of subjects responding by mailed questionnaire and telephone interview varied markedly between cases and controls;

(ii) In the Hirayama study[41] adjustment was for age of the husband, not age of the subject, and mortality tracing was incomplete;

(iii) The Jee study[51] involved only a 35% participation rate of subjects, increasing the likelihood of nonrepresentativeness;

(iv) In the Johnson and Anderson studies[40,59] non-response rates were very high due to use of mailed questionnaires;

(v) In the Liu study[45] the adjusted analyses reported made no logical sense (see footnote to Table 2), so only unadjusted risks could be used;

(vi) The Rookus, Woo, Zhu and Chilian-Herrera studies[33,36-38] were only reported as abstracts, so full details were not available to assess study quality;

(vii) In the two Lash studies[34,35] the rate of proxy interviews was high and differed between cases and controls; and

(viii) In the Kropp study[49] the cases were identified in 1992-1995 but the smoking histories were not obtained until 1999-2000, with the interview rate low.

(ix) In the Alberg study[42] the cases were identified in 1990-1995 but the smoking histories were not obtained until 1995.

(x) In the Sillanpaa study[70], response rates were 26% lower for controls than for cases.

(xi) In the Rollison study[68], participation rates were low overall, and differed markedly between cases and controls.

(xii) In the Slattery study[72], not all cases in non-Hispanic subjects were included. Instead a random sample was chosen, with the ratio to Hispanic/American Indian cases varying between states.

(xiii) In the Ahern study[69], participation rates were very low and differed between cases and controls. Additionally, cases were restricted to subjects with a telephone number and a driver's licence, while controls were sampled by

driving licence or Medicare rosters, according to their age. Thus, there may be issues with the representativeness of the subjects in this study.

(xiv) In the Conlon study[60] unadjusted relative risks had to be estimated, as the adjusted risks given used subjects with the lowest exposure as the reference group. In addition, cases were selected from cancer registries while controls were restricted to those with a telephone number, so may not be a representative sample. Overall, participation rates were low in this study and varied between the case and control groups.

(xv) In the De Silva study[61], cases were selected from participating hospitals, while the controls came from community clinics and thus may not be strictly comparable. In addition, there was no adjustment for the subject's age in this study.

(xvi) In the Tang study[46], the response rate in the cases varied considerably between hospitals and in some, was lower than in the controls. Additionally, controls were selected from the primary care databases of the case hospitals so may not be a representative sample.

(xvii) In the Dossus study[74], one cohort was selected from members of a health insurance plan covering state school employees, two cohorts were selected from members of local blood donor associations, two cohorts were selected from women attending for breast cancer screening and one cohort partially consisted of vegetarians and healthy eaters. None of these cohorts appears to be a representative sample of the population. Furthermore, the questions regarding passive smoking exposure varied between study site. In particular, information on exposure during childhood was only collected in three countries, so that in other countries women defined as never exposed may in fact include subjects with childhood exposure to passive smoking.