EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND BREAST CANCER

A Review With Meta-Analyses

Executive Summary

Results of 33 studies relating breast cancer in women to ETS exposure in non-smokers 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 30 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 1.06 (95% CI 0.99-1.14). However, the 30 estimates were significantly ($p<0.01$) heterogeneous, with estimates close to 1.00 for prospective studies, North American and Asian studies, larger studies (>500 cases) and studies taking more confounding variables than average into account, significantly elevated in case-control studies (1.14, 1.01-1.29) and in those studies that had taken fewer confounding variables than average into account (1.17, 1.01-1.37), and non-significantly raised in European studies (1.20, 0.99-1.44) and in smaller studies (1.14, 0.95-1.36). In those studies providing relevant data, there was no evidence of an association in postmenopausal women, but some increase in premenopausal women (1.30, 1.06-1.59).

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

Authors: Peter Lee, Alison Thornton and Jan Hamling

other cohabitant. However it was notable that from those 12 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 somewhat higher (1.18, 1.04-1.35).

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.

Contents

Acknowledgement

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

Authors: Peter Lee, Alison Thornton and Jan Hamling

1. Introduction

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 non-smokers 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], and 2008[9] 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 non-smokers. This requirement means that some studies which might at first have seemed relevant[10-15] have been excluded from consideration.

We also comment briefly on similar reviews by Johnson[16], the California EPA[17] and the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk[18].

2. Methods

In August 2010, publications describing the results of epidemiological studies relating the risk of breast cancer in non-smoking women to ETS exposure, that were not included in our previous reviews[7-9], were sought from MEDLINE searches (using search terms "cancer" and "tobacco smoke pollution" and the date range 2001 to August 2010), 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[19] 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 the 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. pre- and post-menopausal women), estimates for the total population were combined by fixed-effect meta-analysis[20], 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[21,22] (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[20]. 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 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

* 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.

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[23,24], 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[25]. Other endpoints used in meta-analyses are discussed later. Three studies reported only as abstracts could not be included in the principal meta-analysis: the first[26] because the comparison group consists of the lowest quartile of duration of exposure (not no or minimal exposure), the second[27] 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, and the third[28] because detailed results were not presented for exposure at home.

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[29,30] identified as Lash I and Lash II. As shown in Table 1, two of the studies were published in the 1980s, five in the 1990s, 25 between the years 2000 and 2009, and one in 2010. This reflects a massive upsurge of interest in studying the possibility that ETS might cause breast cancer. Five studies[26-28,31,32] were published only as abstracts.

Of the 33 studies, 17 have been conducted in North America (14 in the USA, three in Canada), eight in Asia (four in Japan, three in China, one in Korea) and eight in Europe (three in the UK and one each in the Switzerland, Netherlands, Germany, Norway/Sweden and Poland).

Eleven of the studies were of prospective design, with follow-up varying from 3.5 to 16 years. The majority of these studies were of breast cancer onset, but the Hirayama and Wartenberg studies[4,33] were of breast cancer mortality, based on death certificates. The Woo study[32] was a case-control study nested within a prospective study of incident breast cancer. The remaining 21 studies were of case-control design, mainly using population controls. However, the Sandler study[34] used friends of cases or controls, which are not necessarily representative of the population, and two used hospital-based controls, the Delfino study[35] using benign breast disease patients, and the Liu study[36] 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[29,30] used proxy interviews for deceased cases and their matched controls. The Smith study[37] had an upper age limit of 36 years for cases, and the Roddam study[38] an upper age limit of 45. Two studies[39,40] had an age limit of 50 years and two[31,36] 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[33,41], both conducted in Asia, and in the Roddam study[38] in the UK, only exposure from the spouse/partner was studied. An additional 10 studies[29,30,32,34,35,40,42-45] restricted attention to at-home exposure. The other 20 studies

collected information on more extensive sources of exposure, either individually or totally.

Results were mainly reported for all breast cancer cases combined, but two studies[44,46] reported some results by hormone receptor status of the cases, while one of these[44] also reported results separately for *in situ* and invasive cases.

Twenty-four of the 33 studies presented results not only for the whole population of non-smokers studied, but also for subgroups of the population. Most commonly (18 studies), this was for subgroups defined by menopausal status, but seven studies gave results by age (or age of husband) and nine 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[39,46,47] exposure had to be for at least 1 hour/day for a year, while in the Johnson study[48] the women had to be in the presence, specifically, of regular smokers. The Rookus study[31] 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 Conlon study[26] presented results using the lowest quartile of exposure duration as the comparison.

Table 2 lists the potential confounding variables adjusted for in analysis. The studies by Rookus, Woo, Zhu and Anderson[27,28,31,32] published only as abstracts did not make it particularly clear which variables had been adjusted for. Of the other 29 studies, all had adjusted for age, except for the Hirayama study[33], which adjusted for age of the husband. The Hirayama, Sandler and Conlon studies[26,33,34] 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), education (or socio-economic status) and hormone

use. These are all well known risk factors for breast cancer[49,50]. Other less commonly considered variables included physical activity, 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 26 studies. Statistically significantly increased ($p<0.05$) RRs and/or dose-related trends were seen in three studies[29,36,46], but the more recent studies show no evidence of an increase. In fact, in one study[51], a significantly reduced risk of breast cancer was reported in association with past exposure to cohabitant's smoking.

Ten of these studies presented results specifically for exposure from the spouse (or partner in the Smith[37], Roddam[38] and Pirie[45] 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 (0.96-1.14), 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[46] and the low RR estimate of 0.58 in the Nishino study[43]. When random-effects meta-analysis is carried out, the RR estimate is slightly increased, to 1.10, but remains non-significant (95% CI 0.95-1.28).

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 1.01 (0.96-1.06) while the random-effects estimate is 1.03 (0.96-1.12). Again, the high estimate from the Morabia study[46] 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 15 studies. Ten studies gave results for workplace exposure (or not-home exposure), with the Liu, Shrubsole and Anderson studies[28,36,52] showing

significant RRs and/or trends. However, the RR from the Anderson study was restricted to women with the highest exposure and is not included in the meta-analyses. The nine 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[53] and 0.80 (0.49-1.32) from the Rollison study[54] contrasting with estimates 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 nine studies for either any adult exposure or for home or workplace exposure. Significantly increased RRs are seen in the Johnson and Kropp studies[39,48], but the overall estimates of risk are not clearly elevated, with the fixed-effect estimate (1.09, 1.01-1.17) marginally significant and the random-effects estimate (1.11, 0.995-1.24) not quite significant. There was some indication of heterogeneity between the results ($p<0.1$).

The results for childhood exposure shown in Table 5 are from 16 studies. Most of the RRs are quite close to 1.00 and none are statistically significant, although the Liu study[36] did report a significant positive trend. 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 (0.94-1.05) and a random-effects estimate of 1.01 (0.94-1.08).

Table 6 presents results from 14 studies for an index of total lifetime exposure, seven[26,31,39,45,47,48,54] based on questions restricted to home and work, and seven based on a wider definition[27,37,46,55-58]. Significant increases and/or dose-related positive trends were seen in the Morabia, Johnson, Kropp and Reynolds studies[39,46,48,58]. Two studies reported only in abstracts[26,27] found dose-related positive trends but give insufficient detail to quote overall relative risks. Though the 12 RR estimates in Table 6 were significantly ($p<0.01$) heterogeneous, 10 of the estimates were above 1, and significant overall estimates were seen using either fixed-effect (1.08, 1.01-1.16) or random-effects (1.18, 1.04-1.35) 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[30], 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 15 studies that reported results separately for pre- and postmenopausal women, the studies by Sandler, Woo and Hanaoka[32,55,59] reported RRs that were significantly higher in premenopausal than postmenopausal women, indeed finding no increase at all for postmenopausal women. In the Delfino and Johnson studies[35,48] a similar pattern was seen, but the variation by menopausal status was not significant. In the study by Pirie[45], the RR for premenopausal women was significantly decreased, while no association was seen for peri- or postmenopausal women. The remaining nine studies showed no evidence of variation in risk according to menopausal status.

As shown in Table 8, the 15 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 ($p<0.01$) and the random-effects estimate (1.30, 1.06-1.59) was higher than the fixed-effect estimate (1.16, 1.03-1.30). 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 1.33 (1.07-1.66). The random-effects estimate for premenopausal women was little changed, to 1.34 (1.11-1.62), if RRs for two additional case-control studies of young women[37,39] 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[4,33] 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, IL6, ESR1 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[27] by use of

oral contraceptives and by use of other female hormones, and in the Gammon study[44] by BMI, where the variation was not systematic, and may well be due to chance.

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 30 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 25 RRs considered in the meta-analysis of spouse or cohabitant exposure (Table 3), together with the RRs from the Johnson study[48], the Kropp study[39] and the Ahern study[57] shown in Table 4, and from the Rookus study[31] and the Slattery study[56] shown in Table 6. They are marked with an "m" in the notes column of these three tables.

Overall, these 30 studies give a fixed-effect estimate of 1.03 (0.98-1.08) which is not quite significant. However, there is highly significant ($p<0.01$) heterogeneity, the largest contribution being from the high RRs in the Morabia study[46] and the Kropp study[39]. As a result, the random-effects estimate is slightly higher (1.06, 0.99-1.14), although it is still not 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 11 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 19 case-control studies do show an association, with the fixed-effect estimate (1.08, 1.00-1.17) being of borderline significance, and the random-effects estimate (1.14, 1.01-1.29) being statistically significant. The estimates for the case-control studies are significantly heterogeneous ($p<0.01$).

Continent : The results from the 15 North American studies show no heterogeneity and both the fixed-effect estimate (1.00, 0.95-1.06) and the random-effects estimate (1.02, 0.94-1.10) are close to 1. In contrast, the results from the eight

European studies, though heterogeneous ($p<0.01$), show an increase, which just fails to reach statistical significance, for both the fixed-effect model (1.09, 0.998-1.19), and the random-effects model (1.20, 0.99-1.44). The estimates from the seven Asian studies are also significantly heterogeneous ($p<0.05$), but show little increase in risk for either model (fixed-effect: 1.02, 0.90-1.16, random-effects: 1.02, 0.83-1.26). The heterogeneity between continents is not statistically significant.

Study size : The results from the 11 largest studies, involving over 500 cases, show no evidence of heterogeneity and combined risk estimates of 1.00. In contrast, the 17 smaller studies show significant ($p<0.001$) heterogeneity and a non-significant increase, whether fixed-effect (1.07, 0.97-1.19) or random-effects (1.14, 0.95-1.36) 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 less. In both groups, there is significant heterogeneity. In the 15 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 0.99, 0.94-1.05, random-effects 1.01, 0.93-1.10) but, in the group that had adjusted for eight or less, there was a significant relationship (fixed-effect 1.17, 1.05-1.30, random-effects 1.17, 1.01-1.37). 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 30 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 non-significantly increased RR estimate of 1.06 (0.99-1.14). 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[17,60]. 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[19]. 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[18], it was concluded that "the relationship between active smoking and breast cancer is consistent with causality", as is the relationship between ETS and breast cancer in younger, primarily menopausal 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[61].

In contrast, IARC has concluded that there is evidence suggesting a lack of carcinogenicity of tobacco smoking for female breast cancer[60], a combined analysis from 53 studies showing that a weak association can be explained by confounding by alcohol consumption[1]. A review by the US Surgeon General[62] has 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.

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 non-smokers, 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 side stream 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[63]. 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[25]. 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 30 estimates are significantly ($p<0.01$) heterogeneous. Risk estimates (random-effects) are close to 1.00 for prospective studies, for North American 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 1.14, 1.01-1.29) and in studies that had taken fewer confounding variables than average into account (1.17, 1.01-1.37), and are non-significantly raised in European studies (1.20, 0.99-1.44) and in smaller studies (1.14, 0.95-1.36).

It is also notable that in those 15 studies which provided separate estimates, there is evidence of an association in premenopausal women (1.30, 1.06-1.59) 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 12 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 1.18 (1.04-1.35). Also, as shown by additional analysis, there was a relatively high random-effects estimate of 1.14 (0.99-1.31) when the principal meta-analysis was restricted to those 13 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[31,37,39,46,48].

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[25]. Marriage to a smoker has also had a long history of use in studies of ETS and other diseases, notably lung cancer (e.g. Hackshaw[64]). 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 30 estimates for the principal ETS exposure index, dose-response data were available for only 14 studies. No significant trend was seen in 12 of these, with estimates close to unity for all levels of the dose-response metrics considered in six of them: the Wartenberg, Egan, Lash II, Gammon, Shrubsole and Roddam studies[4,5,30,38,44,52]. Only two studies showed a statistically significant trend (both calculated including the unexposed group). Of these Liu[36] showed a response that clearly increased within the exposed groups, but the Morabia study[46] 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. 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, Conlon and Zhu studies[26,27,39,48,65]. 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 last two are reported only as abstracts so no detailed comment can be made.

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[66], 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 9 variables or more, but a significant increase in studies that adjusted for 8 variables or less. 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 9 variables or more included all the four large prospective studies (Wartenberg, Egan, Pirie and Reynolds[4,5,45,58]) that found no association of ETS exposure with breast cancer risk, and which together contributed nearly 50% 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, Egan, Hanaoka and Lin studies[4,5,37,51,55] 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[67]. 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[68,69] 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 eight 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[29,30], 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.

Some other issues related to specific studies also deserve comment:

(i) In the Sandler study[34] 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[33] adjustment was for age of the husband, not age of the subject, and mortality tracing was incomplete;

(iii) The Jee study[41] involved only a 35% participation rate of subjects, increasing the likelihood of nonrepresentativeness;

(iv) In the Johnson study[48] non-response rates were very high due to use of mailed questionnaires;

(v) In the Liu study[36] the adjusted analyses reported made no logical sense (see footnote to Table 2), so only unadjusted risks could be used;

(vi) The Rookus, Woo, Conlon, Zhu and Anderson studies[26-28,31,32] were only reported as abstracts, so full details were not available to assess study quality;

(vii) In the two Lash studies[29,30] the rate of proxy interviews was high and differed between cases and controls; and

(viii) In the Kropp study[39] 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 Rollison study[54], participation rates were low overall, and differed markedly between cases and controls.

(x) In the Slattery study[56], 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.

(xi) In the Ahern study[57], 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.

Of the 30 estimates included in the principal meta-analysis, 13 relate to studies cited in the previous paragraph. 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 1.00, 95% CI 0.92-1.09) but a significantly increased risk in the poorer studies (random-effects RR 1.19, 95% CI 1.04-1.36). 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 15 studies that allowed comparison of the risks associated with ETS exposure in pre- and post-menopausal women, 11 were case-control studies, three were prospective studies and one was a case-control study nested in a prospective study. 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. The abstract[32] does not make the position clear for the nested, Woo, study. Given the length of follow-up in the prospective Hanaoka study[55], 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[45] where follow-up was only for 3.5 years. The follow-up in the prospective study by Reynolds[58] 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[70] 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[16] and the California EPA[17] 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[31,32], omit giving any results from the study with apparently unreliable adjusted estimates[36] and include results from a study by Zhao *et al*[13] 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 Millikan study, they use an estimate from one source[42] when there is a later estimate from another source[71] that is based on considerably more cases. Also, for the Smith study[37] 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 pre-menopausal but not post-menopausal 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[16] 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[46,48] 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[46] 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[48] 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[17] 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[18], which included all of the studies in the California EPA review, plus those by Bonner[53], Lissowska[72], Roddam[38] and Pirie[45], 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[16-18], 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]. 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[25] 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.

Generally, the reviews by Johnson[16], the California EPA[17] and the Canadian Expert Panel[18] do not provide convincing evidence of a true relationship of ETS exposure to breast cancer risk.

5. Summary and conclusions

Results of 33 studies relating breast cancer in women to ETS exposure in non-smokers 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 30 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 1.06 (95% CI 0.99-1.14). However, the 30 estimates were significantly ($p<0.01$) heterogeneous, with estimates close to 1.00 for prospective studies, North American and Asian studies, larger studies (>500 cases) and studies taking more confounding variables than average into account, significantly elevated in case-control studies (1.14, 1.01-1.29) and in those studies that had taken fewer confounding variables than average into account (1.17, 1.01-1.37), and non-significantly raised in European studies (1.20, 0.99-1.44) and in smaller studies (1.14, 0.95-1.36). In those studies providing relevant data, there was no evidence of an association in postmenopausal women, but some increase in premenopausal women (1.30, 1.06-1.59).

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 12 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 somewhat higher (1.18, 1.04-1.35).

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[34,59,73]	1985	USA, N Carolina	CC-F	Sp, Ma, Pa	Age, menopause
Hirayama[33,59,73]	1987	Japan, 6 prefectures	P(16)	Sp	Age of husband
Smith[37]	1994	UK, 11 regions	CC-P	Sp, Oc, Wk, Oa, Ch	-
Morabia[46,74,75]	1996	Switzerland, Geneva	CC-P	Sp, Wk, Oa[f]	Menopause, NAT2 acetylation genotype
Millikan[42,71]	1998	USA, N Carolina	CC-P	Co	Menopause, p53 expression NAT1 and NAT2 acetylation genotypes,
Jee[41]	1999	Korea, nationwide	P(6)	Sp	-
Lash I[29]	1999	USA, Massachusetts	CC-P	Co	-
Delfino[35]	2000	USA, California	CC-B	Co	Menopause, NAT2 acetylation genotype
Johnson[48]	2000	Canada, 8 provinces	CC-P	Co, Wk, Ch	Menopause
Liu[36]	2000	China, Chongqing	CC-H	Co, Wk, Ch	-
Rookus[31]	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[32]	2000	USA, Maryland	NCC	Co	Menopause
Nishino[43]	2001	Japan, Miyagi	P(9)	Sp, Oc	-
Egan[5]	2002	USA, Nationwide	P(15)	Co, Wk, Ma, Pa	Menopause
Kropp[39,76,77]	2002	Germany, 2 regions	CC-P	Co, Wk, Ch	NAT2 acetylation genotype, SULT1A1 genotype
Lash II[30]	2002	USA, Massachusetts	CC-P	Co	-
Gammon[44,78]	2004	USA, New York	CC-P	Sp, Oc	Age, menopause, HRT use, BMI, alcohol, use of oral contraceptives, family history of breast cancer, MnSOD genotype
Shrubsole[52]	2004	China, Shanghai	CC-P	Sp, Wk	Menopause, most recent job
Bonner[53]	2005	USA, New York state	CC-P	Co, Wk, Ch	Menopause
Gram[40]	2005	Norway and Sweden	P(10)	Co	-
Hanaoka[55]	2005	Japan, 14 districts	P(10)	Co, Ob	Menopause
Conlon[26]	2006	Canada, Ontario	CC-P	Co, Wk	Acetylation genotype
Lissowska[47,72]	2006	Poland, Warsaw and Łódź	CC-P	Co, Wk	Age, menopause
Zhu[27]	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[38]	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[51]	2008	Japan, nationwide	P(13)	Co, Ob, Ch	-
Pirie[45]	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[54]	2008	USA, Delaware	CC-P	Co, Ch, Wk, To	-
Slattery[56]	2008	USA, 4 states	CC-P	To	Menopausal status, race, IL6 genotype, ESR1 genotype
Ahern[57]	2009	USA, Massachusetts	CC-P	Co, Wk, Ma, Pa, To	-
Reynolds[6,58,70]	2009	USA, California	P(10)	Co,,Wk, Ch, To	Age at diagnosis, menopause at baseline
Anderson[28]	2010	Canada, Ontario	CC-P	Co, Ob,Wk, Ch	Menopause, 11 candidate genes

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

[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

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[34,59,73]	1985	Age (only in spousal analyses)
Hirayama[33,59,73]	1987	Age of husband
Smith[37]	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[46,74,75]	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
Millikan[42,71]	1998	Age, race, sampling fraction, p53 expression
Jee[41]	1999	Age, socioeconomic status, residency, husband's age, husband's vegetable consumption, husband's occupation
Lash I[29]	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[35]	2000	Age, menopausal status, family history of breast cancer
Johnson[48]	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[36]	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[31]	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[32]	2000	Menopausal status and possibly other confounders
Nishino[43]	2001	Age, study area, alcohol, green and yellow vegetable intake, fruit intake, age at first birth, number of live births, age at menarche, BMI
Egan[5]	2002	Age, age at menarche, age at first birth, parity, history of benign breast disease, family history of breast cancer, menopausal status, age at menopause, weight at 18 years, adult weight change, adult height, alcohol, carotenoid intake, menopausal hormone use

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[39,76,77]	2002	Age, alcohol, breastfeeding, education, family history of breast cancer, menopausal status, BMI
Lash II[30]	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
Gammon[44]	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[52]	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[53]	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[40]	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[55]	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
Conlon[26]	2006	Age
Lissowska[47,72]	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
Zhu[27]	2006	Not specified
Roddam[38]	2007	Age, region, socioeconomic status, alcohol, BMI, parity, use of oral contraceptives, family history of breast cancer, age at menarche, menopausal status
Lin[51]	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
Pirie[45]	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[54]	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[56]	2008	Age, centre, BMI, aspirin/NSAID use, parity, alcohol, physical activity, recent hormone use (postmenopausal women only)

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
Ahern[57]	2009	Age, menopausal status, BMI, parity, alcohol, family history of breast cancer
Reynolds[6,58,70]	2009	Age, race, family history of breast cancer, age at menarche, parity, age at first pregnancy, physical activity, alcohol, BMI, menopausal status[d], BMI and menopausal status interaction[d], HRT use[d], menopausal status with HRT use interaction[e], lifetime duration of breast feeding[e]
Anderson[28]	2010	Not specified

[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 references[6] and[70] only
[e] Analyses from reference[58] 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[73]	USA	CC	Spouse (ever)	32	1.62 (0.76-3.44)	-	am
Hirayama[73]	Japan	P	Spouse (ever)	115	1.32 (0.83-2.09)	No	C(1)m
Smith[37]	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[46]	Switzerland	CC	Spouse (ever)[g]	90	3.1 (1.6-6.1)	d1	ac(9)m
Millikan[71]	USA	CC	Cohabitant (ever)	352	0.80 (0.55-1.16)	-	ac(3)em
Jee[41]	Korea	P	Spouse (ever)	138	1.27 (0.91-1.77)	-	ac(5)em
Lash I[29]	USA	CC	Cohabitant (ever)	120	2.0 (1.1-3.7)[h]	No	ac(7)m
Delfino[35]	USA	CC	Cohabitant (ever)[i]	64	1.50 (0.79-2.87)	-	ac(2)m
Liu[36]	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[32]	USA	NCC	Cohabitant (current)	(706)	1.03 (0.81-1.31)	-	c(1?)em
Nishino[43]	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)
Egan[5]	USA	P	Cohabitant (adulthood)[k]	1221	0.94 (0.83-1.06)	No	ac(13)em
Lash II[30]	USA	CC	Cohabitant (ever)	305	0.85 (0.63-1.1)[l]	No	ac(9)m
Gammon[44]	USA	CC	Cohabitant (ever)[m]	598	1.04 (0.81-1.35)[n]	No	ac(7)m
Shrubsole[52]	China	CC	Spouse (ever)	813	1.0 (0.8-1.2)	No	ac(10)m
Bonner[53]	USA	CC	Cohabitant (ever)	525	1.18 (0.86-1.63)	No	ac(11)em
Gram[40]	Norway and Sweden	P	Cohabitant (ever)	(1130)	1.21 (0.98-1.50)	-	ac(8)m
Hanaoka[55]	Japan	P	Cohabitant (ever)[o]	154	1.0 (0.7-1.4)	-	ac(11)m
Lissowska[47]	Poland	CC	Cohabitant (ever)	1034	0.92 (0.74-1.14)	-	ac(12)em
Roddam[38]	UK	CC	Spouse/partner (ever)	297	0.89 (0.64-1.25)	No	ac(9)m
Lin[51]	Japan	P	Cohabitant (past)	131	0.68 (0.47-0.97)	No	ac(10)em
Pirie[45]	UK	P	Spouse/partner (current)	1915	1.02 (0.89-1.16)	-	ac(10)m
Rollison[54]	USA	CC	Cohabitant (ever)	124	0.98 (0.58-1.64)	-	ac(8)m
Reynolds[6]	USA	P	Cohabitant (adulthood)[p] Cohabitant (ever)	1150 1164	0.97 (0.87-1.10) 0.94 (0.82-1.07)	-	ac(11)em ac(11)
Anderson[28]	Canada	CC	Cohabitant (adulthood)	920	No association	-	-

continued

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

[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] Reference group is lived with smoker as an adult for less than 5 years
[l] 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 $p<0.05$)
[m] 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
[n] 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)
[o] Reference group is never exposed at home during life and not exposed daily outside the home at baseline
[p] 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	Number of breast	Relative risk	Dose	
Author [ref][a]	Location	Type[b]	(timing)[c]	cancers[d]	(95% CI)	response[e]	Notes[f]
Smith[37]	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[48]	Canada	CC	Home or workplace (NOS)	606	1.47 (1.06-2.04)	-	ac(11)em
Liu[36]	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
Egan[5]	USA	P	Home or workplace (current)	1158	1.09 (0.93-1.28)	No	ac(13)e
Kropp[39]	Germany	CC	Home or workplace (NOS)	197	1.69 (1.16-2.45)	No	ac(6)em
Shrubsole[52]	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[53]	USA	CC	Workplace (ever)	522	0.80 (0.64-1.01)	No	ac(11)e
Hanaoka[55]	Japan	P	Outside home, daily (current)[h]	77	1.3 (0.9-1.9)	.	ac(11)
Lissowska[47]	Poland	CC	Workplace (ever)	1034	1.05 (0.88-1.27)	-	ac(12)e
Lin[51]	Japan	P	Public spaces (past)	140	0.79 (0.56-1.13)	No	ac(10)e
Rollison[54]	USA	CC	Workplace (ever)	124	0.80 (0.49-1.32)	No	ac(8)
Ahern[57]	USA	CC	Any (ever)[j]	232	0.86 (0.57-1.31)	-	a(5)em
Reynolds[58]	USA	P	Any (ever)	1754	1.04 (0.91-1.19)	-	ac(10)
			Workplace (ever)	1754	1.02 (0.93-1.13)	-	ac(10)
Anderson[28]	Canada	CC	Workplace (adulthood)	920	Not available	d3	ac(?)d

[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 risk of 2.27 (1.19-4.31) is given for 19-40 years of exposure versus none; relative risk not given for <19 years of exposure

[f] Notes:
- a adjusted for age of subject
- c adjusted for other confounding variables (see Table 2) – number adjusted for shown in brackets
- d risk estimate for premenopausal subjects with 19-40 years of exposure
- 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

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

Study Author [ref][a]	Location	Type[b]	Source of exposure[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Sandler[34]	USA	CC	Mother	29	0.92 (0.26-3.34)	-	ue
			Father	28	0.91 (0.41-2.04)	-	ue
Smith[37]	UK	CC	Any	94	1.19 (0.55-2.55)	No	ac(9)e
Lash I[29]	USA	CC	At home	99	2.40 (0.78-7.40)[g]	-	ac(8)e
Johnson[48]	Canada	CC	At home	606	1.24 (0.93-1.64)	-	ac(11)e
Liu[36]	China	CC	At home	186	1.16 (0.73-1.84)[h]	d1	ac(2)e
Egan[5]	USA	P	Mother	1222	0.88 (0.74-1.04)	-	ac(13)e
			Father	1222	1.08 (0.96-1.21)	-	ac(13)e
Kropp[39]	Germany	CC	At home	197	1.09 (0.77-1.55)	No	ac(6)e
Lash II[30]	USA	CC	At home	224	1.12 (0.82-1.54)	-	ac(9)e
Bonner[53]	USA	CC	At home	525	1.24 (0.96-1.60)	No	ac(11)e
Lin[51]	Japan	P	At home	178	1.24 (0.84-1.85)	-	ac(10)
Pirie[45]	UK	P	Mother	2344	0.96 (0.88-1.05)	-	ac(11)
			Father	2344	1.03 (0.93-1.14)	-	ac(11)
Rollison[54]	USA	CC	At home	123	0.81 (0.47-1.40)	No	ac(8)
Slattery[56]	USA	CC	Any	1347	No association	-	-
Ahern[57]	USA	CC	Any[i]	232	1.20 (0.78-1.84)	-	ac(5)e
Reynolds[6,58]	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)
Anderson[28]	Canada	CC	Any	920	No association	-	-

[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 $p<0.05$)
[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

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

Study Author [ref][a]	Location	Type[b]	Source of exposure[c]	Number of breast cancers[d]	Relative risk (95% CI)	Dose response[e]	Notes[f]
Smith[37]	UK	CC	All	94	2.58 (0.96-6.94)	No	ac(9)e
Morabia[46]	Switzerland	CC	All[g]	126	3.2 (1.7-5.9)[h]	d1	ac(9)
Johnson[48]	Canada	CC	Home or work	606	1.49 (1.02-2.18)	d2	ac(11)e
Rookus[31]	Netherlands	CC	Home or work[i]	918	1.2 (0.8-1.7)[j]	-	c(?)m
Kropp[39]	Germany	CC	Home or work	197	1.59 (1.06-2.39)[k]	d3	ac(6)
Hanaoka[55]	Japan	P	All	162	1.1 (0.8-1.6)	-	ac(11)
Conlon[26]	Canada	CC	Home or work	(347)	Not available	d4	a
Lissowska[47,72]	Poland	CC	Home or work	1034	1.11 (0.85-1.46)	No	ac(12)
Zhu[27]	China	P	All	390	Not available	d5	n
Pirie[45]	UK	P	Parents/spouse	2344	0.98 (0.88-1.09)	-	ac(11)
Rollison[54]	USA	CC	Cohabitants	122	1.06 (0.56-2.02)	No	ac(8)
Slattery[56]	USA	CC	Any (ever)	1347	1.05 (0.88-1.27)	No	ac(9)[l]em
Ahern[57]	USA	CC	Any (ever)	232	0.91 (0.54-1.55)	-	ac(5)e
Reynolds[58]	USA	P	All	1754	1.10 (0.94-1.30)	d6,d7,d8	ac(10)

[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 risk for highest quartile of duration vs lowest is 1.86 (1.01-3.44); no other details given
- d5 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.
- d6 relative risks are 1.10, 1.10, 1.12 for ≤15, 15.1-30.0, and >30.0 years of exposure
- d7 relative risks are 1.09, 1.08, 1.14 for intensity of exposure of ≤2.0, 2.1-3.0, >3.0
- d8 relative risks are 1.10, 1.10, 1.11 for ≤17.5, 17.6-42.0, >42.0 intensity-years of 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
- m included in principal meta-analysis
- n adjustment not specified

[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

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[59]	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[59]	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[74]	All (ever)[e]	Premenopausal	2.21 (1.03-4.75)	0.03 (1), NS	ae
		Postmenopausal	2.04 (1.19-3.48)		
Morabia[75]	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)		
Millikan[42]	Cohabitant (ever)	Premenopausal	1.5 (0.8-2.8)	0.27 (1), NS	ac_2
		Postmenopausal	1.2 (0.7-2.2)		
		NAT1 * 10	1.38 (0.78-2.44)	0.02 (1), NS	ac_3e
		NAT1 – non * 10	1.30 (0.66-2.56)		
		NAT2 slow acetylator	1.46 (0.76-2.80)	0.21 (1), NS	ac_3e
		NAT2 fast acetylator	1.19 (0.66-2.16)		
Millikan[71]	Cohabitant (ever)	p53-	0.8 (0.5-1.3)	0.00 (1), NS	ac_4
		p53+	0.8 (0.5-1.2)		
Delfino[35]	Cohabitant (ever)	Premenopausal	2.69 (0.91-8.00)	2.01 (1), NS	ac_5
		Postmenopausal	1.01 (0.45-2.27)		
		NAT2 slow acetylator	Data not shown	NS	ac_6
		NAT2 fast acetylator	Data not shown		
Johnson[48]	Home or work (ever)	Premenopausal	2.3 (1.2-4.6)	2.64 (1), NS	ac_7f
		Postmenopausal	1.2 (0.8-1.8)		
Rookus[31]	Home or work (ever)	p53 normal	Data not shown	NS	c_8
		p53 overexpressed	Data not shown		
Wartenberg[4]	Spouse (ever)	Age at baseline - <50	1.14 (0.81-1.59)	0.65 (3), NS	ac_9eg
		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_9eg
		20+	1.00 (0.84-1.19)		
Woo[32]	Cohabitant (current)	Premenopausal	2.78 (1.37-5.63)	8.50 (1), p<0.01	u
		Postmenopausal	0.91 (0.71-1.18)		
Egan[5]	Home and work (adulthood)	Premenopausal	Data not shown	NS	ac_7
		Postmenopausal	Data not shown		
Kropp[76]	Home or work (lifetime)	NAT2 slow acetylator	1.16 (0.66-2.04)	1.30 (1), NS	ac_9h
		NAT2 fast acetylator	1.98 (0.96-4.09)		
Kropp[77]	Home or work (lifetime)	SULT1A1*1/*1 genotype	1.69 (0.89-3.21)	0.17 (1), NS	ac_9i
		SULT1A1*2 allele carrier	1.40 (0.74-2.64)		

continued

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

Study author [ref][1]	Exposure index (timing)[2]	Subgroup		Relative risk (95% CI)	Heterogeneity[3]	Notes[4]
Gammon[44]	Cohabitant (ever)	Premenopausal		1.21 (0.78-1.90)	0.89 (1), NS	ac_7
		Postmenopausal		0.93 (0.68-1.29)		
		BMI	<22.3	1.70 (1.00-2.90)	10.31 (3), p<0.05	ac_7
			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_7
			- ever	1.13 (0.78-1.64)		
		Use of hormone replacement therapy	- never	1.03 (0.78-1.37)	0.09 (1), NS	ac_7
			- ever	1.14 (0.61-2.12)		
		Use of oral contraceptives				
			- never	1.03 (0.74-1.42)	0.01 (1), NS	ac_7
			- ever	1.05 (0.69-1.59)		
		Family history of breast cancer	- no	0.98 (0.74-1.30)	1.39 (1), NS	ac_7
			- yes	1.49 (0.79-2.82)		
		Age	<65	1.09 (0.79-1.51)	0.43 (1), NS	ac_7
			65+	0.91 (0.59-1.41)		
Gammon[78]	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)		
Shrubsole[52]	Spouse (ever)	Premenopausal		1.0 (0.8-1.3)	0.24 (1), NS	ac_7j
		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_{10}e
		- service		1.29 (0.41-4.09)		
		- clerical		0.77 (0.40-1.49)		
		- professional actuarial		1.38 (0.87-2.21)		
Bonner[53]	Cohabitant (ever)	Premenopausal		1.35 (0.78-2.33)	0.35 (1), NS	ac_7
		Postmenopausal		1.10 (0.74-1.64)		
	Workplace (ever)	Premenopausal		0.63(0.41-0.96)	1.79 (1), NS	ac_7
		Postmenopausal		0.89 (0.68-1.18)		
	At home (childhood)	Premenopausal		1.35 (0.84-2.18)	0.17 (1), NS	ac_7
		Postmenopausal		1.20 (0.89-1.63)		
Hanaoka[55]	Cohabitant (ever)[f]	Premenopausal		1.6 (0.9-2.7)	4.71 (1), p<0.05	ac_7k
		Postmenopausal		0.7 (0.4-1.1)		
Conlon[26]	Home or work (ever)	NAT2 slow acetylator		Data not shown	NS	a
		NAT2 fast acetylator		Data not shown		
Lissowska[47,72]	Home or work (ever)	Age	<45	1.28 (0.52-3.11)	0.50 (2), NS	ac_9n
			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_9ep
		Postmenopausal		0.97 (0.71-1.34)		

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]
Zhu[27]	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		
Roddam[38]	Spouse (ever)	Premenopausal	0.83 (0.59-1.17)	0.31 (1), NS	ac_{11}
		Peri/postmenopausal	1.51 (0.19-12.2)		
		Alcohol Never drinker	0.93 (0.51-1.69)	0.04 (1), NS	ac_{11}
		Drinker	0.86 (0.56-1.30)		
		Oral contraceptive use			
		Never	0.68 (0.25-1.91)	4.91 (2), p<0.1	ac_{11}
		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_{11}
		Yes	1.12 (0.20-6.41)		
		Parity Nulliparous	0.64 (0.21-1.91)	1.60 (2), NS	ac_{11}
		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_{11}
		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_{11}
		25+	1.07 (0.54-2.14)		
		Age at menarche <13	1.09 (0.66-1.79)	1.91 (1), NS	ac_{11}
		13+	0.67 (0.42-1.09)		
Pirie[45]	Parents (ever)/spouse (current)	Premenopausal	0.54 (0.30-0.99)	3.80 (2), NS	ac_7
		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_7
		56+	1.04 (0.91-1.19)		
		Employed when passive exposure reported Yes	0.94 (0.80-1.10)	0.31 (1), NS	ac_9
		No	1.00 (0.86-1.16)		
		Age at menarche <13	0.97 (0.82-1.16)	0.01 (1), NS	ac_7
		13+	0.98 (0.86-1.13)		
		Parity Nulliparous	0.97 (0.74-1.28)	0.01 (1), NS	ac_7
		Parous	0.98 (0.87-1.10)		
		Age at first birth <21	1.09 (0.73-1.63)	0.35 (1), NS	ac_7
		21+	0.96 (0.85-1.09)		
		Alcohol Non-drinker	1.04 (0.87-1.25)	1.54 (1), NS	ac_7
		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/3)

Study author [ref][a]	Exposure index (timing)[b]	Subgroup		Relative risk (95% CI)	Heterogeneity[c]	Notes[d]
Pirie[45](continued)		Oral contraceptive use				
			Ever	0.96 (0.83-1.11)	0.08 (1), NS	ac_9
			Never	0.99 (0.84-1.16)		
		HRT use	Current user	1.08 (0.90-1.30)	2.16 (1), NS	ac_7
			Not current user	0.91 (0.80-1.05)		
		BMI	<25	1.01 (0.86-1.18)	0.30 (1), NS	ac_7
			25+	0.95 (0.82-1.11)		
		Strenous physical activity				
			< Once/week	0.99 (0.85-1.14)	0.01 (1), NS	ac_7
			Once+/week	1.00 (0.85-1.18)		
		Living with partner	Yes	1.01 (0.90-1.13)	0.49 (1), NS	ac_7
			No	0.92 (0.73-1.17)		
Slattery[56]	Any (ever)	Pre/perimenopausal		1.13 (0.85-1.50)	0.42 (1), NS	$ac_{12}e$
		Postmenopausal		1.00 (0.79-1.27)		
		Non-Hispanic		1.07 (0.82-1.38)	0.02 (1), NS	$ac_{13}e$
		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_7f
		Postmenopausal (at baseline)		0.92 (0.78-1.08)		
Reynolds[70]	Cohabitant (ever)	Age (at diagnosis/end of follow-up)	<50	1.05 (0.76-1.45)	0.96 (1), NS	ac_9ef
			≥50	0.88 (0.76-1.01)		
Anderson[28]	Childhood/adulthood	11 candidate genes		Data not shown, but risk estimates reported to be modified by certain genetic variants	-	-

continued

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

[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 race, age at menarche, age at first full-term pregnancy, parity, family history of breast cancer, benign breast biopsy, alcohol
  - c_3 as c_2 plus menopausal status
  - c_4 race, sampling fraction
  - c_5 family history of breast cancer
  - c_6 family history of breast cancer, menopausal status
  - c_7 all variables listed in Table 2 except the subgroup variable
  - c_8 lifetime physical activity, other unspecified confounders
  - c_9 all variables listed in Table 2
  - c_{10} all variables listed in Table 2, and passive smoking from husband
  - c_{11} region, parity and oral contraceptive use
  - c_{12} all variables listed in Table 2, and ethnicity
  - c_{13} 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 pre-menopausal than post-menopausal 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

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	10	1.05 (0.96-1.14)	1.10 (0.95-1.28)	20.13	9	<0.05
Spouse or cohabitant (Table 3)[f]	All	25	1.01 (0.96-1.06)	1.03 (0.96-1.12)	43.99	24	<0.01
Workplace (Table 4)[g]	All	9	1.01 (0.94-1.08)	1.02 (0.90-1.15)	15.93	8	<0.05
Any adult (Table 4)[h]	All	9	1.09 (1.01-1.17)	1.11 (0.995-1.24)	13.68	8	<0.1
Child (Table 5)[i]	All	14	0.99 (0.94-1.05)	1.01 (0.94-1.08)	14.63	13	NS
Total (Table 6)	All	12	1.08 (1.01-1.16)	1.18 (1.04-1.35)	24.99	11	<0.01
Various (Table 7)[j]	Premenopausal	15	1.16 (1.03-1.30)	1.30 (1.06-1.59)	34.80	14	<0.01
	Postmenopausal	15	0.96 (0.90-1.03)	0.96 (0.90-1.03)	13.51	14	<0.1
	Ratio pre/post	15	1.27 (1.08-1.48)	1.33 (1.07-1.66)	22.70	14	NS
Principal[k]	All	30	1.03 (0.98-1.08)	1.06 (0.99-1.14)	57.36	29	<0.01
	Prospective	11	0.995 (0.94-1.05)	1.002 (0.93-1.08)	15.16	10	NS
	Case-control	19	1.08 (1.004-1.17)	1.14 (1.01-1.29)	39.18	18	<0.01
				(Between study type	*3.02*	*1*	*<0.1)*
	N.America	15	1.002 (0.95-1.06)	1.02 (0.94-1.10)	19.31	14	NS
	Asia	7	1.02 (0.90-1.16)	1.02 (0.83-1.26)	13.83	6	<0.05
	Europe	8	1.09 (0.998-1.19)	1.20 (0.99-1.44)	21.75	7	<0.01
				(Between continent	*2.47*	*2*	*NS)*
	>500 cases	11	1.004 (0.95-1.06)	1.002 (0.95-1.06)	9.49	10	NS
	<500 cases[l]	17	1.07 (0.97-1.19)	1.14 (0.95-1.36)	44.29	16	<0.001
				(Between study size	*0.58*	*1*	*<0.1)*
	9+ confounders	15	0.99 (0.94-1.05)	1.01 (0.93-1.10)	27.33	14	<0.05
	<9 confounders[m]	13	1.17 (1.05-1.30)	1.17 (1.01-1.37)	22.09	12	<0.05
				(Between adjustments	*7.22*	*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] The number of cases in nonsmokers was not known for two studies (see Table 3)
[m] Two studies were excluded as the number of confounding variables adjusted for other than age was not clear (see Table 2)

7. References

Style BMJ

1. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58515 women with breast cancer and 95067 women without the disease. *Br J Cancer* 2002;**87**:1234-45.

2. Khuder SA, Simon VJ, Jr. Is there an association between passive smoking and breast cancer? *Eur J Epidemiol* 2000;**16**:1117-21.

3. Morabia A. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. *Environ Mol Mutagen* 2002;**39**:89-95.

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

5. Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, *et al.* Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* 2002;**13**:138-45.

6. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, *et al.* Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst* 2004;**96**:29-37.

7. Lee PN, Hamling J. *Epidemiological evidence on environmental tobacco smoke and breast cancer*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2005. www.pnlee.co.uk/reflist.htm [Download LEE2005Q]

8. Lee PN, Hamling J. Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women: a review with meta-analyses. *Inhal Toxicol* 2006;**18**:1053-70.

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

10. Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, *et al.* A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn J Cancer Res* 1995;**86**:146-54.

11. Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, *et al.* Perinatal factors and risk of breast cancer. *Epidemiology* 1996;**7**:34-7.

12. Weiss HA, Potischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, *et al.* Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 1997;**8**:181-7.

13. Zhao Y, Shi Z, Liu L, Wu X, Fang J, Li H. Matched case-control study for detecting risk factors of breast cancer in women living in Chengdu. *Zhonghua Liu Xing Bing Xue Za Zhi* 1999;**20**:91-4.

14. Marcus PM, Newman B, Millikan RC, Moorman PG, Day Baird D, Qaqish B. The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes Control* 2000;**11**:271-8.

15. Wang Q, Li L, Zhu W, Xing X, Zhou Y. [Study on risk factors of breast cancer among urban women in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2000;**21**:216-20.

16. Johnson KC. Accumulating evidence on passive and active smoking and breast cancer risk. *Int J Cancer* 2005;**117**:619-28.

17. California Environmental Protection Agency. *Proposed identification of environmental tobacco smoke as a toxic air contaminant - as approved by the Scientific Review Panel on June 24, 2005*. 2005. www.arb.ca.gov/toxics/ets/finalreport/finalreport.htm

18. Collishaw NE, Boyd NF, Cantor KP, Hammond SK, Johnson KC, Millar J, *et al. Canadian expert panel on tobacco smoke and breast cancer risk,* April 2009. Toronto, Canada: Ontario Tobacco Research Unit; 2009. (OTRU special report series.) http://www.otru.org/pdf/special/expert_panel_tobacco_breast_cancer.pdf

19. Lee PN. An assessment of the epidemiological evidence relating lung cancer risk in never smokers to environmental tobacco smoke exposure. In: Kasuga H, editor. *Environmental tobacco smoke, Discussion on ETS, Tokyo, 2 April, 1993*. New York: Springer-Verlag, 1993;28-70.

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

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

22. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135**:1301-9.

23. National Cancer Institute. Shopland DR, editor. *Respiratory health effects of passive smoking: lung cancer and other disorders. The report of the US Environmental Protection Agency*. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1993. (Smoking and Tobacco Control. Monograph No. 4.) NIH Pub. No. 93-3605. http://cancercontrol.cancer.gov/tcrb/monographs/

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

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

26. Conlon M, Johnson K, Bewick M, Lafrenie R, Donner A. Smoking (passive and active), N-acetyltransferase 2 (NAT2), and risk of breast cancer [Abstract (SER)]. *Am J Epidemiol* 2006;**163(Suppl)**:S100.

27. Zhu HH, Gao YT, Blair A, Ji BT, Samet JM, Yang G, *et al.* Secondhand smoke and breast cancer risk: a community-based prospective cohort study [Abstract (SER)]. *Am J Epidemiol* 2006;**163(Suppl)**:S98.

28. Anderson LN, Cotterchio M, Mirea L, Kreiger N, Ozcelik H. Passive cigarette smoke exposure, genetic variants and breast cancer among never-smokers [Abstract]. *Ann Epidemiol* 2010;**20**:692-3.

29. Lash TL, Aschengrau A. Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* 1999;**149**:5-12.

30. Lash TL, Aschengrau A. A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat* 2002;**75**:181-4.

31. Rookus MA, Verloop J, de Vries F, van der Kooy K, Van Leeuwen FE. Passive and active smoking and the risk of breast cancer [Abstract (SER)]. *Am J Epidemiol* 2000;**151(Suppl)**:S28.

32. Woo C, Davis D, Gravitt P, Skinner H, Ward C, White JE, *et al.* A prospective study of passive cigarette smoke exposure and breast cancer [Abstract (SER)]. *Am J Epidemiol* 2000;**151(Suppl)**:S72.

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

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

35. Delfino RJ, Smith C, West JG, Lin HJ, White E, Lao S-Y, *et al.* Breast cancer, passive and active cigarette smoking and *N*-acetyltransferase 2 genotype. *Pharmacogenetics* 2000;**10**:461-9.

36. Liu L, Wu K, Lin X, Yin W, Zheng X, Tang X, *et al.* Passive smoking and other factors at different periods of life and breast cancer risk in Chinese women who have never smoked - a case-control study in Chongqing, People's Republic of China. *Asian Pac J Cancer Prev* 2000;**1**:131-7.

37. Smith SJ, Deacon JM, Chilvers CED. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br J Cancer* 1994;**70**:112-9.

38. Roddam AW, Pirie K, Pike MC, Chilvers C, Crossley B, Hermon C, *et al.* Active and passive smoking and the risk of breast cancer in women aged 36-45 years: a population based case-control study in the UK. *Br J Cancer* 2007;**97**:434-9.

39. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol* 2002;**156**:616-26.

40. Gram IT, Braaten T, Terry PD, Sasco AJ, Adami HO, Lund E, *et al.* Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:61-6.

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

42. Millikan RC, Pittman GS, Newman B, Tse C-KJ, Selmin O, Rockhill B, *et al.* Cigarette smoking, *N*-acetyltransferases 1 and 2, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;7:371-8.

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

44. Gammon MD, Eng SM, Teitelbaum SL, Britton JA, Kabat GC, Hatch M, *et al.* Environmental tobacco smoke and breast cancer incidence. *Environ Res* 2004;**96**:176-85.

45. Pirie K, Beral V, Peto R, Roddam A, Reeves G, Green J. Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. *Int J Epidemiol* 2008;**37**:1069-79. Advance access published June 10, 2008. doi:10.1093/ije/dyn110

46. Morabia A, Bernstein M, Héritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol* 1996;**143**:918-28.

47. Lissowska J, Brinton LA, Zatonski W, Blair A, Bardin-Mikolajczak A, Peplonska B, *et al.* Tobacco smoking, *NAT2* acetylation genotype and breast cancer risk. *Int J Cancer* 2006;**119**:1961-9. Erratum appears in Int.J.Cancer 2007;120:2517-2518.

WARNING: MULTINAT

The first 'a' in the author Dabrowska should be a multinat character - but not done as it causes cwyw to seize up

48. Johnson KC, Hu J, Mao Y. Passive and active smoking and breast cancer risk in Canada, 1994-97. *Cancer Causes Control* 2000;**11**:211-21.

49. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995;**87**:1681-5.

50. Gammon MD, Neugut AI, Santella RM, Teitelbaum SL, Britton JA, Terry MB, *et al.* The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res Treat* 2002;**74**:235-54.

51. Lin Y, Kikuchi S, Tamakoshi K, Wakai K, Kondo T, Niwa Y, *et al.* Active smoking, passive smoking, and breast cancer risk: findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. *J Epidemiol* 2008;**18**:77-83.

52. Shrubsole MJ, Gao Y-T, Dai Q, Shu X-O, Ruan Z-X, Jin F, *et al.* Passive smoking and breast cancer risk among non-smoking Chinese women. *Int J Cancer* 2004;**110**:605-9.

53. Bonner MR, Nie J, Han D, Vena JE, Rogerson P, Muti P, *et al.* Secondhand smoke exposure in early life and the risk of breast cancer among never smokers (United States). *Cancer Causes Control* 2005;**16**:683-9.

54. Rollison DE, Brownson RC, Hathcock HL, Newschaffer CJ. Case-control study of tobacco smoke exposure and breast cancer risk in Delaware. *BMC Cancer* 2008;**8**:157.

55. Hanaoka T, Yamamoto S, Sobue T, Sasaki S, Tsugane S. Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer* 2005;**114**:317-22.

56. Slattery ML, Curtin K, Giuliano AR, Sweeney C, Baumgartner R, Edwards S, *et al.* Active and passive smoking, *IL6*, *ESR1*, and breast cancer risk. *Breast Cancer Res Treat* 2008;**109**:101-11.

57. Ahern TP, Lash TL, Egan KM, Baron JA. Lifetime tobacco smoke exposure and breast cancer incidence. *Cancer Causes Control* 2009;**20**:1837-44.

58. Reynolds P, Goldberg D, Hurley S, Nelson DO, Largent J, Henderson KD, *et al.* Passive smoking and risk of breast cancer in the California Teachers Study. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:3389-98.

59. Wells AJ. Breast cancer, cigarette smoking, and passive smoking [Letter]. *Am J Epidemiol* 1991;**133**:208-10.

60. International Agency for Research on Cancer. *Tobacco smoke and involuntary smoking,* Volume 83. Lyon, France: IARC; 2004. (IARC Monographs on the evaluation of carcinogenic risks to humans.) http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf

61. Johnson KC, Glantz SA. Evidence secondhand smoke causes breast cancer in 2005 stronger than for lung cancer in 1986. *Prev Med* 2008;**46**:492-6.

62. US Surgeon General. *The health consequences of smoking. A report of the Surgeon General.* Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004. http://www.surgeongeneral.gov/library/reports/index.html

63. Miller AB. Breast cancer and passive smoking. *Prev Med* 2008;**46**:497-8.

64. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997;**315**:980-8.

65. Morabia A, Bernstein M, Héritier S. Smoking and breast cancer: reconciling the epidemiologic evidence by accounting for passive smoking and/or genetic susceptibility [Letter]. *Am J Epidemiol* 1998;**147**:992-3.

66. Lee PN, Forey BA, Fry JS. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. III. Adjustment for the biasing effect of misclassification of smoking habits. *Indoor Built Environ* 2001;**10**:384-98.

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

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

69. LeVois ME, Layard MW. Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. *Regul Toxicol Pharmacol* 1995;**21**:184-91.

70. Reynolds P, Hurley S, Goldberg D. Accumulating evidence on passive and active smoking and breast cancer risk [Letter]. *Int J Cancer* 2006;**119**:239.

71. Furberg H, Millikan RC, Geradts J, Gammon MD, Dressler LG, Ambrosone CB, *et al.* Environmental factors in relation to breast cancer characterized by p53 protein expression. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:829-35.

72. Lissowska J, Brinton LA, Garcia-Closas M. Re: More data regarding the effects of passive smoking on breast cancer risk among women [Letter]. *Int J Cancer* 2007;**120**:2517-8.

73. Wells AJ. Breast cancer, cigarette smoking, and passive smoking [Letter]. *Am J Epidemiol* 1998;**147**:991-2.

74. Morabia A, Bernstein M, Ruiz J, Héritier S, Diebold Berger S, Borisch B. Relation of smoking to breast cancer by estrogen receptor status. *Int J Cancer* 1998;**75**:339-42.

75. Morabia A, Bernstein MS, Bouchardy I, Kurtz J, Morris MA. Breast cancer and active and passive smoking: the role of the *N*-acetyltransferase 2 genotype. *Am J Epidemiol* 2000;**152**:226-32.

76. Chang-Claude J, Kropp S, Jäger B, Bartsch H, Risch A. Differential effect of *NAT2* on the association between active and passive smoke exposure and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:698-704.

77. Lilla C, Risch A, Kropp S, Chang-Claude J. *SULT1A1* genotype, active and passive smoking, and breast cancer risk by age 50 years in a German case-control study. *Breast Cancer Res* 2005;**7**:R229-R237. doi 10.1186/bcr976

78. Gaudet MM, Gammon MD, Santella RM, Britton JA, Teitelbaum SL, Eng SM, *et al.* MnSOD Val-9Ala genotype, pro- and anti-oxidant environmental modifiers, and breast cancer among women on Long Island, New York. *Cancer Causes Control* 2005;**16**:1225-34.