Cancer Causes Control (2017) 28:667–675
DOI 10.1007/s10552-017-0903-1

ORIGINAL PAPER

Breast cancer and exposure to tobacco smoke during potential windows of susceptibility

Alexandra J. White[1] · Aimee A. D'Aloisio[1,2] · Hazel B. Nichols[3] · Lisa A. DeRoo[4] · Dale P. Sandler[1]

Received: 7 February 2017 / Accepted: 3 May 2017 / Published online: 18 May 2017

Abstract
Purpose An association between smoking and breast cancer is unresolved, although a higher risk from exposure during windows of susceptibility has been proposed. The objective of this prospective study was to evaluate the association between tobacco smoke and breast cancer with a focus on timing of exposure, especially during early life.
Methods Sister study participants ($n = 50{,}884$) aged 35–74 were enrolled from 2003 to 2009. Women in the United States and Puerto Rico were eligible if they were breast cancer-free but had a sister with breast cancer. Participants completed questionnaires on smoking and environmental tobacco smoke (ETS) exposure. Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for breast cancer risk.
Results During follow-up (mean = 6.4 years), 1,843 invasive breast cancers were diagnosed. Neither active smoking nor adult ETS was associated with breast cancer risk. However, never smoking women exposed to ETS throughout their childhood had a 17% higher risk of breast cancer (95% CI 1.00–1.36) relative to those with no exposure. In utero ETS exposure was also associated with breast cancer (HR = 1.16, 95% CI 1.01–1.32) and the HR was most elevated for women born in earlier birth cohorts (<1940, HR = 1.44, 95% CI 1.02–2.02; 1940–1949, HR = 1.28, 95% CI 1.01–1.62).
Conclusion In utero ETS and ETS exposure during childhood and adolescence were associated with increased risk of breast cancer and associations varied by birth cohort.

Keywords Breast cancer · Tobacco smoke · Early life · Environmental tobacco smoke

Introduction

Active smoking and environmental tobacco smoke (ETS) exposure can result in inhaling tobacco-related carcinogens relevant to breast cancer risk. Tobacco smoke contains several established carcinogenic compounds, including polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and *N*-nitrosamines [1, 2]. Metabolites and chemicals from cigarette smoke have been shown to reach the breast, as both nicotine and cotinine have been measured in breast fluid [3]. Smoking has also been associated with DNA adducts [3–5] and *p53* mutation smoking signatures in breast tissue [6] which promote carcinogenesis. The 2014 Surgeon General's report stated that "the evidence is suggestive but not sufficient to infer a causal relationship" between breast cancer and active smoking or ETS exposure [7]. Since the report was published, there have been a number of cohort studies that have supported an association between tobacco smoke and breast cancer [8–15].

Electronic supplementary material The online version of this article (doi:10.1007/s10552-017-0903-1) contains supplementary material, which is available to authorized users.

✉ Alexandra J. White
alexandra.white@nih.gov

[1] Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC 27709-2233, USA

[2] Social & Scientific Systems, Inc., Durham, NC 27703, USA

[3] Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599, USA

[4] Department of Global Public Health & Primary Care, University of Bergen, Bergen, Norway

The Surgeon General's report on tobacco smoke identified a number of areas for improvement including more research on the effect of early age at smoking initiation or timing of ETS exposure on breast cancer risk, variation by tumor subtype and potential confounding by alcohol intake [7]. Exposure to carcinogens during early life, a hypothesized biological window of susceptibility [16], may be especially relevant for breast cancer risk. Breast duct cells remain undifferentiated prior to first full-term pregnancy and, thus, may be particularly susceptible to carcinogens; any genetic errors before first pregnancy would then be propagated by the extensive proliferation during pregnancy [17]. Previous studies have found initiating smoking prior to first birth to be associated with breast cancer [8–11, 13, 15, 18].

In the study reported here, we aimed to evaluate the association between active smoking and ETS exposure on breast cancer risk with a focus on timing of exposure. We considered intensity and duration of tobacco smoke exposure, evaluated alcohol as a confounder and effect measure modifier, and assessed variability by tumor estrogen receptor (ER) status.

Materials and methods

Study population

The National Institute of Environmental Health Sciences (NIEHS) Sister Study is a prospective cohort study of 50,884 women that was designed to investigate environmental and lifestyle risk factors for breast cancer. During 2003–2009, women throughout the US and Puerto Rico were recruited using a multi-media campaign as well as a network of volunteers, breast cancer professionals, and advocates. Women, aged 35–74, were eligible for the study if they had no history of breast cancer themselves but they had a sister who had been diagnosed with breast cancer. At baseline, study participants completed an extensive computer-assisted baseline telephone questionnaire on demographics, medical and family history, and lifestyle factors including active smoking history and lifetime exposure to environmental tobacco smoke. They also completed a mailed questionnaire on early life exposures that included questions on maternal and paternal smoking.

This research was approved by the Institutional Review Boards of the NIEHS, NIH, and the Copernicus Group. Written informed consent was obtained from all participants. We included cases diagnosed with breast cancer as of 1 July 2014 (Sister Study Data Release 4.1).

Study participants update information on risk factors and report any changes in health status during annual health updates and biennial surveys. Response rates have been high at 94% over follow-up [19].

Outcome assessment

Medical records are requested for women who report an incident breast cancer diagnosis to confirm diagnosis and obtain other relevant diagnostic and treatment information. Currently, medical records have been successfully obtained for greater than 80% of cases. Agreement between self-reported and medical record-abstracted data is high [20]; thus, self-reported data were used when medical record data were unavailable. Tumor characteristics considered included whether the tumor was [1] stage 0, I, II–IV, [2] estrogen receptor-positive (ER+) or estrogen receptor-negative (ER−), and [3] ductal or lobular histologic type. Additionally, menopausal status at diagnosis (pre-menopausal or postmenopausal) was evaluated.

Exposure and covariate assessment

As part of the baseline questionnaire, women were asked about their own use of cigarettes and exposure to cigarette smoke from other people. Active smoking was defined as smoking at least 1 cigarette/day for at least 6 months. Participants reported the ages that they began and stopped smoking and the number of cigarettes per day/week/month that they smoked. This information was used to calculate year and decade-specific estimates of smoking duration and intensity, as well as lifetime summary estimates. Women were categorized by ever versus never smoking status and ever smokers were further classified into current and past smokers (defined as not smoking within the previous 12 months). Age started smoking (<15, 15–19, 20+ years), total pack-years (<10, 10–19, 20–29, 30+ pack-years), total years (<10, 10–19, 20–29, 30+ years), time since smoking in past smokers (<10, 10–24, 25+ years) and usual cigarettes per day in current smokers (<10, 10–19, 20+ cigarettes/day) were considered relative to never smokers. We conducted a secondary analysis restricting the referent group, never smokers, to those also without ETS exposure during childhood or adulthood.

Limiting to parous women, smoking status relative to first full-term pregnancy was considered as pack-years of smoking (<5, 5–9, 10+ pack-years) completed before and after first full-term pregnancy ($\geq$37 weeks gestation). We also considered pack-years by decade of young life (<30 years, 30–39, 40–49) in all women.

ETS exposure was evaluated for three time periods: [1] in utero, [2] childhood and adolescence (defined as exposures occurring from birth to 18 years of age), and [3] adult (>18 years of age). For both childhood and adult periods, women were determined to be ETS exposed if someone smoked $\geq$1 cigarettes/day in their presence for a period of at least 6 months. Total years of ETS (none, 0–9, 10–19, 20–29, 30+), years of adult ETS (none, 0–9, 10–19, 20+),

and years of childhood ETS (none, 0–9, 10–14, 15–17, 18) were characterized. To assess in utero exposure to ETS, women were asked whether their mother or anyone else in the household smoked while she was pregnant and whether their biological father smoked in the 3 months prior to conception. Response options (definitely yes, probably yes, probably no, definitely no) were collapsed into two categories [1] definitely or probably yes and [2] definitely or probably no. All ETS exposures were evaluated in never smoking women.

Covariates of interest, including demographics, reproductive history, lifetime alcohol intake (average drinks/year prior to baseline interview), use of postmenopausal hormones, and oral contraceptives were obtained from the interview. Height and weight at baseline were measured in a home visit by a trained examiner and were used to calculate body mass index (BMI, kg/m^2).

Statistical analysis

Multivariable Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between active smoking and ETS exposure measures and breast cancer risk. Statistical models used age as the time scale and person-time was accrued from age at study enrollment. Follow-up extended until study participants had an invasive breast cancer diagnosis or were censored at the date of last follow-up or if diagnosed with in situ disease. Outcome subgroup analyses were performed evaluating stage (0, I, II–IV), invasive hormone receptor status (ER+, ER−), histologic type (ductal, lobular), and menopausal status at diagnosis (premenopausal, postmenopausal). For subgroup analyses, cases who did not have the outcome of interest (for example: ER− tumors when estimating the association for ER+ tumors) were censored at time of diagnosis. Similarly, in analyses investigating associations with menopausal status at the time of breast cancer diagnosis as an outcome, women who became postmenopausal during the follow-up period were censored at the time of menopause with respect to the outcome of premenopausal breast cancer. Consequently, the person-time that accumulated after menopause contributed to postmenopausal person-time at risk. The proportional hazard assumption was visually assessed using log–log survival plots as well as with the inclusion of an interaction term with survival time in the regression model, using $\alpha = 0.05$ to test for deviations. There was no suggestion of time-variant associations.

Stratified models were used to assess average lifetime alcohol intake (defined in quartiles: ≤20.4, 20.5–61.2, 61.3–143.8, 143.9+ average drinks/year over the lifetime) and birth cohort (<1940, 1940–1949, 1950–1960, 1960+) as potential effect measure modifiers. We also considered whether there was an interaction between active smoking and ETS exposure with breast cancer risk. Confounders were identified using the prior literature and a directed acyclic graph [21]. Multivariable-adjusted models included the following confounders: age, race (non-Hispanic white, other), education (≤high school or equivalent, some college, 4-year degree or higher), age at menarche (continuous), age at first birth (nulliparous, <21, 21 to <25, 25 to <29, 29 to <32, ≥32 years), parity (nulliparous or 1, 2–3, 4+), use of oral contraceptives (ever, never), postmenopausal hormone use (none, estrogen only, estrogen and progesterone combined or both estrogen and estrogen and progesterone combined), age at menopause (premenopausal, <40, 40–50, 51–55, 55+ years based on enrollment information), lifetime alcohol consumption, and body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30+ kg/m^2). For early life exposures, specifically childhood and in utero ETS, a separate adjustment set was used which included age, race, and childhood socioeconomic variables including household composition (two parents, single parent, other) at age 13, family income (well off, middle income, low income, poor) and highest household education at age 13 (less than high school, high school or equivalent, some college, 4-year degree or higher). A sensitivity analysis was conducted with childhood and in utero ETS exposure included in the model as potential confounders for the association between adult ETS exposure and breast cancer risk. Tests of trend used Chi-square tests of continuous variables.

Two-sided tests were used with a p value of 0.05 to evaluate statistical significance. All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

Results

Study population characteristics are displayed in Table 1. Past smokers were more often white and slightly older compared to current or never smokers. Never smokers were more likely to have completed a 4-year college degree relative to smokers. Current smokers had an earlier age at menopause and had the highest average intake of alcohol.

Little to no association was observed with current or past smoking status, early age at initiation of smoking or with increasing years and pack-years of smoking (Table 2). After further adjustment for lifetime alcohol intake most estimates were attenuated towards the null. Results for duration and intensity of smoking for past (not shown) and current smokers were similar, as were results when those with any ETS exposure were removed from the referent group (Supplemental Table I). There was no interaction observed between smoking status (never, former, current)

Table 1 Study population characteristics at baseline, NIEHS sister study

	Never smokers (n = 28,483) Mean (SD)		Past smokers (n = 18,088) Mean (SD)		Current smokers (n = 4,162) Mean (SD)	
Continuous measures						
Age at baseline	54.9 (9.1)		57.4 (8.6)		53.1 (8.2)	
Age at menarche	12.6 (1.5)		12.7 (1.5)		12.7 (1.6)	
Age at first birth[a]	25.0 (5.2)		24.4 (5.3)		23.0 (5.1)	
Parity[a]	2.4 (1.1)		2.4 (1.1)		2.3 (1.1)	
Age at menopause[b]	48.5 (6.3)		48.5 (6.4)		45.5 (7.2)	
Average lifetime alcohol consumption (drinks/year)[c]	82.5 (103.1)		137.0 (163.2)		172.1 (217.7)	
Body mass index (kg/m^2)	27.7 (6.3)		28.1 (6.3)		27.8 (6.1)	
	n	(%)	n	(%)	n	(%)
Categorical measures						
Race						
Non-Hispanic white	23,167	81.4	15,880	87.8	3,393	81.5
Other	5,309	18.6	2,207	12.2	769	18.5
Education						
High school degree/equivalent or less	3,799	13.3	2,946	16.3	1,036	24.9
Some college	8,769	30.8	6,506	36.0	1,862	44.7
4-year degree or more	15,911	55.9	8,635	47.7	1,264	30.4
Use of oral contraceptives						
Never	4,878	17.1	2,655	14.7	575	13.8
Ever	23,585	82.9	15,416	85.3	3,585	86.2
Postmenopausal hormone use[b]						
None	6,827	40.0	4,572	35.7	1,064	43.0
Estrogen (E) only	4,825	28.3	3,598	28.1	704	28.5
Estrogen and progesterone (E+P) or E and E+P	5,398	31.7	4,646	36.3	706	28.5

[a] Limited to parous women (n = 41,530)

[b] Limited to those who were postmenopausal at baseline (n = 32,457)

[c] Limited to ever alcohol drinkers (n = 48,796)

and lifetime average alcohol intake, although the strongest breast cancer effect was observed among former smoking heavier drinkers (HR 1.44, 95% CI 1.11–1.85) (Supplemental Table II). In analyses adjusted for lifetime alcohol intake, there was a suggestive positive association between current smoking and invasive postmenopausal breast cancer (HR = 1.15, 95% CI 0.91–1.44), but not premenopausal breast cancer (Supplemental Table III).

When limited to parous women, 10+ pack-years of smoking prior to first pregnancy was associated with a suggestive elevated risk of breast cancer (HR = 1.22, 95% CI 0.94–1.59) (Fig. 1). The association with smoking 10+ pack-years before age 30 did not largely differ from that of smoking 10+ pack-years later in life.

No elevated risk was observed for overall ETS or total years of ETS in never smokers (Table 3). Rather, an inverse association was observed with adult ETS and breast cancer incidence (HR = 0.86, 95% CI 0.74–1.00). This association remained unchanged with the addition of childhood and in utero ETS included in the model (data not shown). In contrast, having any childhood or adolescent ETS was associated with a higher breast cancer risk (HR = 1.12, 95% CI 0.98–1.29) after adjustment for early life SES factors, age, and race. Being exposed to ETS throughout childhood and adolescence (18 years) was also associated with an elevated risk (HR = 1.17, 95% CI 1.00–1.36) relative to those with no childhood ETS exposure (p for trend = 0.04). Study participant's mother's household ETS exposure while pregnant was associated with a higher breast cancer risk of similar magnitude (HR = 1.16, 95% CI 1.01–1.32) as was paternal smoking in the 3 months prior to the mother's pregnancy

Table 2 Cigarette smoking history and invasive breast cancer, NIEHS sister study

Cigarette smoking status	Person-years (326,242)	Invasive breast cancer ($n = 1843$)	Age adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]	Fully adjusted plus alcohol HR (95% CI)[c]
Cigarette smoking status					
Never smoked	183,487	985	1	1	1
Ever smoked	142,655	858	1.07 (0.98, 1.17)	1.08 (0.98, 1.18)	1.00 (0.90, 1.12)
Past smoker	116,535	721	1.08 (0.98, 1.19)	1.08 (0.98, 1.19)	1.00 (0.89, 1.12)
Current smokers	26,120	137	1.03 (0.86, 1.24)	1.09 (0.91, 1.31)	1.03 (0.85, 1.26)
Age started smoking					
Never smoked	183,487	985	1	1	1
<15 years	17,971	98	1.05 (0.85, 1.29)	1.07 (0.87, 1.32)	0.95 (0.76, 1.20)
15–19 years	91,471	572	1.11 (1.00, 1.23)	1.13 (1.02, 1.25)	1.05 (0.93, 1.18)
20+ years	33,192	187	0.96 (0.82, 1.12)	0.95 (0.81, 1.11)	0.91 (0.77, 1.08)
Current smokers, usual cigarettes/day					
Never smoked	183,487	985	1	1	1
<10 cig/day	8,088	46	1.14 (0.85, 1.53)	1.15 (0.85, 1.55)	1.05 (0.76, 1.47)
10–19 cigs/day	8,536	40	0.93 (0.68, 1.28)	1.00 (0.73, 1.38)	1.00 (0.71, 1.40)
20+ cigs/day	9,463	51	1.04 (0.79, 1.38)	1.14 (0.86, 1.52)	1.13 (0.83, 1.54)
Current smokers, total pack-years					
Never smoked	183,487	985	1	1	1
<20 pack-years	11,304	48	0.91 (0.68, 1.21)	0.95 (0.71, 1.27)	0.82 (0.59, 1.14)
20+ pack-years	13,834	82	1.10 (0.88, 1.38)	1.17 (0.93, 1.48)	1.19 (0.93, 1.53)
Current smokers, total years					
Never smoked	183,487	985	1	1	1
<30 years	11,623	47	0.90 (0.67, 1.21)	0.95 (0.70, 1.28)	0.91 (0.66, 1.25)
30+ years	13,847	87	1.13 (0.91, 1.41)	1.21 (0.96, 1.51)	1.18 (0.92, 1.51)
Total pack-years					
Never smoked	183,487	985	1	1	1
<10 pack-years	71,233	391	1.00 (0.89, 1.12)	1.00 (0.89, 1.13)	0.93 (0.82, 1.06)
10–19 pack-years	29,545	185	1.13 (0.97, 1.33)	1.14 (0.97, 1.33)	1.06 (0.89, 1.26)
20–29 pack-years	19,183	123	1.13 (0.93, 1.36)	1.15 (0.95, 1.39)	1.10 (0.90, 1.35)
30+ pack-years	20,910	146	1.14 (0.96, 1.36)	1.18 (0.99, 1.41)	1.07 (0.88, 1.30)
Total years smoked cigarettes					
Never smoked	183,487	985	1	1	1
<10 years	45,446	255	1.04 (0.90, 1.19)	1.04 (0.90, 1.19)	0.95 (0.82, 1.11)
10–19 years	39,139	231	1.07 (0.93, 1.24)	1.06 (0.91, 1.22)	0.98 (0.84, 1.15)
20–29 years	30,351	185	1.08 (0.92, 1.26)	1.10 (0.94, 1.29)	1.05 (0.88, 1.25)
30+ years	26,996	183	1.11 (0.94, 1.30)	1.16 (0.99, 1.37)	1.08 (0.90, 1.30)
Past smokers, time since last smoked					
Never smoked	183,487	985	1	1	1
<10 years	18,026	109	1.17 (0.96, 1.42)	1.20 (0.98, 1.46)	1.12 (0.90, 1.39)
10–24 years	47,002	284	1.10 (0.96, 1.26)	1.09 (0.95, 1.25)	1.00 (0.86, 1.16)
25+ years	51,455	328	1.04 (0.91, 1.18)	1.04 (0.91, 1.18)	0.97 (0.84, 1.11)

[a] Adjusted for age

[b] Adjusted for age, race, education, age at menarche, age at first birth, parity, use of hormonal birth control, use of postmenopausal hormones, age at menopause and menopausal status and BMI

[c] Adjusted for covariates in model 2 plus alcohol

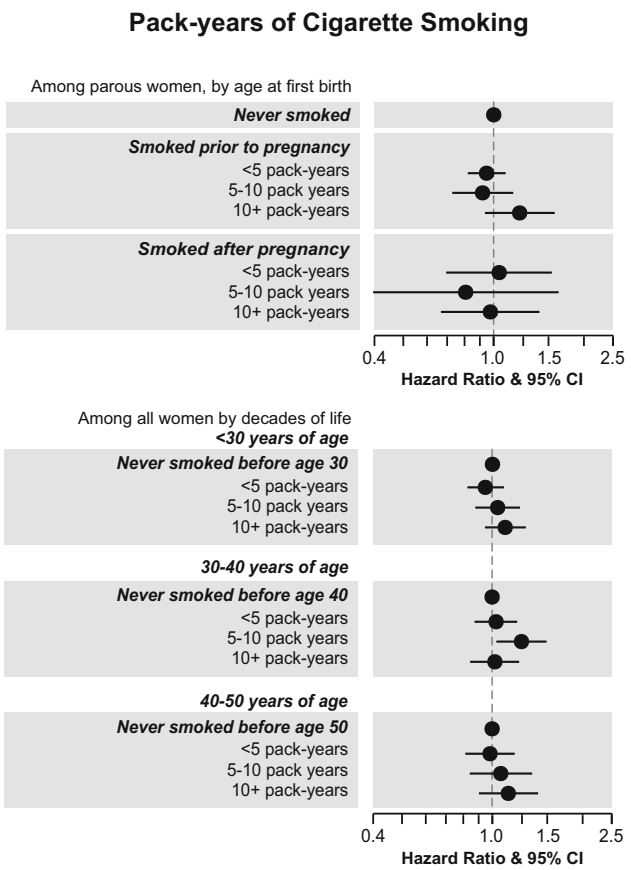

Fig. 1 Invasive breast cancer risk in association with pack-years of cigarette smoking among parous women by age at first birth and in all women by decades of life, NIEHS sister study

(HR = 1.11, 95% CI 0.97–1.28). There was evidence of variability in the association between household ETS and breast cancer risk by birth cohort (p for interaction = 0.04) with elevated estimates observed for those who were born prior to 1940 (HR = 1.44, 95% CI 1.02–2.02) or between 1940 and 1949 (HR = 1.28, 95% CI 1.28, 1.01–1.62) but did not persist in women born between 1950 and 1959 or after 1960 (Fig. 2).

The association of any ETS exposure and invasive breast cancer was limited to women who were postmenopausal at diagnosis (postmenopausal HR = 1.14, 95% CI 0.89–1.46, versus premenopausal HR = 0.79, 95% CI 0.58–1.46) (Supplemental Table IV). We did not observe evidence of an interaction between active smoking and ETS exposure (data not shown).

Discussion

In this prospective cohort study, we found that early life exposure to ETS, defined by in utero or childhood tobacco smoke exposure, was modestly associated with the risk of invasive breast cancer. We found little evidence to support previously reported associations with active smoking.

Early life events, such as birth weight [22] and in utero exposure to diethylstilbestrol [23], have previously been found to be associated with later development of breast cancer. Maternal smoking during pregnancy may result in altered hormone levels and thus may impact the fetus [24]. Administration of carcinogens to the adult animal during pregnancy can result in mammary tumors in the mature offspring [25]. Previous case–control studies have largely suggested modest positive associations with measures of in utero ETS exposure from either maternal or paternal sources, although results have not been statistically significant [26–32]. However, interpretation of these studies is complicated by the potential for recall bias and these findings do conflict with prospective studies which have demonstrated inverse associations between maternal smoking during pregnancy and breast cancer risk [33] and breast cancer mortality [34]. In this prospective study, we found that household ETS exposure while in utero, but not maternal smoking during pregnancy, was positively associated with breast cancer incidence, consistent with the findings from prior case–control studies. These associations were stronger in women who were born prior to 1950, which was likely due to increased intensity of smoking during that time. Paternal smoking prior to pregnancy was also associated with an increased risk, although this exposure may be, at least in part, conflated with the increase in risk observed for household ETS.

Exposure to ETS during childhood and adolescence was associated with an elevated risk of breast cancer, particularly with 18 years of ETS exposure. Previous studies on childhood ETS exposure and breast cancer risk overall are inconsistent [7]. Lin et al. [35] and Luo et al. [36] both reported positive, but nonsignificant association with childhood ETS in prospective cohort studies. Lin et al. [35] relied on an ever/never childhood ETS assessment in a Japanese cohort. In the Women's Health Initiative, Luo et al. did include duration of childhood ETS; results were positive for postmenopausal women, but not statistically significant [36]. In contrast, other studies have found null associations [37, 38] despite incorporating duration [38]. The positive findings for both in utero and childhood ETS reported here require replication in other study populations.

In order to indirectly validate the assessment of the early life exposures, approximately 1,000 participant's mothers were asked the same questions as their daughters. In a preliminary analysis, agreement for in utero ETS exposures was high ($\kappa \geq 0.8$ for maternal and paternal smoking and $\kappa = 0.7$ for household ETS) but was lower for childhood ETS exposure ($\kappa = 0.5$) (A. D'Aloisio, personal communication). The lower kappa levels for childhood ETS were driven by mothers reporting ETS exposure whereas

Table 3 Environmental tobacco smoke (ETS) exposure in never smokers, NIEHS sister study

Environmental tobacco smoke (ETS) in never smokers	Person-years (183,487)	Invasive breast cancer ($n = 985$)	Age adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)
Ever ETS[b]				
None	36,047	177	1	1
Yes	143,982	791	1.06 (0.90, 1.25)	0.98 (0.81, 1.18)
Total years of ETS[b]				
None	36,047	177	1	1
0–9	25,741	125	0.99 (0.79, 1.25)	0.94 (0.73, 1.22)
10–19	56,864	313	1.11 (0.92, 1.33)	1.03 (0.84, 1.27)
20–29	30,030	172	1.11 (0.89, 1.37)	0.95 (0.75, 1.22)
30+	31,347	181	1.01 (0.81, 1.25)	0.93 (0.73, 1.20)
Adult ETS[b]				
No	85,383	462	1	1
Yes	97,074	517	0.89 (0.79, 1.02)	0.86 (0.74, 1.00)
Years of adult ETS[b]				
None	85,383	462	1	1
0–9	45,381	227	0.90 (0.77, 1.06)	0.86 (0.72, 1.03)
10–19	22,706	137	1.00 (0.83, 1.22)	0.95 (0.76, 1.19)
20+	28,986	153	0.80 (0.66, 0.97)	0.77 (0.62, 0.97)
Childhood ETS[c]				
No	63,042	314	1	1
Yes	117,909	658	1.12 (0.98, 1.29)	1.12 (0.98, 1.29)
Years of childhood ETS[c]				
None	63,042	314	1	1
<10	20,465	98	0.99 (0.79, 1.24)	1.00 (0.79, 1.25)
10–14	17,477	95	1.13 (0.89, 1.42)	1.10 (0.87, 1.40)
15–17	15,034	84	1.13 (0.88, 1.43)	1.12 (0.88, 1.43)
18	64,933	381	1.17 (1.00, 1.35)	1.17 (1.00, 1.36)
Maternal smoking during pregnancy[c]				
Definitely no/probably no	125,496	669	1	1
Definitely yes/probably yes	47,972	258	1.07 (0.92, 1.23)	1.06 (0.92, 1.23)
Paternal smoking 3 months prior to pregnancy[c]				
Definitely no/probably no	64,758	324	1	1
Definitely yes/probably yes	104,923	586	1.11 (0.97, 1.27)	1.11 (0.97, 1.28)
Household smoking during pregnancy[c]				
Definitely no/probably no	76,849	383	1	1
Definitely yes/probably yes	92,153	530	1.15 (1.00, 1.31)	1.16 (1.01, 1.32)

[a] Adjusted for age

[b] Adult level fully adjusted models adjusted for age, race, education, age at menarche, age at first birth, parity, use of hormonal birth control, alcohol intake, use of postmenopausal hormones, age at menopause and menopausal status and BMI

[c] Early life level fully adjusted models adjusted for age, race, household composition at age 13, family income during childhood, and highest education in household at age 13

daughters reported no childhood ETS. This suggests that our results underestimate the proportion of women exposed to ETS during childhood and, thus, may be attenuating the observed association towards the null.

Smoking prior to first pregnancy was not strongly associated with breast cancer risk although the observed HR for women with 10+ years of smoking prior to first pregnancy, though not statistically significant, was consistent with results from a recent meta-analysis that found a 20% increased risk of breast cancer for initiating smoking prior to first pregnancy [8], when breast tissue may be most susceptible to genotoxic exposures [39]. It is possible our study was underpowered to statistically test this association.

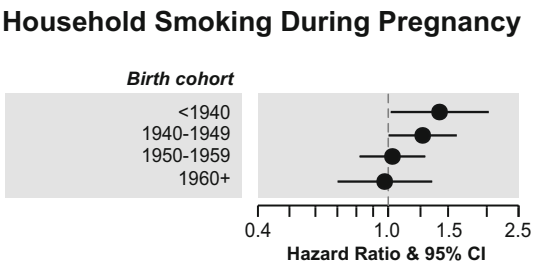

Fig. 2 Household smoking during mother's pregnancy and invasive breast cancer risk in never smokers, NIEHS sister study

Overall, we found only limited evidence for associations between active smoking and breast cancer risk regardless of duration or intensity of exposure. Observed associations were not more pronounced after limiting the referent group to women who were also non-ETS exposed. However, the point estimates reported here are similar in magnitude to a recent meta-analysis [8] although our confidence intervals included the null value. Similarly, we found little to no association with adult ETS. The Surgeon General's report found a summary RR = 1.04 (95% CI 0.99–1.09) for adult ETS exposure [7].

A remaining concern in studies of smoking and breast cancer risk is the potential for residual confounding by alcohol intake [40]. Alcohol is consistently associated with breast cancer incidence and is correlated with cigarette smoking status [40]. This possibility of residual confounding is exacerbated by the fact that most studies do not have information on lifetime alcohol intake. In this study population, we observed modest positive associations with active smoking prior to adjustment for lifetime alcohol intake. After adjustment, estimates were attenuated towards the null. We also considered that alcohol intake may be a potential effect measure modifier of this relationship. However, no statistically significant interaction was observed which is consistent with two prior cohort studies [41, 42], although other studies have noted an elevated risk for cigarette smoking in non-drinkers [11, 13, 14].

This study has limitations. We were unable to specifically consider spousal ETS exposure, which may lead to higher and more direct exposure. We also did not have information to evaluate intensity of ETS exposure. Although the cohort is large, the number of current smokers was small and at this point of time in follow-up, we could consider ER hormone receptor status, but not other potentially relevant tumor subtypes. Similarly, we had limited power to consider interactions. Women in this study population, by enrollment criteria, have a family history of breast cancer. Thus, we cannot rule out that possibility that this study population may not be generalizable to all women particularly those without a family history. However, to address this, we also carried out analyses stratified by degree of family history and found little evidence of variation by degree of family history (data not shown). Strengths of this study include its prospective study design with detailed exposure assessment that permitted us to evaluate multiple windows of biologic susceptibility. We were able to jointly consider the impact of active smoking and ETS. Additionally, the evaluation of alcohol consumption across the life course was an important strength of this study and permitted a more sophisticated adjustment of confounding by alcohol.

The findings in this prospective cohort support modest associations between tobacco smoke and breast cancer risk for both childhood and in utero ETS exposure.

Acknowledgments The authors recognize the helpful feedback from Drs. Lauren Wilson and Katie O'Brien.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

Sources of financial support This research was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES044005).

References

1. Smith CJ, Perfetti TA, Rumple MA, Rodgman A, Doolittle DJ (2000) "IARC group 2A Carcinogens" reported in cigarette mainstream smoke. Food Chem Toxicol 38:371–383
2. Terry PD, Rohan TE (2002) Cigarette smoking and the risk of breast cancer in women: a review of the literature. Cancer Epidemiol Biomark Prev 11:953–971
3. Hecht SS (2002) Tobacco smoke carcinogens and breast cancer. Environ Mol Mutagen 39:119–126
4. Li DH, Wang MY, Dhingra K, Hittelman WN (1996) Aromatic DNA adducts in adjacent tissues of breast cancer patients: clues to breast cancer etiology. Cancer Res 56:287–293
5. Perera FP, Estabook A, Hewer A et al (1995) Carcinogen-DNA adducts in human breast-tissue. Cancer Epidemiol Biomark Prev 4:233–238
6. Conway K, Edmiston SN, Cui L et al (2002) Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. Cancer Res 62:1987–1995
7. US Department of Health and Human Services (2014 Printed with corrections, January 2014) The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. 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. Atlanta, GA
8. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ (2013) Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst 105:515–525
9. Bjerkaas E, Parajuli R, Weiderpass E et al (2013) Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. Cancer Causes Control 24:1347–1356

10. Rosenberg L, Boggs DA, Bethea TN, Wise LA, Adams-Campbell LL, Palmer JR (2013) A prospective study of smoking and breast cancer risk among African-American women. Cancer Causes Control 24:2207–2215
11. Dossus L, Boutron-Ruault MC, Kaaks R et al (2014) Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer 134:1871–1888
12. Nyante SJ, Gierach GL, Dallal CM et al (2014) Cigarette smoking and postmenopausal breast cancer risk in a prospective cohort. Br J Cancer 110:2339–2347
13. Gram IT, Little MA, Lund E, Braaten T (2016) The fraction of breast cancer attributable to smoking: the Norwegian women and cancer study 1991–2012. Br J Cancer 9:154
14. Gram IT, Park SY, Kolonel LN et al (2015) Smoking and risk of breast cancer in a racially/ethnically diverse population of mainly women who do not drink alcohol: the MEC study. Am J Epidemiol 182:917–925
15. Catsburg C, Miller AB, Rohan TE (2015) Active cigarette smoking and risk of breast cancer. Int J Cancer 136:2204–2209
16. Hiatt RA, Haslam SZ, Osuch J (2009) The breast cancer and the environment research centers: transdisciplinary research on the role of the environment in breast cancer etiology. Environ Health Perspect 117:1814–1822
17. 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 Biomark Prev 4:567–571
18. DeRoo LA, Cummings P, Mueller BA (2011) Smoking before the first pregnancy and the risk of breast cancer: a meta-analysis. Am J Epidemiol 174:390–402
19. Nichols HB, Baird DD, DeRoo LA, Kissling GE, Sandler DP (2013) Tubal ligation in relation to menopausal symptoms and breast cancer risk. Br J Cancer 109:1291–1295
20. National Institutes of Environmental Health Sciences. Breast Cancer Validation. https://sisterstudy.niehs.nih.gov/English/brca-validation.htm. Accessed 1 Dec 2015
21. Greenland S, Pearl J, Robins JM (1999) Causal diagrams for epidemiologic research. Epidemiology 10:37–48
22. Xu X, Dailey AB, Peoples-Sheps M, Talbott EO, Li N, Roth J (2009) Birth weight as a risk factor for breast cancer: a meta-analysis of 18 epidemiological studies. J Womens Health. 18:1169–1178
23. Hilakivi-Clarke L (2014) Maternal exposure to diethylstilbestrol during pregnancy and increased breast cancer risk in daughters. Breast Cancer Res 16:208
24. Bernstein L, Pike MC, Lobo RA, Depue RH, Ross RK, Henderson BE (1989) Cigarette smoking in pregnancy results in marked decrease in maternal hCG and oestradiol levels. Br J Obstet Gynaecol 96:92–96
25. Tomatis L (1989) Overview of perinatal and multigeneration carcinogenesis. IARC Sci Publ 96:1–15
26. Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. Am J Epidemiol 121:37–48
27. Sanderson M, Williams MA, Malone KE et al (1996) Perinatal factors and risk of breast cancer. Epidemiology 7:34–37
28. Sanderson M, Williams M, Daling J et al (1998) Maternal factors and breast cancer risk among young women. Paediatr Perinat Epidemiol 12:397–407
29. Weiss HA, Potischman NA, Brinton LA et al (1997) Prenatal and perinatal risk factors for breast cancer in young women. Epidemiology 8:181–187
30. Hodgson ME, Newman B, Millikan RC (2004) Birthweight, parental age, birth order and breast cancer risk in African-American and white women: a population-based case–control study. Breast Cancer Res 6:R656–R667
31. Park SK, Garcia-Closas M, Lissowska J et al (2006) Intrauterine environment and breast cancer risk in a population-based case–control study in Poland. Int J Cancer 119:2136–2141
32. Park SK, Kang D, McGlynn KA et al (2008) Intrauterine environments and breast cancer risk: meta-analysis and systematic review. Breast Cancer Res 10:R8
33. Strohsnitter WC, Noller KL, Titus-Ernstoff L et al (2005) Breast cancer incidence in women prenatally exposed to maternal cigarette smoke. Epidemiology. 16:342–345
34. Sanderson M, Daling JR, Doody DR, Malone KE (2006) Perinatal factors and mortality from breast cancer. Cancer Epidemiol Biomark Prev 15:1984–1987
35. Lin Y, Kikuchi S, Tamakoshi K et al (2008) Active smoking, passive smoking, and breast cancer risk: findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. J Epidemiol. 18:77–83
36. Luo J, Margolis KL, Wactawski-Wende J, et al (2011) Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ 342:d1016
37. Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB (2011) Cigarette smoking and the incidence of breast cancer. Arch Intern Med 171:125–133
38. Reynolds P, Goldberg D, Hurley S et al (2009) Passive smoking and risk of breast cancer in the California teachers study. Cancer Epidemiol Biomark Prev 18:3389–3398
39. Russo J, Tay LK, Russo IH (1982) Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 2:5–73
40. Hamajima N, Hirose K, Tajima K et al (2002) Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 87:1234–1245
41. Cui Y, Miller AB, Rohan TE (2006) Cigarette smoking and breast cancer risk: update of a prospective cohort study. Breast Cancer Res Treat 100:293–299
42. Gram IT, Braaten T, Terry PD et al (2005) Breast cancer risk among women who start smoking as teenagers. Cancer Epidemiol Biomark Prev 14:61–66