Cancer Causes and Control (2005) 16:683–689
DOI 10.1007/s10552-005-1906-x

Secondhand smoke exposure in early life and the risk of breast cancer among never smokers (United States)

Matthew R. Bonner[1,*], Jing Nie[1], Daikwon Han[1], John E. Vena[2], Peter Rogerson[3], Paola Muti[1], Maurizio Trevisan[4], Stephen B. Edge[4] & Jo L. Freudenheim[1]
[1]*Department of Social and Preventive Medicine, School of Public Health and Health Professions, University at Buffalo, Buffalo, 14214, New York;* [2]*Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, 29208, South Carolina;* [3]*Department of Geography, University at Buffalo, Buffalo, 14214, New York;* [4]*Department of Surgery, Roswell Park Cancer Institute, Buffalo, 14263, New York*

Received 16 December 2004; accepted in revised form 08 February 2005

Key words: breast cancer, secondhand smoke, passive smoking.

Abstract

Evidence is increasing that some early life exposures affect breast cancer risk. Exposure to secondhand smoke (SHS) during childhood may be one such exposure. As part of the WEB Study (Western New York Exposures and Breast Cancer Study), we conducted a population-based, case-control study with 1166 women aged 35 to 79 diagnosed with histologically confirmed, primary, incident breast cancer. Controls (n = 2105) were randomly selected from the Department of Motor Vehicles driver's license list ($\leqslant$age 65) and the Center for Medicare & Medicaid Services rolls ($>$age 65). Participants were queried regarding household and workplace SHS exposure. Person-years of lifetime cumulative SHS exposure were computed as well as cumulative exposure up to 21 years of age. Unconditional logistic regression adjusting for potential confounders was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). Lifetime cumulative exposure to household SHS was not associated with an increase in breast cancer risk for premenopausal (OR = 1.17, 95% CI = 0.54–2.56) or postmenopausal (OR = 1.29; 95% CI = 0.82–2.01) women. Neither was risk increased among women exposed to SHS before the age of 21 or at the time of birth, menarche, or a women's first birth. In this study, exposure to SHS either in adult or early life does not appear to be associated with the risk of breast cancer.

Introduction

Interest that early life exposures may be related to breast cancer risk [1–3] is increasing because of evidence that breast epithelia may be more vulnerable to carcinogenic insults during this period of tissue proliferation and initial differentiation. Pregnancy and lactation result in further differentiation after which it seems that breast tissue is more resistant to carcinogenic insults [4–6]. It has been hypothesized that exposures before a woman gives birth for the first time may be particularly important in relation to disease etiology [7, 8]. Secondhand smoke is one such exposure that may affect the risk of developing breast cancer.

Exposure to secondhand smoke is relatively common among US children where an estimated 43% reside with at least one smoker [9]. Tobacco smoke consists of numerous compounds that are carcinogenic to several organ sites including the lung [10–12], bladder [13], and pancreas [14]. Among these compounds are polycyclic aromatic hydrocarbons (PAHs) and aromatic amines. PAHs accumulate in adipose tissue, including the breast [15, 16], and are known skin and mammary carcinogens in rodent models [17–19]. In addition, aromatic amines have been shown to be mammary carcinogens in rodents [20]. The effect of tobacco smoke on breast cancer risk, however, is not clear. McMahon *et al.* [21] hypothesized

* Address correspondence to: Matthew R. Bonner, Occupational and Environmental Epidemiology Branch, National Cancer Institute, 6120 Executive Blvd. EPS 8121, MSC 7240, Bethesda, 20892-7240, Maryland. Ph.: +301-402-7825; Fax: +301-402-1819; E-mail: bonnerm@mail.nih.gov

that tobacco smoke may reduce the risk of breast cancer because of evidence that cigarette smoke has antiestrogenic effects. Conversely, Hiatt and Fireman [22] reasoned that tobacco smoke could increase breast cancer risk because mutagens from cigarette smoke concentrate in the breast fluid of non-lactating women. Despite conflicting hypotheses about the effect of tobacco smoke on breast cancer risk, an association between cigarette smoking and breast cancer has yet to be clearly demonstrated [23, 24]. Further, there is conflicting evidence that secondhand smoke (SHS) affects breast cancer risk [12, 25–34]. With regards to early life exposure, there have been a few studies of SHS and risk; SHS has been found to be associated with increased risk of breast cancer in one [35], but not in most studies [36–38].

In this study, we explored lifetime cumulative exposure to household SHS and workplace SHS with particular focus on early life exposure (up to 21 years of age) in relation to the risk of breast cancer. Specifically, we hypothesized that residing with one or more household smokers in early life would increase the risk of breast cancer compared with women who did not reside with household smokers. In addition, we examined exposure to household smokers at the time of birth, menarche, and a woman's first birth in relation to the risk of breast cancer. We hypothesized that exposure to SHS at these time periods may increase the risk of breast cancer because breast epithelia appear be particularly sensitive to carcinogenic insults at these times of rapid cellular proliferation and differentiation.

Materials and methods

The Western New York Exposures and Breast Cancer Study (WEB Study) is a population-based, case-control study in Western New York and the details have been previously published [39, 40]. Briefly, cases (n = 1166) included women aged 35 to 79 years diagnosed with histologically-confirmed, primary, incident breast cancer currently residing in Erie or Niagara Counties in Western New York. Nurse case finders visited the pathology departments at regular intervals to identify cases. After identification, the case's physician was contacted to verify the diagnosis of breast cancer and to obtain permission to contact the case. Cases were then contacted and asked to participate in the study. Controls (n = 2105) were also current residents of Erie and Niagara counties randomly selected from the New York State Department of Motor Vehicles driver's license list (aged 65 and less) and the Center for Medicare & Medicaid Services (over 65 years). Controls were frequency matched by age, race, and county of residence. A total of 1638 cases and 3396 controls met our inclusion criteria of between 35 and 79 years of age, current resident of Erie or Niagara County, no previous cancer diagnosis other than non-melanoma skin cancer and an ability to speak English. The response rates were 71% (1166/1638) and 62% (2105/3396) for cases and controls, respectively. All participants provided informed consent; the protocol was approved by the University at Buffalo School of Medicine and Biomedical Sciences' and participating hospitals' Institutional Review Boards.

Extensive in-person interviews and self-administered questionnaires were used to ascertain medical history, diet, lifetime alcohol consumption, residential history, occupational history, and smoking history. We evaluated exposure to SHS with two methods. First, questions about exposure to secondhand smoke from other household residents and co-workers were asked for seven age periods: (1) <21 years, (2) 21–30, (3) 31–40, (4) 41–50, (5) 51–60, (6) 61–70, (7) >70. The number of people living with the participant who smoked cigarettes, cigars, or pipes during the specified time period was ascertained. In addition, participants were also asked for the number of years that they resided with these smokers. These two questions were used to compute person-years of SHS exposure for participants for each age period. For lifetime cumulative exposure to household SHS, person-years for each age period were summed. Cumulative exposure to household SHS before 21 years of age was derived from the first time period only. Workplace SHS exposure was estimated by inquiring about the number of hours per week participants were exposed to co-workers' cigarette smoke. In addition, participants were asked how many years were you exposed to co-workers' cigarette smoke. These two questions were combined to compute cumulative hours of workplace SHS exposure for each of the seven time periods previously mentioned. Lifetime cumulative exposure to workplace SHS was calculated by summing the seven time periods. Cumulative exposure before 21 years of age to household SHS, lifetime cumulative exposure to household SHS, and cumulative lifetime exposure to workplace SHS were categorized into five groups. Participants reporting no exposure were the reference group and quartiles of exposure were derived from the exposed controls for each measure of SHS exposure.

The second evaluation of SHS exposure was part of the residential history assessment. Participants listed each residence for their entire life with corresponding information on the number of other people who resided at that residence and the number of those residents who smoked cigarettes. The analysis was restricted to those with complete household smoking information at both

birth and menarche (n = 334 for cases and 609 for controls). For exposure at the time of first birth, the analysis was further restricted to those with residential information for all three time periods. Household smoking was categorized into a binary variable denoting either the presence or absence of household smokers.

Unconditional logistic regression [41] was used to calculate odds ratios (OR) and 95 % confidence intervals (CI), adjusting for age, race, education, age at first birth, age at menarche, parity, previous benign breast disease, family history of breast cancer in a first degree relative, body mass index (weight (kg)/height $(m)^2$), total lifetime alcohol consumption, and age at menopause for post-menopausal women only. All analyses were stratified by menopausal status and were restricted to never active smokers. A reduced model including age, race, previous benign breast disease, and parity was determined by removing covariates that did not alter the OR by more than 10%. *p* for trend statistics was determined by the *p*-value for the coefficient of the continuous exposure variable, while adjusting for covariates.

Results

A total of 525 cases and 1012 controls, all of whom were never smokers, were included in this analysis. Demographic characteristics for these study participants by menopausal status are shown in Table 1. As expected, both pre- and post-menopausal cases were more likely to have a family history of breast cancer and previous benign breast disease. Among premenopausal women, the mean age was statistically higher than the controls, although the difference was only 1.6 years. All other characteristics were similar.

Odds ratios and 95% CIs for lifetime cumulative exposure to household secondhand smoke, stratified by menopausal status are shown in Table 2. The ORs for quartiles of lifetime cumulative exposure to household SHS ranged from 1.17 to 1.57 (pre-menopausal women) and 0.83 to 1.29 (post-menopausal women), but none was statistically significant and there was not a trend of increasing risk with pack-years in either pre- or post-menopausal women. With regards to workplace SHS, the ORs for quartiles of lifetime cumulative exposure ranged from 0.46 to 0.83 (pre-menopausal women) and 0.71 to 1.04 (post-menopausal women) compared with women who were not exposed to SHS in the workplace (Table 2).

There was no evidence of an exposure-response gradient with cumulative exposure to household SHS before the age of 21 for either pre- or post-menopausal women (Table 3). Although for pre-menopausal women, the ORs were non-significantly elevated in each quartile.

We examined exposure to household SHS in the participant's residence at the time of their birth, menarche,

Table 1. Descriptive characteristics of study participants; among never smokers: Western New York Exposures and Breast Cancer Study (WEB Study) (1996–2001)

	Pre-menopausal		Post-menopausal	
	Mean (SD)		Mean (SD)	
	Cases (n = 149)	Controls (n = 326)	Cases (n = 376)	Controls (n = 686)
Age (years)	45.7 (4.5)	44.1 (4.6)	64.1 (9.2)	64.2 (8.9)
Education (years)	12.6 (1.6)	14.6 (2.3)	13.2 (2.5)	13.1 (2.3)
Age at Menarche (years)	12.6 (1.6)	12.5 (1.6)	12.7 (1.6)	12.8 (1.6)
Age at Menopause (years)	–	–	48.1 (5.6)	48.2 (6.0)
Age at first birth (years)	26.3 (4.8)	26.4 (4.7)	24.3 (24.8)	24.1 (4.2)
Body mass index	26.7 (6.0)	27.5 (6.5)	29.1 (5.9)	28.6 (6.0)
Total lifetime alcohol intake (oz.)	1284.1 (2008.5)	1629.1 (4693.7)	1397.8 (3182.8)	1944.8 (9723.4)
Lifetime cumulative household SHS[a] exposure (person-years)	26.9 (19.8)	23.5 (20.9)	34.3 (25.7)	33.9 (26.1)
Lifetime cumulative workplace SHS exposure (hours)	5721.9 (10,255.9)	5523 (10,0056.5)	12,195.6 (20,156.7)	10,623.2 (18,261.7)
Proportion				
Parity				
0	30 (20%)	50 (15%)	76 (20%)	75 (11%)
1–2	81 (54%)	168 (52%)	138 (37%)	191 (28%)
3+	38 (26%)	108 (33%)	162 (43%)	420 (61%)
Benign breast disease (yes)	49 (33%)	64 (19%)	104 (28%)	125 (18%)
Relative with breast cancer (yes)	28 (19%)	32 (10%)	76 (20%)	86 (13%)

[a] SHS, secondhand smoke.

Table 2. Risk of breast cancer associated with lifetime cumulative exposure to secondhand smoke from co-habitants and workers; among never smokers: Western New York Exposures and Breast Cancer Study (WEB Study) (1996–2001)

	Pre-menopausal				Post-menopausal			
	Cases (n = 149)	Controls (n = 326)	Reduced Model OR[a] (95% CI)	Full Model OR[b] (95%CI)	Cases (n = 376)	Controls (n = 684)	Reduced Model OR[a] (95%CI)	Full Model OR[b] (95%CI)
Household SHS[c] (person-years)								
0	23	70	1.00	1.00	45	89	1.00	1.00
>0 – ≤20	42	101	1.27 (0.69–2.34)	1.31 (0.70–2.44)	104	153	1.30 (0.83–2.03)	1.24 (0.79–1.95)
>20 – ≤33	30	49	1.57 (0.79–3.11)	1.56 (0.77–3.14)	52	128	0.83 (0.51–1.36)	0.82 (0.50–1.36)
>33 – ≤49	35	72	1.31 (0.68–2.49)	1.35 (0.69–2.63)	71	140	1.05 (0.66–1.69)	1.03 (0.64–1.66)
>49	19	34	1.17 (0.54–2.56)	1.16 (0.51–2.62)	104	174	1.29 (0.82–2.01)	1.25 (0.79–1.96)
p for trend			0.62	0.60			0.31	0.38
Workplace SHS (hours)								
0	57	109	1.00	1.00	141	249	1.00	1.00
>0 – ≤1716	20	69	0.46 (0.25–0.86)	0.44 (0.24–0.83)	37	91	0.71 (0.45–1.10)	0.71 (0.45–1.11)
>1716–≤6240	37	64	0.83 (0.48–1.43)	0.86 (0.49–1.50)	57	100	0.93 (0.63–1.39)	0.92 (0.62–1.38)
>6240–≤17,615	18	47	0.54 (0.28–1.04)	0.54 (0.27–1.07)	51	100	0.75 (0.50–1.13)	0.76 (0.45–1.14)
17,615+	17	28	0.83 (0.40–1.72)	0.79 (0.37–1.70)	87	128	1.04 (0.73–1.49)	1.09 (0.76–1.57)
p for trend			0.47	0.38			0.49	0.41

[a] Adjusted for age, race, previous benign breast disease,and parity.
[b] Adjusted for age, education, race, previous benign breast disease, parity, age at menarche, BMI, age at first birth, relative with breast cancer, total alcohol consumption and age at menopause for post-menopausal women only.
[c] SHS, secondhand smoke.

Table 3. Risk of breast cancer associated with exposure to secondhand smoke before age 21; among never smokers: Western New York Exposures and Breast Cancer Study (WEB Study) (1996–2001)

	Pre-menopausal				Post-menopausal			
	Cases (n = 149)	Controls (n = 326)	Reduced Model OR[a] (95% CI)	Full Model OR[b] (95%CI)	Cases (n = 376)	Controls (n = 684)	Reduced Model OR[a] (95%CI)	Full Model OR[b] (95%CI)
SHS[c] (person-years)								
0	33	96	1.00	1.00	89	194	1.00	1.00
>0–≤18	32	69	1.32 (0.73–2.40)	1.39 (0.76–2.55)	66	120	1.09 (0.73–1.64)	1.02 (0.68–1.54)
>18–≤20	38	73	1.29 (0.72–2.30)	1.33 (0.74–2.40)	143	236	1.30 (0.93–1.82)	1.30 (0.93–1.83)
>20–≤36	14	29	1.31 (0.60–2.87)	1.39 (0.62–3.09)	20	37	1.17 (0.63–2.17)	1.10 (0.59–2.05)
>36	32	59	1.26 (0.68–2.31)	1.33 (0.71–2.49)	58	97	1.33 (0.87–2.04)	1.26 (0.82–1.94)
p for trend			0.90	0.99			0.07	0.09

[a] Adjusted for age, race, previous benign breast disease, and parity.
[b] Adjusted for age, education, race, previous benign breast disease, parity, age at menarche, BMI, age at first birth, relative with breast cancer, total alcohol consumption and age at menopause for post-menopausal women only.
[c] SHS, secondhand smoke.

and first birth and breast cancer to determine if exposure in particular time periods was associated with breast cancer (Table 4). For premenopausal women, exposure to household SHS at the time of birth was associated with a non-significant increase in the risk of breast cancer (reduced model OR = 1.35, 95% CI: 0.79–2.30). For post-menopausal women, exposure to household SHS at the time of birth was not associated with risk of breast cancer (reduced model OR = 1.07, 95% CI: 0.71–1.60) breast cancer. Odds ratios for household SHS exposure at the time of menarche and breast cancer were similar to the ORs for exposure at birth. Exposure to SHS at the time of a women's first birth was not associated with pre-menopausal (reduced model OR = 1.22, 95% CI: 0.68–2.17) or post-menopausal (reduced OR = 0.78, 95% CI: 0.52–1.18). For post-menopausal women, however, exposure to household smoke at the time of first birth was suggestive, if anything, of a reduction in risk. We attempted to examine each time period while adjusting for the other two time periods to investigate whether one time period in particular was associated with an increased odds ratio. However, household smoking status at each of the time periods was highly correlated and the results were not interpretable.

Table 4. Risk of breast cancer associated with exposure to secondhand smoke exposure at the time of birth, menarche, and first birth; among never smokers: Western New York Exposures and Breast Cancer Study (WEB Study) (1996–2001)

SHS[a] exposure	Pre-menopausal				Post-menopausal			
	Cases (n = 106)	Controls (n = 238)	Reduced Model OR[b] (95% CI)	Full Model OR[c] (95% CI)	Cases (n = 228)	Controls (n = 371)	Reduced Model OR[b] (95% CI)	Full Model OR[c] (95% CI)
Birth								
No	27	84	1.00	1.00	52	89	1.00	1.00
Yes	79	154	1.35 (0.79–2.30)	1.34 (0.77, 2.32)	176	282	1.07 (0.71–1.60)	1.07 (0.72–1.59)
Menarche								
No	29	92	1.00	1.00	50	89	1.00	1.00
Yes	77	146	1.47 (0.87–2.50)	1.49 (0.87, 2.57)	178	282	1.11 (0.74–1.67)	1.15 (0.77–1.71)
First birth[d]								
No	52	140	1.00	1.00	66	108	1.00	1.00
Yes	31	56	1.22 (0.68–2.17)	1.11 (0.59, 2.11)	93	188	0.78 (0.52–1.18)	0.80 (0.54–1.20)

[a] SHS, secondhand smoke.
[b] Adjusted for age, race, previous benign breast disease, and parity.
[c] Adjusted for age, race, education, previous benign breast disease, parity, age at menarche, BMI, age at first birth, family history of breast cancer, total alcohol consumption, and age at menopause for post-menopausal women only.
[d] Restricted to cases and controls with known addresses at the time of birth, menarche and first birth.

Discussion

Overall, this study provides little evidence that lifetime cumulative exposure to SHS either in the workplace or at home is associated with an increase in the risk of breast cancer. In addition, pack-years of household SHS exposure before 21 years of age were not clearly associated with the risk of breast cancer. Although all the ORs for household SHS exposure before 21 years of age were slightly elevated, there was no evidence of a trend with increasing household SHS exposure. The literature on adult exposure to SHS and breast cancer has been mixed. While several studies [27–30] have found evidence of an association between SHS exposure and breast cancer, other studies [12, 25, 31–34], including our own, have found little evidence supporting an association. One cohort study of Japanese women even found that women who's spouses smoked were at reduced risk of breast cancer (RR = 0.58; 95 CI = 0.34–0.99) [42]. Some studies have lacked internal consistency raising doubt about the observed association. For instance, Gammon *et al.* [34] observed a two-fold increase among women exposed to 326+ months of spousal smoking (OR = 2.10; 95 CI = 1.47–3.02), although there was no evidence of an exposure-response gradient. Further, when they considered total residential passive smoke exposure from all smoking co-habitants including spouses, there was no association between SHS exposure and breast cancer.

In the studies that have examined early life exposure to SHS, the results have also been mixed. In one study, Sandler *et al.* [37] found no increase in the risk of breast cancer in women exposed to either maternal or paternal household smoking before participants attained 10 years of age. In another study, Smith *et al.* [38] assessed exposure to SHS up to age 16 and found women exposed to SHS in childhood had an OR of 1.98 (95% CI: 0.35–11.36) compared with those never exposed. In addition, women exposed to 201 to 400 cigarette-years in childhood were observed to have an OR of 2.09 (95% CI: 1.05–4.16), however the OR was 1.51 (95% CI: 0.72–3.20) in women exposed to >400 cigarette-years in childhood. Smith *et al.* concluded that there was no association between SHS exposure in childhood and breast cancer. Lash and Aschengrau [35] examined women who were exposed to SHS before the age of 12 and found an OR of 4.5 (95% CI: 1.2–16). However, these results were not replicated in a more recent case-control study where exposure to SHS before the age of 13 was not associated with an increase in the risk of breast cancer (OR: 1.1, 95% CI: 0.4–3.0).[36] Gammon *et al.* [34] found no association between parental passive smoke exposure prior to age 18 (OR = 0.85; 95 CI = 0.70–1.03).

All of these studies, including ours, relied on questionnaires to assess exposure to SHS. Questionnaire-based exposure assessments of SHS have been criticized because they may not precisely measure SHS exposure [43, 44] and biomarkers of exposure have been offered as potentially superior alternatives to questionnaire-based exposure assessment of SHS. Cotinine, the major metabolite of nicotine, has been used as a biomarker of tobacco exposure; although its biologic half-life is 16.5 h and may be a valid only for recent exposure to tobacco smoke [45]. While biomarkers of SHS exposure have the potential to greatly increase the accuracy of exposure

assessments, they are currently limited to only recent exposure and are not yet able to estimate long-term exposure. Given these circumstances, questionnaire-based exposure assessment to SHS may be superior to biomarkers because they are able to estimate historical or long-term exposure; although questionnaires may contain considerable exposure misclassification.

There are several limitations of this study that should be considered when interpreting the results. Among these is recall bias. While such a bias is possible, it would seem less likely, given the request for information pertained to SHS exposure and that there is no well-known hypothesis linking SHS exposure and breast cancer risk. This is particularly true for childhood exposure. As previously noted, misclassification of exposure is likely given that we used questionnaires to measure SHS. Further, we did not take into account other sources of SHS, although we did examine workplace exposure separately and found no relationship. In addition, misclassification of SHS exposure could have occurred because some smokers may not have smoked in the presence of that participant. In particular, we could not distinguish smokers who restricted their smoking activities around the participant, thereby decreasing exposure, from those who did not. In addition, we assumed that early life exposure to SHS would predominantly occur in the household. This is particularly likely for the time period between birth and menarche.

In addition to exposure misclassification and recall bias, the possibility of selection bias cannot be ruled out. Comparisons between respondents and non-respondents indicated that smokers were less likely to participate in this study. Since smokers are more likely to have parents who smoked [46], a selection bias may have altered the distribution of SHS exposure in the controls from that of the source population from which the cases arose resulting in magnified risk estimates. Selection bias of this type, however, seems unlikely because we restricted the analysis to never active smokers.

In summary, our study examined lifetime cumulative exposure to household and workplace SHS. We also examined cumulative exposure up to 21 years of age, as well as household SHS exposure at the time of birth, menarche, and first birth in relation to the risk of breast cancer. We had hypothesized that the chemical carcinogens present in tobacco smoke such as PAHs would affect breast cancer risk and that exposure to tobacco smoke in early life would have particular importance. We did not find evidence that either lifetime cumulative exposure to SHS or early life exposure was associated with the risk of breast cancer. However, the recent trends toward limiting SHS exposure particularly for children remains appropriate, given our knowledge of other effects of SHS on health [47] and the relatively high prevalence of SHS exposure in the US population [9].

Acknowledgements

This work has been supported in part by CA-09051 NCI, 5R21CA8713802 NCI, and DAMD-170010417.

References

1. Potischman N, Troisi R (1999) In-utero and early life exposures in relation to risk of breast cancer. *Cancer Causes Control* **10**: 561–573.
2. Trichopoulos D (1990) Is breast cancer initiated in utero. *Epidemiology* **1**: 95–96.
3. Trichopoulos D (1990) Hypothesis: does breast cancer originate in utero. *Lancet* **335**: 939–940.
4. Russo J, Reina D, Frederick J, Russo IH (1988) Expression of phenotypical changes by human breast epithelial cells treated with carcinogens *in vitro*. *Cancer Res* **48**: 2837–2857.
5. Russo J, Calaf G, Sohi N, Tahin Q, Zhang PL, Alvarado ME, *et al*. (1993) Critical steps in breast carcinogenesis. *Ann NY Acad Sci* **698**: 1–20.
6. Russo J, Hu YF, Yang X, Russo IH (2000) Developmental, cellular, and molecular basis of human breast cancer. J Natl Cancer Inst Monogr, 17–37.
7. Berkey CS, Frazier AL, Gardner JD, Colditz GA (1999) Adolescence and breast carcinoma risk. *Cancer* **85**: 2400–2409.
8. Colditz GA, Frazier AL (1995) Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiol Biomarkers Prev* **4**: 567–571.
9. Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR (1996) Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. *Jama* **275**: 1233–1240.
10. Lubin JH (1999) Estimating lung cancer risk with exposure to environmental tobacco smoke. *Environ Health Perspect* **107**: 879–883.
11. Bennett WP, Alavanja MC, Blomeke B, Vahakangas KH, Castren K, Welsh JA, *et al*. (1999) Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. *J Natl Cancer Inst* **91**: 2009–2014.
12. Jee SH, Ohrr H, Kim IS (1999) Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol* **28**: 824–828.
13. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, *et al*. (2000) Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer* **86**: 289–294.
14. Kuper H, Boffetta P, Adami HO (2002) Tobacco use and cancer causation: association by tumour type. *J Intern Med* **252**: 206–224.
15. Obana H, Hori S, Kashimoto T, Kunita N (1981) Polycyclic aromatic hydrocarbons in human fat and liver. *Bull Environ Contam Toxicol* **27**: 23–27.
16. Morris JJ, Seifter E (1992) The role of aromatic hydrocarbons in the genesis of breast cancer. *Med Hypotheses* **38**: 177–184.
17. Bostrom CE, Gerde P, Hanberg A, Jernstrom B, Johansson C, Kyrklund T, *et al*. (2002) Cancer risk assessment, indicators, and

guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environ Health Perspect* **110** (Suppl 3): 451–488.
18. Phillips DH (1983) Fifty years of benzo(a)pyrene. *Nature* **303**: 468–472.
19. Rubin H (2001) Synergistic mechanisms in carcinogenesis by polycyclic aromatic hydrocarbons and by tobacco smoke: a bio-historical perspective with updates. *Carcinogenesis* **22**: 1903–1930.
20. Dunnick JK, Elwell MR, Huff J, Barrett JC (1995) Chemically induced mammary gland cancer in the National Toxicology Program's carcinogenesis bioassay. *Carcinogenesis* **16**: 173–179.
21. MacMahon B, Trichopoulos D, Cole P, Brown J (1982) Cigarette smoking and urinary estrogens. *N Engl J Med* **307**: 1062–1065.
22. Hiatt RA, Fireman BH (1986) Smoking, menopause, and breast cancer. *J Natl Cancer Inst* **76**: 833–838.
23. Palmer JR, Rosenberg L (1993) Cigarette smoking and the risk of breast cancer. *Epidemiol Rev* **15**: 145–156.
24. Terry PD, Rohan TE (2002) Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev* **11**: 953–971.
25. Egan KM, Stampfer MJ, Hunter D, Hankinson S, Rosner BA, Holmes M, *et al.* (2002) Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* **13**: 138–145.
26. Morabia A, Bernstein M, Heritier S, Khatchatrian N (1996) Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol* **143**: 918–928.
27. Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. *Am J Epidemiol* **121**: 37–48.
28. Sandler DP, Everson RB, Wilcox AJ (1986) Cigarette smoking and breast cancer. *Am J Epidemiol* **123**: 370–371.
29. Johnson KC, Hu J, Mao Y (2000) Passive and active smoking and breast cancer risk in Canada, 1994–97. The Canadian Cancer Registries Epidemiology Research Group. *Cancer Causes Control* **11**: 211–221.
30. Kropp S, Chang-Claude J (2002) Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol* **156**: 616–626.
31. Wartenberg D, Calle EE, Thun MJ, Heath CW Jr., Lally C, Woodruff T (2000) Passive smoking exposure and female breast cancer mortality. *J Natl Cancer Inst* **92**: 1666–1673.
32. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, *et al.* (2004) Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst* **96**: 29–37.
33. Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD, Qaqish B (2000) 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* **11**: 271–278.
34. Gammon MD, Eng SM, Teitelbaum SL, Britton JA, Kabat GC, Hatch M, *et al.* (2004) Environmental tobacco smoke and breast cancer incidence. *Environ Res* **96**: 176–185.
35. Lash TL, Aschengrau A (1999) Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* **149**: 5–12.
36. Morabia A, Lash TL (2002) Breast cancer, passive and active cigarette smoking and N-acetyltransferase 2 genotype. *Pharmacogenetics* **12**: 85–88.
37. Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985) Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health* **75**: 487–492.
38. Smith SJ, Deacon JM, Chilvers CE (1994) Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. UK National Case-Control Study Group. *Br J Cancer* **70**: 112–119.
39. McCann SE, Muti P, Vito D, Edge SB, Trevisan M, Freudenheim JL (2004) Dietary lignan intakes and risk of pre- and post-menopausal breast cancer. *Int J Cancer* **111**: 440–443.
40. McCann SE, Ip C, Ip MM, McGuire MK, Muti P, Edge SB, *et al.* (2004) Dietary intake of conjugated linoleic acids and risk of premenopausal and postmenopausal breast cancer, Western New York Exposures and Breast Cancer Study (WEB Study). *Cancer Epidemiol Biomarkers Prev* **13**: 1480–1484.
41. Hosmer DW, Lemeshow S (2000) *Applied Logistic Regression*, New York, Wiley.
42. Nishino Y, Tsubono Y, Tsuji I, Komatsu S, Kanemura S, Nakatsuka H, *et al.* (2001) Passive smoking at home and cancer risk: a population-based prospective study in Japanese non-smoking women. *Cancer Causes Control* **12**: 797–802.
43. Woodward A, al-Delaimy W (1999) Measures of exposure to environmental tobacco smoke. Validity, precision, and relevance. *Ann NY Acad Sci* **895**: 156–172.
44. Coultas DB, Peake GT, Samet JM (1989) Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am J Epidemiol* **130**: 338–347.
45. Haley NJ, Sepkovic DW, Hoffmann D (1989) Elimination of cotinine from body fluids: disposition in smokers and nonsmokers. *Am J Public Health* **79**: 1046–1048.
46. Bauman KE, Foshee VA, Linzer MA, Koch GG (1990) Effect of parental smoking classification on the association between parental and adolescent smoking. *Addict Behav* **15**: 413–422.
47. American Association of Pediatrics. (1997) *Environmental Tobacco Smoke: A Hazard to Cchildren*. American Academy of Pediatrics Committee on Environmental Health. In Pediatrics Vol. 99, pp. 639–642.