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Passive smoking and breast cancer in never smokers: prospective study and meta-analysis

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Background	Active smoking has little or no effect on women's risk of developing breast cancer, but it has been suggested that passive exposure to tobacco smoke may increase this risk among women who have never smoked.
Objective	To evaluate the possible relationship between passive smoking and breast cancer risk within the Million Women Study, a large UK prospective study, and to report a meta-analysis of published results.
Methods	In the large prospective study, 224 917 never smokers who completed a questionnaire that asked women whether their parents had smoked and if their current partner smoked were followed up for an average of 3.5 years for incident breast cancer. In the meta-analysis, studies that had recorded exposure information prospectively and retrospectively were considered separately.
Main outcome measures	Adjusted relative risk of breast cancer in never smokers who were passively exposed to tobacco smoke at various ages compared with never smokers with no such exposure.
Results	In the prospective study, 2518 incident invasive breast cancers occurred during follow-up and the adjusted relative risk of breast cancer for passive exposure either as a child or as an adult vs neither exposure was 0.98 (95% CI 0.88–1.09); results were similarly null for childhood exposure (0.98, 0.88–1.08) and adult exposure (1.02, 0.89–1.16) separately. We identified seven other studies with prospectively recorded exposure data; when results of all eight studies were combined (including 5743 never smokers with breast cancer), the aggregate relative risk was 0.99 (0.93–1.05) for any passive exposure. The aggregate findings differed substantially ($P=0.0002$) between these 8 studies and 17 other studies with retrospectively recorded information (including 5696 never smokers with breast cancer).

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[†] Refer to Appendix 1 for further details.

Conclusions Aggregate results from studies with prospectively reported information show that the incidence of breast cancer is similar in women who did and did not report passive exposure to tobacco smoke either as a child or as an adult. The aggregate findings from the retrospective studies may have been distorted by some women becoming more likely to report past exposures because they knew that they had breast cancer.

Keywords Passive smoking, female breast cancer, prospective cohort study, meta-analysis

Introduction

A collaborative reanalysis of the worldwide evidence from 53 epidemiological studies found that smoking had little or no independent effect on the risk of women developing breast cancer.¹ The findings were separately reliable for pre-menopausal and for post-menopausal women. Among non-drinkers, the relative risk of breast cancer in current vs never smokers was 0.99 (0.92–1.05).¹ (The analysis was restricted to non-drinkers because smokers generally drink more alcohol than non-smokers and alcohol intake affects the risk of breast cancer.¹) In 2004, the International Agency for Research on Cancer endorsed the ‘lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast’.²

Although active smoking has little or no effect on the incidence of breast cancer it has been suggested, based largely on the findings reported from 14 epidemiological studies, that passive smoking might do so.³ To test this hypothesis we present new, previously unpublished results from a large UK prospective study⁴ on the possible relationship between passive exposure to tobacco smoke and the risk of developing breast cancer, and report a meta-analysis of these results together with the published results from 24 other studies. To exclude any potential confounding by active smoking, this review is restricted to findings in women who reported that they had never smoked.

Methods

The Million Women Study

The Million Women Study has been described elsewhere.^{4,5} In 1996–2001, 1.3 million women aged 50–64 years attending 66 breast cancer screening clinics in the UK completed a questionnaire asking, among other things, about social, demographic and reproductive factors, alcohol consumption and current or past smoking. The first follow-up questionnaire was sent to cohort members at around 3 years after recruitment, with a response rate of about 65%. Every participant was asked at this follow-up if their mother

and if their father had smoked when the participant was born and (separately) when the participant was about 10 years old. They were also asked if the participant was living with a partner, and, if so, whether the partner smoked. For questions about the partner’s smoking, a participant could answer only ‘yes’ or ‘no’, but for parental smoking, participants could answer ‘yes’, ‘no’ or ‘do not know’. At follow-up we also asked participants if they were in paid work, but not about passive exposure to tobacco smoke at work. The questionnaires and other information can be viewed at www.millionwomenstudy.org.

Every participant is routinely followed for cancer registration, death or emigration from the UK by being ‘flagged’ on the NHS Central Registers. These regularly provide study investigators with information on the dates of any such events. For women diagnosed with cancer and those who died, the cancer site and cause of death are coded according to the 10th revision of the International Classification of Diseases (ICD10).⁶ The endpoint for the present analyses is incident invasive breast cancer (ICD10 C50). All participants gave written consent to take part in the study, and approval was provided by the Oxford and Anglia Multi-Centre Research Ethics Committee.

Women were excluded from the analyses if they had any type of cancer except non-melanoma skin cancer (ICD10 C44) registered before they answered the questions about passive smoking or if they had themselves reported a history of breast cancer. Women were also excluded if they reported being current or past smokers, if their smoking status was unknown or if they answered ‘do not know’ or gave no answer to every question on passive smoking. Woman-years were calculated from the date the women answered the questions about passive smoking to the date of cancer registration, death or last follow-up, whichever was first. The last date of follow-up in most areas was December 31, 2004, but in Trent and North Yorkshire it was June 30, 2004, in the North West it was December 31, 2003 and in Scotland it was December 31, 1999. Cox regression models were used to obtain hazard ratios (hereafter referred to as relative risks) and their 95% CIs, using the STATA version 9.0 computing package. Attained age was the underlying time

variable and analyses were additionally adjusted by several factors recorded at recruitment, including region of residence (10 cancer registry areas in the UK); quintiles of socio-economic status (using the Townsend deprivation index, a composite measure based on unemployment, car ownership, home ownership and overcrowding in the area of residence⁷); parity (0, 1, 2, 3 or more); age at first birth (<20, 20–29, 30 or more years); age at menarche (<12, 12–13, 14 or more years); body mass index (<25, 25–30, 30 or more kg/m²); strenuous physical activity (never/rarely, less than weekly, at least weekly) and by the latest values of some time-dependent factors recorded at recruitment and also at follow-up, including menopausal status (pre-, peri-, post-menopausal), use of hormonal therapy (current, not current) and alcohol consumption (0, 1, 2, 3 or more drinks/day). For each adjustment variable, missing values were assigned to a separate stratum. Analyses of adult exposure and of exposure both as a child and as an adult were restricted to women living with a partner, since women who do not have a partner are not at risk of such exposure. All other analyses were stratified by whether or not women were living with a partner.

Meta-analysis of published findings

Relevant publications were identified from reviews (especially those done by the International Agency for Research on Cancer,² the California Environmental Protection Agency³ and the US Surgeon General⁸), discussions with colleagues and computer-aided literature searches [using MEDLINE, EMBASE and Pubmed, with keywords breast cancer (incidence or mortality), passive smoking, second-hand smoke, environmental tobacco smoke] up to January 2008. For each study that had published results we extracted, whenever possible, the fully adjusted relative risk estimate and associated 95% CI for any reported passive exposure to tobacco smoke (i.e. either as a child or as an adult) in never smokers and the numbers of women with breast cancer. Similar information was also extracted, if available, for childhood exposure alone and for adult exposure alone. In summarizing the published evidence we used, whenever possible, the published results for any passive exposure (either as a child or as an adult) and, if this was not given, we used the published results for the exposure that was most commonly reported in the study. Where possible, when results were published for subgroups and not for the whole population, the subgroup-specific results were combined in proportion to the numbers in each subgroup to estimate the overall result.⁹ Results from different studies were combined by calculating the inverse-variance-weighted average of the logarithms of the relative risks. Because the reporting of passive exposure could be influenced by whether or not women knew that they had breast cancer, results from studies that utilized prospective exposure information, i.e. with exposure reported before breast cancer was

known, were considered separately from the results of studies that had utilized retrospective exposure information, i.e. with exposure reported after the diagnosis of breast cancer was known.

Presentation of results

Where results are presented in the form of plots, the relative risks and their corresponding CIs are represented by squares and lines, with the area of the square inversely proportional to the variance of the logarithm of the corresponding relative risk. This provides an appropriate indication of the amount of statistical information involved.

Results

Million Women Study

Information about parents' and partners' smoking habits is currently available for 224 917 never smokers with no previous cancer. Among these women, the mean year of birth was 1941 (91% between 1935 and 1949), the mean year of entry into the study was 1998 (SD 0.9) and the mean year of completing the passive smoking follow-up questionnaire was 2001 (SD 0.9). Among these women 6% (14 270) could not be classified as to whether they were passively exposed to tobacco smoke as a child or as an adult, mainly because they did not know if one of their parents had smoked when they were born. Among the remaining 210 647 women, 83% (174 819) reported one or more sources of passive exposure to tobacco smoke either as a child or as an adult. Their characteristics are shown in Table 1, and are broadly similar to those of never smokers within the original cohort at recruitment. Comparing women classified as passively exposed and not, the exposed drank slightly more alcohol [4.3 vs 3.8 g/day, $P < 0.0001$ —although the difference is smaller than that seen between current and never smokers in this study (5.9 vs 4.2 g/day)]. The exposed women were also more likely to be parous (89 vs 86%, $P < 0.0001$), to have used oral contraceptives (57 vs 54%, $P < 0.0001$) and to be current users of hormone replacement therapy (30 vs 28%, $P < 0.0001$). These differences are explained in part because exposed women were more likely to be living with a partner (84 vs 80%, $P < 0.0001$), since women not living with a partner could not be classified as exposed to their partners' smoke. Restricting comparisons to women living with a partner reduced many of the differences between those classified as passively exposed and not (Table 1).

The 210 647 never smokers who could be classified as passively exposed or not were followed for a mean of 3.5 (SD 1.0) years, during which time 2344 were diagnosed with invasive breast cancer. (The mean follow-up time after recruitment was 6.3 (SD 1.0) years, but questions on passive smoking were asked a mean of 2.8 (SD 0.2) years after recruitment,

Table 1 Characteristics and follow-up of never smokers in the Million Women Study, according to classification of exposure to tobacco smoke either as a child or as an adult

	All women		Women living with a partner	
	Passively exposed	Not passively exposed	Passively exposed	Not passively exposed
Number	174 819	35 828	146 913	28 652
Age, years [mean (SD)]	58.1 (4.6)	57.9 (4.5)	57.9 (4.5)	57.7 (4.5)
Living with a partner [% (n)] ^a	85% (146 913)	80% (28 652)	100%	100%
Socioeconomic status [% (n) in upper third] ^a	33% (58 070)	35% (12 380)	35% (50 890)	37% (10 536)
Employed [% (n)] ^a	48% (82 605)	48% (17 148)	48% (69 903)	48% (13 709)
Age at menarche [mean (SD)]	12.9 (1.5)	12.9 (1.5)	12.9 (1.5)	12.9 (1.5)
Menopausal status, pre-menopausal [% (n)] ^a	3% (4729)	3% (1075)	3% (4158)	3% (914)
Parous [% (n)] ^a	89% (154 944)	86% (30 764)	91% (134 149)	90% (25 859)
Number of children [mean (SD)]	2.1 (1.2)	2.0 (1.2)	2.1 (1.1)	2.1 (1.1)
Age at first birth, years [mean (SD)]	24.5 (4.1)	25.1 (4.2)	24.5 (4.1)	25.2 (4.2)
Alcohol consumption, g/day [mean (SD)]	4.3 (5.7)	3.8 (5.3)	4.5 (5.8)	4.1 (5.4)
Past use of oral contraceptives [% (n)] ^a	57% (99 586)	54% (19 338)	58% (85 470)	56% (15 926)
Current use of hormone therapy [% (n)] ^a	30% (51 901)	28% (9958)	31% (44 572)	29% (8188)
Body-mass index, kg/m ² [mean (SD)]	26.0 (4.4)	25.6 (4.3)	25.9 (4.4)	25.6 (4.2)
Strenuous physical activity more than once a week [% (n)] ^a	23% (39 882)	25% (8664)	23% (33 510)	25% (6929)
Woman-years of follow-up	616 660	127 315	517 999	101 569
Number of incident invasive breast cancers	1937	407	1602	313

^aWomen with missing values are not included in the percentages.

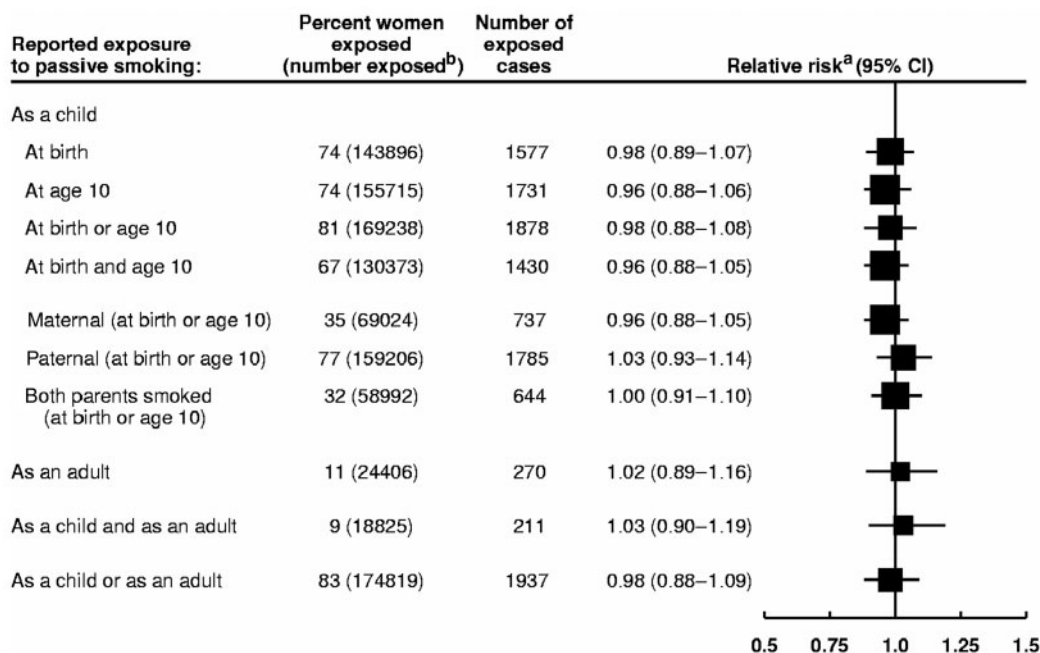
so only the 3.5 years after answering these questions are relevant here.) Figure 1 shows the relative risk of breast cancer for women classified as being passively exposed to tobacco smoke compared with those not, according to the source of exposure. Childhood exposure was much more common than adult exposure. Both at birth and at age 10, 74% of women who could be classified as either exposed or unexposed reported having a parent who smoked, and exposure at one age was strongly predictive of exposure at the other (odds ratio of 69, 95% CI 67–71). In general, if the mother smoked then so too did the father, but in many cases only the father smoked. Irrespective of whether childhood exposure was at one or both ages, or from one or both parents, the relative risk of breast cancer in exposed vs unexposed women was close to 1.0 (ranging from 0.96 to 1.03). Only 11% of the never smokers reported living with a partner who smoked. Results were similarly null for passive exposure as an adult, for exposure both as a child and as an adult and for exposure either as a child or as an adult. Among the 14 270 never smokers whose exposure to passive smoke could not be classified, 174 breast cancers were diagnosed and their risk of developing the malignancy was not materially different from that in unexposed or in exposed women (1.05, 0.87–1.25 and 1.07, 0.92–1.25, respectively). All estimates of relative risk are fully adjusted for all the factors listed in Figure 1, but even if we had adjusted only for age

and region the relative risk for exposure as a child or as an adult would have remained unaltered, at 0.98 (0.88–1.09).

The results for passive exposure either as a child or as an adult were further examined in certain subgroups of women (Figure 2). No major differences were observed between most of the subgroups examined. The only apparently discrepant result is the halving of the risk of breast cancer in passively exposed pre-menopausal women, but this could be a chance finding. The mean time to cancer diagnosis was 1.9 (SD 1.3) years after menopausal status was reported. Although some pre-menopausal women might have become peri- or post-menopausal between answering the questionnaire and their cancer being diagnosed, many of the cancers would have originated when the women were still pre-menopausal, as it takes time for cancer to become detectable.

About half the never smokers did not work, and thus could not have been exposed to passive smoke at work, and their relative risk of breast cancer for passive exposure either as a child or an adult was 1.00, similar to the overall null results (Figure 2).

Results for exposure either as a child or as an adult did not vary according to women's age at menarche or their age when their first child was born; and when exposure shortly before menarche, i.e. at age 10 (the mean age at menarche was 12.9 years, see Table 1), was considered separately the relative risks



^a Relative risks are for exposed compared with unexposed women, adjusted by age, region of residence, socio-economic group, age at menarche, parity, age at first birth, menopausal status, body mass index, physical activity, alcohol consumption and use of hormonal therapy for the menopause. Analyses of adult exposure and of exposure both as an adult and as a child are restricted to women living with a partner, and all other analyses are stratified by whether or not they were living with a partner.

^b The total number of women classified as either exposed or unexposed varies for each source of exposure as a result of differing numbers of missing values for each of the passive smoking questions.

Figure 1 Relative risk^a of breast cancer for never smokers in the Million Women Study, by passive exposure to tobacco smoke

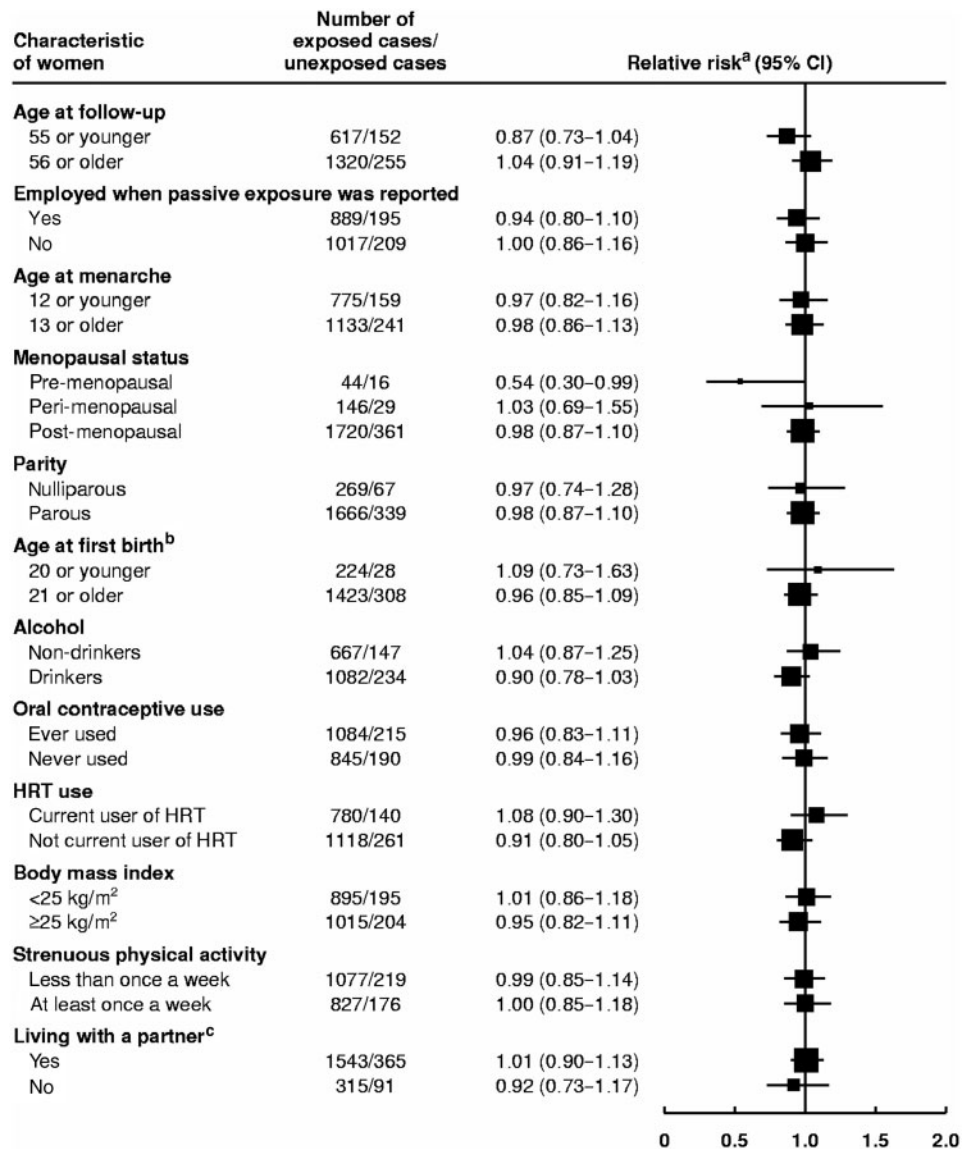
were 0.90 (0.78–1.05) for women whose age at menarche was at age 12 or younger and 1.01 (0.89–1.14) for women whose menarche was at age 13 years or older; and 0.99 (0.72–1.35) for women whose first birth was at age 20 or younger and 0.94 (0.85–1.05) for women whose first birth was when they were older than 20.

Meta-analysis of published findings

We identified 24 other studies that had published on the risk of breast cancer in relation to passive exposure among never smokers.^{10–33} These are summarized in Figure 3, which also shows the study-specific relative risks for breast cancer associated with passive exposure. Results from the eight studies (including the Million Women Study) that collected exposure data prospectively, i.e. before the diagnosis of breast cancer, are shown separately from the results from the 17 studies that collected exposure information retrospectively, i.e. after the diagnosis of breast cancer. (One study,¹¹ although case–control in design, had collected exposure information before the women were diagnosed with breast cancer, and so is included as having prospectively reported exposure data; another study²¹ was cohort in design but asked

some women about passive smoking after they were diagnosed with cancer, and so is included as having retrospectively collected exposure data.) It can be seen in Figure 3 that the studies differ in the type of exposure information collected, and also in the statistical adjustments used. Results for the prospective study by Hirayama¹⁰ were not published by the investigator himself, and are taken from a letter by Wells³⁴ who calculated crude odds ratios from the numbers provided as a personal communication by the late Prof. Hirayama. The results from two other studies^{23,27} were also not adjusted by age. Age, parity, age at first birth and alcohol consumption are relevant potential confounding factors, but only seven studies^{14,15,18,20,24,30,33} published relative risk estimates adjusted for all these factors.

Taken together, the eight studies with prospectively collected information included 5743 never smokers with breast cancer, among whom 4431 (77%) were classified as having passive exposure to tobacco smoke. In these eight prospective studies there was no material difference in the risk of breast cancer between women who reported that they were passively exposed to tobacco smoke compared with those who did not (relative risk = 0.99, 95% CI 0.93–1.05). This combined result for prospective studies remains



^aRelative risks are for exposed compared with unexposed women, adjusted where appropriate by age, region of residence, socio-economic group, age at menarche, parity, age at first birth, menopausal status, body mass index, physical activity, alcohol consumption, use of hormonal therapy for the menopause and whether or not living with a partner.

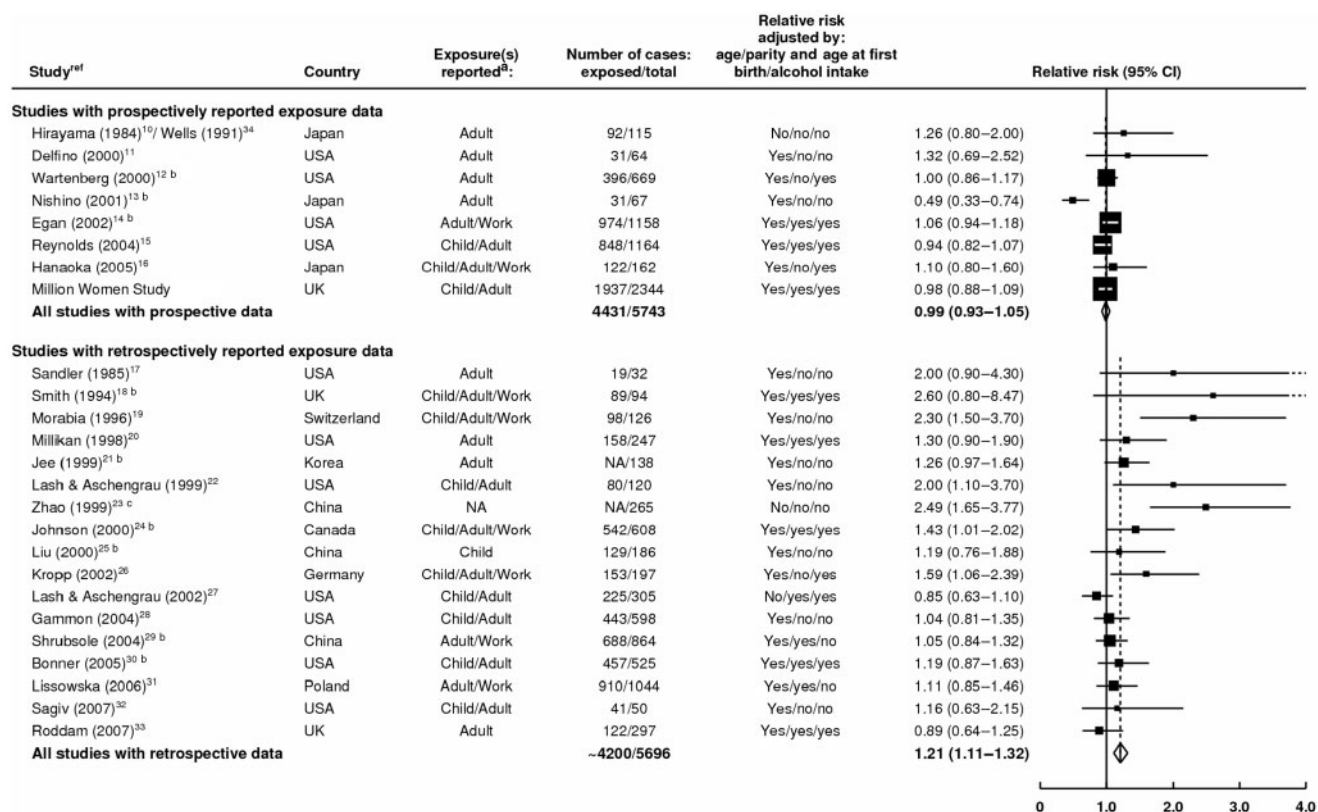
^bIn parous women only.

^cChildhood exposure to passive smoke only, since women who do not live with a partner are not at risk of exposure from their partner's smoke.

Figure 2 Relative risk^a of breast cancer for never smokers in the Million Women Study, by passive exposure to tobacco smoke as a child or as an adult in various subgroups of women

unchanged when the Million Women Study is excluded (1.00, 0.93–1.07). Results for passive exposure as a child were available for the Million Women Study and for two other prospective studies^{14,15} and the aggregate relative risk was 1.00 (0.94–1.07); results for exposure as an adult were available for the Million Women Study and six other prospective studies,^{10–15} and the aggregate relative risk estimate was again 1.00 (0.94–1.07). No prospective study reported separate findings for exposure at work alone.

There was a substantial difference between the findings from studies that had collected information prospectively and those that had collected it retrospectively (χ^2_1 for heterogeneity = 13.8, $P = 0.0002$). The combined relative risk of breast cancer in the 17 studies with retrospective reporting of exposure was 1.21 (1.11–1.32), based on a total of 5696 women with breast cancer. This discrepancy between the aggregate relative risk estimates from studies that had recorded information about passive exposure to tobacco



^aChild indicates residential exposure to passive smoke as a child; Adult indicates residential exposure to passive smoke as an adult.
^bSubgroup specific results were combined to obtain an overall estimate of relative risk for exposure to passive smoke.
^cQuoted in US Surgeon General Report.

Figure 3 Relative risk of breast cancer associated with any reported exposure to passive smoking in never smokers

smoke before and after the diagnosis of breast cancer suggests that study design has a material effect on the aggregate findings. Thus, the results from the prospective and retrospective studies are not combined.

Discussion

Among never smokers in the Million Women Study the risk of breast cancer did not differ between women who reported that they were passively exposed to tobacco smoke in childhood or in adult life and those who did not (relative risk = 0.98, 0.88–1.09). Our results were similarly null when passive exposure as a child and as an adult were considered separately and did not vary with parity, alcohol consumption, body mass index, age at menarche, age at first birth, whether or not the woman worked, whether or not she was living with a partner, use of oral contraceptives or use of hormone replacement therapy.

Most passive exposure to tobacco smoke among never smokers in the Million Women Study occurred during childhood, at a time when there was relatively little public concern about the hazards of smoking. Most study participants were born between 1935

and 1949. At that time, and during the next 20 or so years, the prevalence of smoking among adults of reproductive age in the UK was high,³⁵ consistent with reports by the study participants that, although they themselves were never smokers, 81% had at least one parent who had smoked either when they were born or when they were 10 years old (Figure 1). Since exposure at birth and at age 10 were closely correlated (odds ratio 69), information about exposure at just these two ages must be closely correlated with the proportion of positive responses that would have been obtained if we had asked the same question about exposure at each separate year of age throughout childhood and puberty.

Since relatively few smokers in the UK quit before 1970,³⁵ women in this study whose parents smoked both when they were born and when they were 10 years old would typically have been exposed to their parents' smoke throughout childhood and as young teenagers: yet even among such women, the relative risk of breast cancer was 0.96 (0.88–1.08). It has been postulated that the breast may be particularly sensitive to passive exposure to tobacco during its development and in adolescence.³ However, among women likely to have been passively exposed at around puberty and in early adolescence, i.e. whose

parents smoked when they were 10 years old, there was no apparent increase in the risk of breast cancer, either overall or in women whose menarche was at age 12 or younger, in nulliparous women or in women whose first birth was at age 20 or younger.

In contrast to the large proportion of Million Women Study participants who were exposed during childhood, only 11% of the never smokers reported current passive exposure at home from a partner who smoked. This low prevalence of exposure from a partner in recent years is consistent with the declining prevalence of smoking among adults in the UK, accentuated by the tendency for non-smokers to live together.³⁶ This decline in smoking prevalence means that some women classified as unexposed to passive smoke as an adult would have previously been exposed through a partner who had once smoked, but had stopped before exposure assessment took place. This could result in some misclassification of adult exposure, but would be unlikely to affect the results for exposure to passive smoke in childhood.

There was no increase in the risk of breast cancer among never smokers who reported that their partner smoked, or in women exposed both in childhood and as an adult (Figure 1). We did not ask about passive exposure at work, but the major source of passive exposure in non-smoking adults is exposure at home³⁶ (and, among those who did not work and hence could not have additional exposure at work, the findings for exposure in the home were also null: Figure 2).

Other problems arise when analysing exposure in adulthood. For example, women who live alone cannot be exposed to someone else's second-hand smoke at home and women who do not work cannot be exposed to someone else's smoke at work. Without appropriate stratification, women who live alone or do not work would be over-represented in the 'unexposed' group, and such women may well have atypical reproductive histories and other characteristics, which could affect their risk of developing breast cancer. The Million Women Study analyses of the effect of passive exposure to a partner's smoke were, therefore, restricted to women who had a partner; likewise, in other studies analyses of the effect of passive exposure at work should be restricted to women who work.

A meta-analysis of the Million Women Study and of 24 other studies that had published results on passive smoking and breast cancer found a difference ($P=0.0002$) between the aggregate results from studies that had recorded information on passive smoking prospectively and retrospectively, i.e. before and after the diagnosis of breast cancer. The substantially different findings, according to when the exposure information was reported, are unlikely to be due to the different statistical adjustments used in the individual studies. In the Million Women Study, for example, those classified as passively exposed had slightly more children and reported consuming

slightly more alcohol than unexposed women (Table 1), but adjustment for these and other potential confounding factors did not materially alter the relative risk estimate.

In studies with retrospectively reported exposure information there could be systematic differences in the reporting of past exposures between cases (who know they have breast cancer) and controls, whereas in studies with prospectively reported exposure information there cannot be, as the reporting of exposure predates any diagnosis of breast cancer. The fact that there is a difference between the aggregate results of studies with prospective and retrospective data provides strong evidence that systematic reporting differences between cases and controls did occur in at least some of the studies with retrospectively reported information, distorting the aggregate results from such studies.

There are other instances where the apparent findings from observational studies depend on whether the exposure information is recorded before or after the diagnosis of breast cancer. For example, studies with prospectively recorded data on the incidence of breast cancer after an induced abortion showed no increase in risk, whereas studies with retrospective reporting of induced abortion gave, in aggregate, misleadingly positive results.³⁷ In this case, the discrepant findings may have resulted from women in at least some of the retrospective studies becoming more likely to disclose the fact that they had had an abortion because of the knowledge that they had breast cancer. In the present meta-analysis, if the knowledge that they had breast cancer made women in some retrospective studies become more likely than they would otherwise have been to report passive exposure to tobacco smoke, this too would produce an exaggeratedly positive association between passive smoking and breast cancer.

Given that the aggregate results differ so substantially between studies with prospective and retrospective information, and given the potential for retrospective data to be distorted by systematic reporting differences between cases and controls, the aggregate results from studies with retrospectively reported information on passive exposure to tobacco smoke cannot be trusted. This does not, of course, mean that results from all observational studies with retrospectively reported information on any exposure are untrustworthy. Systematic differences in reporting may be of little relevance when the exposure of interest can be measured reliably and discussed openly: active smoking, for example, may be easier to characterize than passive smoking.²

In the eight studies with prospectively collected exposure information, the aggregate relative risk of breast cancer in never smokers who reported passive exposure vs those who reported no such exposure was 0.99 (95% CI 0.93–1.05), indicating no material hazard. The findings were equally null for exposure

as a child or as an adult (1.00, 0.94–1.07 and 1.00, 0.94–1.07, respectively). These null aggregate results from prospective studies are what might reasonably be expected from the fact that active smoking has little or no net effect on the risk of developing breast cancer.^{1,2} It has been suggested that the relationship between smoking and breast cancer may be modified by the *N*-acetyltransferase 2 (NAT2) genotype,^{38–40} but the evidence to date, based mainly on retrospective studies of active smoking, is inconclusive and only three studies [20, 41, 42] have specifically reported on the association between passive smoking and breast cancer risk by NAT2 genotype.

Since the findings from studies with significant results may be more likely to be written up and published than those with non-significant results, meta-analyses of the published literature in some situations may yield results that are too extreme. In the present situation, however, where a meta-analysis of the published literature from prospective studies has yielded a null result, there is little reason to expect that this null finding would be systematically altered by such 'publication bias'. Although there may well be other studies that have recorded passive exposure to tobacco smoke but not yet chosen to publish their findings for breast cancer, their probable existence does not provide any reason to distrust the present null findings from prospective studies.

By unduly data-dependent emphasis on particular subgroups it is often possible to find one subgroup in which there appears to be a hazard, even if in fact there is no material hazard either overall or in any subgroup. Such misinterpretation of subgroup results could help explain the recent claim that passive smoking appreciably increases the risk of breast cancer in pre-menopausal women.^{3,8} The fact that active smoking has little effect on either pre- or post-menopausal women,¹ however, makes it implausible that pre-menopausal women would be especially sensitive to passive exposure. Indeed, in the Million Women Study, the only noteworthy subgroup-specific result is an apparent protective effect of passive exposure in pre-menopausal women (Figure 2). While this does not provide good evidence of a real *protective* effect, it does provide prospective evidence against the view that passive smoking increases the risk of breast cancer in pre-menopausal women and, perhaps more importantly, it illustrates the statistical unreliability of such subgroup analyses. Given this unreliability, the most appropriate emphasis is on the overall prospective results, and these are null.

Measuring passive exposure to tobacco smoke directly is not simple, but the long-term mean exposure during childhood should be correlated with parental smoking, and the long-term mean exposure during middle-age should be correlated with the partner's smoking at one point in time (even though the partner or the partner's habits may have varied and, in prospective studies, may vary after the

information was reported). Some women do not know if their parents smoked when they were born, but in the Million Women Study those classified as having unknown exposure, mostly for this reason, had risks of breast cancer that were similar to those in exposed and in unexposed women. In both retrospective and prospective studies, sources of non-differential misclassification would tend to dilute any real effects of passive exposure. Prospective studies, however, have the advantage that the classification of exposure would not be differentially influenced by the subsequent development of breast cancer.

In conclusion, the results from prospective studies, where the reporting of passive exposure predates the diagnosis of breast cancer, suggest in aggregate little or no adverse effect on the risk of breast cancer. The published results from studies with retrospectively collected information on passive exposure to tobacco smoke appear, in aggregate, to be misleading, perhaps because of systematic differences in reporting between cases and controls in some studies.

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Conflict of interest: None declared.

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Appendix 1

Million Women Study steering committee

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NHS Breast Screening Centres collaborating in the Million Women Study (in alphabetical order)

Avon, Aylesbury, Barnsley, Basingstoke, Bedfordshire & Hertfordshire, Cambridge & Huntingdon, Chelmsford & Colchester, Chester, Cornwall, Crewe, Cumbria, Doncaster, Dorset, East Berkshire, East Cheshire, East Devon, East of Scotland, East Suffolk, East Sussex, Gateshead, Gloucestershire, Great Yarmouth, Hereford & Worcester, Kent (Canterbury, Rochester, Maidstone), Kings Lynn, Leicestershire, Liverpool, Manchester, Milton Keynes, Newcastle, North Birmingham, North East Scotland, North Lancashire, North Middlesex, North Nottingham, North of Scotland, North Tees,

North Yorkshire, Nottingham, Oxford, Portsmouth, Rotherham, Sheffield, Shropshire, Somerset, South Birmingham, South East Scotland, South East Staffordshire, South Derbyshire, South Essex, South Lancashire, South West Scotland, Surrey, Warrington Halton St Helens & Knowsley, Warwickshire Solihull & Coventry, West Berkshire, West Devon, West London, West Suffolk, West Sussex, Wiltshire, Winchester, Wirral and Wycombe.

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