Air Pollution and Breast Cancer: An Examination of Modification By Underlying Familial Breast Cancer Risk

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ABSTRACT

Background: An increased familial risk of breast cancer may be due to both shared genetics and environment. Women with a breast cancer family history may have a higher prevalence of breast cancer–related gene variants and thus increased susceptibility to environmental exposures. We evaluated whether air pollutant and breast cancer associations varied by familial risk.

Methods: Sister Study participants living in the contiguous United States at enrollment (2003–2009; $N = 48{,}453$), all of whom had at least one first-degree relative with breast cancer, were followed for breast cancer. Annual NO_2 and $PM_{2.5}$ concentrations were estimated at the enrollment addresses. We predicted 1-year familial breast cancer risk using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). Using Cox regression, we estimated HRs and 95% confidence intervals (CI) for associations between each pollutant dichotomized at the median and breast cancer with interaction terms to examine modification by BOADICEA score.

Results: NO_2 was associated with a higher breast cancer risk among those with BOADICEA score >90th percentile (HR, 1.28; 95% CI, 1.05–1.56) but not among those with BOADICEA score ≤90th percentile (HR, 0.98; 95% CI, 0.90–1.06; $P_{interaction} = 0.01$). In contrast to NO_2, associations between $PM_{2.5}$ and breast cancer did not vary between individuals with BOADICEA score >90th percentile and ≤90th percentile ($P_{interaction} = 0.26$).

Conclusions: Our results provide additional evidence that air pollution may be implicated in breast cancer, particularly among women with a higher familial risk.

Impact: Women at higher underlying breast cancer risk may benefit more from interventions to reduce exposure to NO_2.

Introduction

Air pollution has been related to an increased risk of breast cancer (1). Components of air pollution are carcinogenic (2, 3), including compounds that potentially increase oxidative stress or DNA damage (4–6), or have endocrine disrupting properties (5, 7). Nitrogen dioxide (NO_2) and nitrogen oxides (NO_x), traffic-derived air pollutants, have been consistently associated with an increased risk of breast cancer (8). Less consistent evidence has been observed for particulate matter <10 μm (PM_{10}) or <2.5 μm ($PM_{2.5}$) and breast cancer (1, 8), with some studies finding heterogeneity by geographic region and PM composition (9, 10).

However, most studies to date have been conducted in women at an average risk of breast cancer (11). Family history of cancer reflects both genetic factors and a shared environment, and as a result there may be a greater chance of identifying important environmental exposures for breast cancer among women with higher underlying familial risk (11–13). Women with a greater extent of breast cancer family history have been shown to have reduced expression of DNA repair genes (14). It is thus biologically plausible that underlying familial risk may be a modifier of air pollution and breast cancer associations due to interactions between the DNA damage caused by air pollution (15–17) and mutations in certain genes responsible for DNA repair (18).

In the Sister Study, a nationwide population enriched with women with a first-degree family history of breast cancer, we previously reported that an IQR increase in NO_2 (5.8 ppb) was associated with an increased risk of overall breast cancer [HR, 1.06; 95% confidence interval (CI), 1.02–1.11; ref. 9]. An elevated association was also reported for an interquartile range (IQR) increase in $PM_{2.5}$ (3.6 μg/m^3; HR, 1.05; 95% CI, 0.99–1.11), but no association was observed for an IQR increase (5.8 μg/m^3) in PM_{10}. For both NO_2 and $PM_{2.5}$, associations were elevated particularly for ductal carcinoma *in situ* (DCIS) compared with invasive disease. To further understand the role of air pollution in breast cancer etiology, the objective of this study was to examine whether the association between NO_2, $PM_{2.5}$, and PM_{10}, and breast cancer was modified by underlying familial risk as estimated by the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) score. We further examined whether there was additional heterogeneity by age (> vs. ≤50 years), menopausal status, and estrogen receptor (ER) status.

Materials and Methods

Study population

Between 2003 and 2009, 50,884 women enrolled in the Sister Study, a prospective cohort designed to study environmental and lifestyle risk factors for breast cancer. Women were eligible if they had a sister (either half or full) who had been diagnosed with breast cancer but had no history of breast cancer themselves. At enrollment, the women

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2022;31:422–9

doi: 10.1158/1055-9965.EPI-21-1140

resided in all 50 U.S. states plus Puerto Rico and were between the ages of 35 and 74 years. Women provided information about demographic, lifestyle, medical and family history, reproductive, and residential factors on questionnaires completed at enrollment. Annual health updates and follow-up questionnaires were used to identify changes in health and risk factor information. Response rates have remained around 90% throughout follow-up (19).

All participants provided written informed consent. The Sister Study was approved by the Institutional Review Board of the NIH (Bethesda, MD). The study was conducted in accordance with recognized ethical guidelines including the US Common Rule. We utilized data from Sister Study Data Release 9.0 with follow-up through September 30, 2019.

Exposure assessment

As has been described previously (9, 20), annual average NO_2, $PM_{2.5}$, and PM_{10} were estimated at the participant's enrollment residential address. $PM_{2.5}$ and PM_{10} were estimated using a validated regionalized universal kriging model with spatial smoothing using information on a large number of geographic covariates and monitoring data from 2000 (PM_{10}) and 2006 ($PM_{2.5}$; ref. 21). NO_2 was estimated from a similar universal kriging model with spatial smoothing, which not only incorporated ground-level measurements and geographic covariates but also satellite-derived measurements (22). Air pollution estimates were not obtained for individuals who lived outside the contiguous United States at enrollment, so those women were excluded.

Outcome assessment

Women self-reported incident *in situ* or invasive breast cancer diagnoses. Medical records, which also included information on the ER status and invasiveness of the tumor, were obtained for approximately 80% of breast cancer diagnoses. When medical records were not available, self-report was used based on evidence that there is high agreement between the two sources (23). In our main analyses, we considered invasive and DCIS breast cancers combined because familial risk is implicated in both invasive and DCIS disease (24, 25) and to improve our statistical power to examine additional heterogeneity by age, menopausal status, and ER status. Previous studies, however, have supported such an approach (26).

Familial risk score

At enrollment, 98% of the cohort completed a family history questionnaire. The BOADICEA model can be used to calculate the familial risk of invasive breast (based on censoring DCIS as a competing risk) and ovarian cancer in women using pedigree-based information about first- and second-degree relatives (27, 28). The enrollment family history questionnaire included questions about each participant's parents, siblings, children, half-siblings, grandparents, and aunts. Among 810 participants who did not complete the baseline family history questionnaire, 337 completed a follow-up family history questionnaire. Information ascertained from follow-up is backfilled to baseline, using only the data items included on the baseline family history questionnaire and family history status at the time at baseline (e.g., relatives' history of cancer prior to age at baseline).

Information on first-degree family members included year of birth, sex, age at the time of the Sister Study participant's enrollment, age at death, and age at first breast, ovarian, prostate, or pancreatic cancer diagnosis (cancers related to variants in BRCA1 or BRCA2). Some of this information was not obtained for certain family members, such as age at time of the participant's enrollment (all grandparents and aunts), age at breast or ovarian (all grandmothers and aunts) or prostate (all grandfathers) cancer, or history/age of pancreatic cancer (all grandparents and aunts). In Supplementary Table S1, we provide the percent of missing data for these variables. Besides grandparents and aunts for which baseline age and age at cancer diagnoses were missing by design, the amount of missingness for other relatives ranges from 0% (son's breast and pancreatic cancer age) to 28% (father's breast cancer age) (Supplementary Table S1). In these situations, age at enrollment for maternal (or paternal) grandparent was imputed as age of participant's mother (or father) + 29, or average age of the participant and her siblings + 55, and age of enrollment for maternal (or paternal) aunts was imputed as age of the participant's mother (or father), or average age of participant and her siblings + 29. For all relatives with a reported cancer diagnosis but missing age at diagnosis, we imputed age at diagnosis as the median age at each specific cancer diagnosis based on SEER 2004 to 2008 data (29). In a preliminary validation of the Sister Study BOADICEA model, it was found to be well calibrated overall with an expected-to-observed case ratio of 0.97 (95% CI, 0.93–1.01) and the discriminatory power was similar to other risk models with a c-statistic of 0.58 (95% CI, 0.57–0.59). Among the Sister Study women, the range of 1-year BOADICEA risk was 0.05% to 5.4%.

Statistical analyses

All analyses were conducted using Cox proportional hazards regression with age as the time scale to estimate HRs and 95% confidence intervals. Women were followed from age at enrollment through their age at breast cancer diagnosis or were censored at death, loss to follow-up, or end of follow-up, whichever came first. All models were adjusted for age (as the time scale), education (<high school, high school degree or GED, some college/Associate's/technical degree, college degree or higher), parity (0, 1–2, 3+), self-reported race/ethnicity (non-Hispanic/Latina White, non-Hispanic/Latina Black/African American, Hispanic/Latina, other), residence type (urban, suburban, rural, small town or other), physical activity (continuous hours per week), and smoking status (never, past, current). While patterns were similar in models adjusted for age alone, results from the fully adjusted models are presented in the tables. We excluded 393 women who withdrew from the study, had an unknown age at diagnosis, no follow-up time, or a pre-enrollment diagnosis; 1,452 women missing information on the air pollutant concentrations (including those living outside the contiguous United States) or a potential confounder; and 586 women for whom the BOADICEA score could not be calculated. This left 48,453 women (95% of total) in our final analytic sample.

We considered whether the association between each air pollutant and breast cancer was modified by BOADICEA score with air pollution measures characterized at the median (PM_{10}: 21.6 $\mu g/m^3$, $PM_{2.5}$: 10.8 $\mu g/m^3$, NO_2: 9.1 ppb) and BOADICEA score dichotomized at the median (0.46%) and the 90th percentile (0.71%). Decisions about the cut-off points used in this analysis were made *a priori*. For context, the EPA National Ambient Air Quality Standards on an annual basis in 2006 were 12.0 $\mu g/m^3$ for $PM_{2.5}$ and 53 ppb for NO_2 (standards for PM_{10} are not provided on an annual basis; refs. 30, 31). We examined modification on both the additive and multiplicative scales. On the additive scale, single referent HRs and 95% CIs were estimated and used to calculate the interaction contrast ratios (ICR) and 95% CIs (32–34). On the multiplicative scale, we estimated stratified HRs in each category of BOADICEA and calculated the ratio of the HRs (RHR) and 95% CIs and determined the Wald $P_{interaction}$.

We further stratified and examined heterogeneity in the air pollution–breast cancer–BOADICEA modification analyses by age (> vs. ≤50 years), menopausal status, and ER status. Age and menopausal status were considered time-varying. ER status was examined in a competing risk manner where ER^+ events were censored at the age of diagnosis in the analyses for ER^- breast cancer and vice versa.

In sensitivity analyses, we examined the main modification results (i) restricted to invasive breast cancer cases (DCIS cases were censored at the age of event), (ii) using a clinically-based "high risk" BOADICEA cut-off point (0.34%) (35), and (iii) with the air pollutants in quartile-based categories rather than dichotomized at the median. All analyses were conducted in SAS 9.4 (SAS Institute Inc.).

In Supplementary Table S2, we also provide the overall associations between each of the air pollutants (> vs. ≤ median) and breast cancer as well as the BOADICEA score (> vs. ≤ median; > vs. ≤ 90th percentile; > vs. ≤ 0.34%) and breast cancer using the cut-off points and adjustment set used in this analysis and the updated number of cases since our last publication on the air pollutants (9).

Data availability

Requests for deidentified Sister Study data, including the data used in this manuscript, can be requested through the study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

Results

Over an average of 10.9 years of follow-up, 3,853 DCIS or invasive breast cancers (831 DCIS, 3009 invasive, 13 invasiveness unknown) were diagnosed. We report characteristics of the study population stratified on the cross between both median BOADICEA and median NO_2. We used NO_2 because it is the air pollutant that had most consistently been associated with breast cancer in previous studies. Compared with women living at residences with ≤ median NO_2 concentrations and with ≤ median BOADICEA, women living at residences with > median concentrations of NO_2 and with > median BOADICEA were more likely to have a college degree or higher, be past smokers, have had ≥ 3 births, live in an urban or suburban area, live in the Western United States, have ≥2 first-degree relatives with breast cancer, be older ages at enrollment (60.8 vs. 50.6 years), and do more physical activity (3.1 vs. 2.6 hours per week; **Table 1**).

Although BOADICEA classified at the median did not modify the association between NO_2 and breast cancer on either the additive or multiplicative scale, classification at the 90th percentile (0.71%) did modify the association on both scales (**Table 2**). On the multiplicative scale, NO_2 above the median was associated with increased risk of breast cancer among those with high estimated familial risk (>90th percentile stratified; HR, 1.28; 95% CI, 1.05–1.56), but not among those with lower estimated familial risk (≤90th percentile stratified; HR, 0.98; 95% CI, 0.90–1.06; RHR, 1.31; 95% CI, 1.06–1.62, $P_{interaction} = 0.01$). There also was evidence of super-additive interaction for NO_2 (ICR, 0.37; 95% CI, 0.07–0.67). When BOADICEA was categorized at the median, we observed a suggestion of modification of the associations between $PM_{2.5}$ and breast cancer on both the additive (ICR, 0.12; 95% CI, −0.04–0.29) and multiplicative scales (RHR, 1.10; 95% CI, 0.96–1.26; $P_{interaction} = 0.16$). $PM_{2.5}$ associations were not different in strata classified by the 90th percentile (additive ICR, −0.16; 95% CI, −0.45–0.13; multiplicative RHR, 0.90; 95% CI, 0.85–1.08). The relationship between PM_{10} and breast cancer was not modified, on either the additive or multiplicative scales, by the 1-year BOADICEA score categorized at the median or the 90th percentile.

NO_2 was associated with an increased risk of ER^+ breast cancer regardless of BOADICEA score; in those with > median BOADICEA the HR was 1.12 (95% CI, 1.00–1.25) and in those with ≤ median BOADICEA the HR was 1.10 (95% CI, 0.96–1.27; $P_{interaction}$ across BOADICEA strata = 0.89; **Table 3**). An inverse association was observed between NO_2 and ER^- breast cancer among those with > median BOADICEA (HR, 0.69; 95% CI, 0.53–0.91), but this did not differ significantly from the association among those with ≤ median BOADICA ($P_{interaction}$ across BOADICEA strata = 0.45). We did find suggestive evidence that $PM_{2.5}$ was associated with elevated risk of premenopausal breast cancer among those with > median BOADICEA (HR, 1.38; 95% CI, 0.97–1.96), but not ≤ median BOADICEA (HR, 0.96; 95% CI, 0.80–1.16; $P_{interaction}$ across BOADICEA strata = 0.07). The estimates were less precise due to a smaller number of cases in the ≤50 years age stratum compared with the premenopausal stratum, but the magnitude of the point estimates and overall pattern for $PM_{2.5}$ was similar; among individuals ≤ 50 years old, we observed an HR of 1.43 (95% CI, 0.89–2.29) among those with > median BOADICEA and HR of 0.94 (95% CI, 0.75–1.19) among those with ≤ median BOADICEA ($P_{interaction} = 0.12$).

Conclusions were unchanged when restricted to invasive cases (Supplementary Table S3). When BOADICEA was classified on the basis of a clinical cut-off point for high risk (> vs. ≤ 0.34%), patterns were similar to the results with BOADICEA classified at the median (Supplementary Table S4). When the air pollutants were classified in quartiles, results were less precise but provide consistent evidence of increased breast cancer risk associated with increasing categories of NO_2 only among those with the highest (>90th percentile) BOADICEA score (Supplementary Table S5).

Discussion

In this large prospective cohort study of women from across the United States, we report findings from a novel investigation considering whether the relationship between air pollution and breast cancer is modified by a pedigree-based family history risk score. NO_2 was associated with an increased risk of breast cancer among individuals at very high underlying familial risk (BOADICEA >0.71%) but not among those with lower underlying risk. We additionally found that $PM_{2.5}$ was associated with an elevated risk of premenopausal breast cancer in individuals at moderate to high underlying familial risk (BOADICEA >0.46%), but not those at lower underlying familial risk. Our results provide further evidence that air pollution may be implicated in breast cancer, particularly among those who have increased susceptibility.

Individuals with a higher degree of family history are more likely to have reduced expression of DNA repair genes (11, 14). Therefore, differences in the association between air pollution and breast cancer among women with higher versus lower familial risk is plausible given an interaction between the DNA damage from air pollutants and reduced capability of DNA repair due to mutations in DNA repair genes among higher risk women. For example, PAHs, which are formed from the incomplete combustion of organic material, damage DNA by forming adducts (18, 36). Studies have reported a stronger association between PAHs and breast cancer risk among women with variants in certain DNA repair genes (18, 37). Similar to NO_2, vehicular traffic is a major source of PAHs. Our findings could also reflect the improved power to identify important environmental risk factors at higher levels of familial risk where women have shared environmental, lifestyle factors, and genetic factors with the affected relatives that comprise the familial risk score.

Table 1. Characteristics of the study population by NO_2 and BOADICEA, The Sister Study, 2003–2009.

	≤ median NO_2/ ≤ median BOADICEA ($n = 11,898$)		> median NO_2/ ≤ median BOADICEA ($n = 12,328$)		≤ median NO_2/ > median BOADICEA ($n = 12,342$)		> median NO_2/ > median BOADICEA ($n = 11,885$)	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Race/ethnicity								
Non-Hispanic/Latina white	10,251	86	9,438	77	11,471	93	10,307	87
Non-Hispanic/Latina Black/African American	929	8	1,878	15	409	3	1,012	9
Hispanic/Latina	367	3	684	6	159	1	298	3
Other	351	3	328	3	303	2	268	2
Highest level of education								
Less than high school	120	1	127	1	128	1	89	1
High school or equivalent	1,770	15	1,350	11	2,148	17	1,558	13
Some college	4,403	37	3,874	31	4,387	36	3,702	31
College degree or higher	5,605	47	6,977	57	5,679	46	6,536	55
Smoking status								
Never	7,067	59	7,256	59	6,601	53	6,145	52
Past	3,689	31	3,905	32	4,893	40	4,958	42
Current	1,142	10	1,167	9	848	7	782	7
Parity								
0	2,082	18	2,918	24	1,651	13	2,152	18
1–2	6,596	55	6,529	53	6,006	49	5,745	48
≥3	3,220	27	2,881	23	4,685	38	3,988	34
Residence type								
Urban	900	8	3,698	30	981	8	3,576	30
Suburban	3,093	26	6,700	54	2,925	24	6,255	53
Rural	4,502	38	416	3	4,522	37	364	3
Small town or Other	3,403	29	1,514	12	3,914	32	1,690	14
Region of residence								
Northeast	1,789	15	2,391	19	1,882	15	2,277	19
Midwest	3,448	29	3,356	27	3,473	28	3,133	26
South	5,184	44	3,063	25	5,155	42	2,775	23
West	1,477	12	3,518	29	1,832	15	3,700	31
Number of first-degree relatives with breast cancer								
1	10,714	90	11,184	91	6,833	55	6,604	56
≥2	1,184	10	1,154	9	5,509	45	5,281	44
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age at enrollment	50.6	7.4	50.3	7.2	61.0	7.2	60.8	7.4
Hours/week of physical activity	2.6	2.8	2.7	2.9	2.9	3.1	3.1	3.1

Our findings of a synergistic relationship between underlying familial risk and air pollution is consistent with a previous study that observed an interaction between BOADICEA and PAH–albumin adducts in relation to breast cancer risk (38). On an absolute scale the association with PAH adducts was stronger the higher the familial risk.

A recent meta-analysis concluded that the positive associations for NO_2 were stronger for ER^+/progesterone receptor–positive (PR^+) than for ER^-/PR^- tumors (1). In line with those conclusions, we found that there was increased risk of ER^+ breast cancer associated with higher exposure to NO_2 irrespective of the underlying familial risk score. In contrast, there was an inverse association between NO_2 and ER^- breast cancer among women with BOADICEA > median. Although $PM_{2.5}$ had been inconsistently associated with overall breast cancer in past studies, the same meta-analysis suggested that there may be an elevated risk for premenopausal breast cancer (1). Our results suggest that the higher risk of premenopausal breast cancer for $PM_{2.5}$ may be specifically among those with a BOADICEA risk score > the median (0.46%). To our knowledge, this is the first study to examine whether a familial risk score modifies the association between air pollution and breast cancer. A few prior studies of air pollutants and breast cancer risk stratified on the number of first-degree relatives with breast cancer, a crude measure of familial history. In the Black Women's Health Study, the relationship between NO_2 or $PM_{2.5}$ and breast cancer was similar among those with 1+ versus 0 first-degree relatives with breast cancer (10). The remaining studies have been conducted in the Sister Study where all women have at least a half or full sister with breast cancer, so results were stratified on 2+ versus 1 first-degree relative with breast cancer. Associations between NO_2, $PM_{2.5}$, or PM_{10} and breast cancer did not vary by number of first-degree relatives with breast cancer (9). In addition, in the Sister Study, the presence of a median/barrier on a cross-street within 100 feet of a woman's childhood residence (a marker of high traffic-related air pollution exposure) was associated with increased risk of breast cancer in adulthood among women with 1 first-degree relative with breast cancer, but not those with 2+ first-degree relatives with breast cancer (39). The use of the BOADICEA model to estimate a family history score is a more precise measure of familial risk compared with a simple count of number of relatives with a history of breast cancer. BOADICEA incorporates additional information about the age of the diagnoses in relatives and the family structure. For example, a woman with a larger number of first- or second-degree relatives and whose affected relatives were diagnosed at older ages may have a lower risk than a woman with a smaller number of first- or second-degree

Table 2. Associations between air pollutants and breast cancer risk examining modification by 1-year BOADICEA risk on the additive and multiplicative scales.

Air pollutant		Single referent HR (95% CI)[a]	Single referent HR (95% CI)[a]	Additive ICR (95% CI)[a]	Stratified HR (95% CI)[a]	Stratified HR (95% CI)[a]	Multiplicative RHR (95% CI)[a]	$P_{interaction}$
	Cases ≤/> median BOADICEA	≤ median BOADICEA	> median BOADICEA		≤ median BOADICEA	> median BOADICEA		
NO_2								
≤ Median	726/1,140	1.00 (Ref.)	1.69 (1.24–2.31)		1.00 (Ref.)	1.00 (Ref.)		
> Median	810/1,177	1.01 (0.89–1.13)	1.74 (1.28–2.35)	0.04 (−0.17–0.24)	1.01 (0.89, 1.13)	1.03 (0.93–1.13)	1.02 (0.87–1.19)	0.82
$PM_{2.5}$								
≤ Median	755/1,164	1.00 (Ref.)	1.62 (1.20–2.18)		1.00 (Ref.)	1.00 (Ref.)		
> Median	781/1,153	0.95 (0.86–1.05)	1.69 (1.26–2.28)	0.12 (−0.04–0.29)	0.95 (0.86–1.05)	1.05 (0.96–1.14)	1.10 (0.96–1.26)	0.16
PM_{10}								
≤ Median	739/1,196	1.00 (Ref.)	1.80 (1.33–2.45)		1.00 (Ref.)	1.00 (Ref.)		
> Median	797/1,121	1.02 (0.91–1.13)	1.72 (1.27–2.32)	−0.10 (−0.30–0.09)	1.02 (0.91–1.13)	0.95 (0.87–1.04)	0.94 (0.82–1.07)	0.34
	Cases ≤/> 90th perc. BOADICEA	≤ 90th percentile BOADICEA	> 90th percentile BOADICEA		≤ 90th percentile BOADICEA	> 90th percentile BOADICEA		
NO_2								
≤ Median	1,610/256	1.00 (Ref.)	1.24 (0.81–1.90)		1.00 (Ref.)	1.00 (Ref.)		
> Median	1,677/310	0.98 (0.90–1.06)	1.59 (1.07–2.37)	0.37 (0.07–0.67)	0.98 (0.90–1.06)	1.28 (1.05–1.56)	1.31 (1.06–1.62)	0.01
$PM_{2.5}$								
≤ Median	1626/293	1.00 (Ref.)	1.65 (1.10–2.47)		1.00 (Ref.)	1.00 (Ref.)		
> Median	1661/273	1.02 (0.95–1.09)	1.51 (1.02–2.25)	−0.16 (−0.45–0.13)	1.02 (0.95–1.09)	0.92 (0.77–1.09)	0.90 (0.75–1.08)	0.26
PM_{10}								
≤ Median	1,644/291	1.00 (Ref.)	1.58 (1.05–2.40)		1.00 (Ref.)	1.00 (Ref.)		
> Median	1,643/275	0.98 (0.91–1.05)	1.50 (1.01–2.23)	−0.06 (−0.35–0.22)	0.98 (0.91–1.05)	0.95 (0.79–1.13)	0.97 (0.80–1.17)	0.72

Abbreviations: ICR, interaction contrast ratio for additive interaction; RHR, ratio of HRs for multiplicative interaction.
[a]Adjusted for age, education, parity, race/ethnicity, residence type, physical activity, and smoking status.

Table 3. Associations between air pollutants and breast cancer risk examining modification by 1-year BOADICEA risk (> vs. ≤ median), additionally stratified by age, menopausal, and ER status.

	Cases ≤/> median BOADICEA	≤ median 1-year BOADICEA HR (95% CI)[a]	> median 1-year BOADICEA HR (95% CI)[a]	$P_{interaction}$	Cases ≤/> median BOADICEA	≤ median 1-year BOADICEA HR (95% CI)[a]	> median 1-year BOADICEA HR (95% CI)[a]	$P_{interaction}$	$P_{heterogeneity}$
	≤50 years				>50 years				
NO_2									
≤ Median	142/35	1.00 (Ref.)	1.00 (Ref.)		584/1,105	1.00 (Ref.)	1.00 (Ref.)		
> Median	173/43	1.03 (0.80–1.33)	1.24 (0.72–2.11)	0.55	637/1,134	1.00 (0.88–1.14)	1.02 (0.92–1.12)	0.82	0.59
$PM_{2.5}$									
≤ Median	149/30	1.00 (Ref.)	1.00 (Ref.)		606/1,134	1.00 (Ref.)	1.00 (Ref.)		
> Median	166/48	0.94 (0.75–1.19)	1.43 (0.89–2.29)	0.12	615/1,105	0.95 (0.85–1.07)	1.03 (0.95–1.13)	0.16	0.23
PM_{10}									
≤ Median	154/38	1.00 (Ref.)	1.00 (Ref.)		585/1,158	1.00 (Ref.)	1.00 (Ref.)		
> Median	161/40	1.00 (0.89–1.13)	1.14 (0.96–1.36)	0.16	636/1,081	0.97 (0.77–1.21)	1.09 (0.89–1.33)	0.25	0.95
	Premenopausal				Postmenopausal				$P_{heterogeneity}$
NO_2									
≤ Median	215/71	1.00 (Ref.)	1.00 (Ref.)		511/1,069	1.00 (Ref.)	1.00 (Ref.)		
> Median	264/69	1.01 (0.82–1.25)	0.98 (0.66–1.47)	0.90	546/1,108	1.00 (0.86–1.15)	1.03 (0.93–1.13)	0.95	0.82
$PM_{2.5}$									
≤ Median	231/58	1.00 (Ref.)	1.00 (Ref.)		524/1,106	1.00 (Ref.)	1.00 (Ref.)		
> Median	248/82	0.96 (0.80–1.16)	1.38 (0.97–1.96)	0.07	533/1,071	0.95 (0.84–1.07)	1.03 (0.94–1.12)	0.12	0.19
PM_{10}									
≤ Median	232/73	1.00 (Ref.)	1.00 (Ref.)		507/1,123	1.00 (Ref.)	1.00 (Ref.)		
> Median	247/67	0.96 (0.80–1.16)	0.92 (0.65–1.31)	0.85	550/1,054	1.04 (0.92–1.18)	0.95 (0.87–1.04)	0.52	0.81
	ER^+				ER^-				$P_{heterogeneity}$
NO_2									
≤ Median	496/813	1.00 (Ref.)	1.00 (Ref.)		95/177	1.00 (Ref.)	1.00 (Ref.)		
> Median	595/901	1.10 (0.96–1.27)	1.12 (1.00–1.25)	0.89	92/127	0.92 (0.65–1.30)	0.69 (0.53–0.91)	0.45	0.22
$PM_{2.5}$									
≤ Median	545/862	1.00 (Ref.)	1.00 (Ref.)		82/150	1.00 (Ref.)	1.00 (Ref.)		
> Median	546/852	0.94 (0.84–1.07)	1.06 (0.96–1.16)	0.16	105/154	1.19 (0.88–1.61)	1.07 (0.85–1.36)	0.33	0.30
PM_{10}									
≤ Median	523/895	1.00 (Ref.)	1.00 (Ref.)		95/154	1.00 (Ref.)	1.00 (Ref.)		
> Median	568/819	1.04 (0.91–1.17)	0.92 (0.83–1.02)	0.15	92/150	0.94 (0.69–1.28)	1.06 (0.83–1.34)	0.30	0.28

[a]Adjusted for age, education, parity, race/ethnicity, residence type, physical activity, and smoking status.
[b]PM_{10} IQR = 5.84 μg/m^3, $PM_{2.5}$ IQR = 3.59 μg/m^3, NO_2 IQR = 6.30 ppb.

relatives but where those affected were diagnosed at younger ages. Nevertheless, due to limitations in our questionnaire, for certain relatives there was missing information on the age of the relative at the time of the participant's enrollment as well as the relatives' age at cancer diagnosis, which we had to impute. While our BOADICEA score was found to be well-calibrated overall with an expected-to-observed ratio of 0.97 (95% CI, 0.93–1.01), we cannot not exclude the possibility of misclassification of the BOADICEA score for risk specific quantiles. Depending on the family structure, this could result in either over- or under-estimation of familial risk and, as a modifier, the direction of impact on the results could be in either direction.

Our study utilized an enriched population of women who by enrollment criteria have at least a sister who had been diagnosed with breast cancer and therefore on average this population is at two times higher risk of breast cancer than the general population (40). The cohort includes a wide distribution of BOADICEA risk scores, including more higher risk women than the general population, which facilitated examination of the associations at cut-off points both for moderate and very high underlying familial risk.

Another strength of our study was that our air pollution estimates came from validated models and were at a fine spatial resolution of a woman's individual address rather than at a census-tract level. In addition, our study population resided across the contiguous United States, which gave us a larger range of air pollution exposures upon which to estimate our associations compared with studies limited to one state or region. The Sister Study population is residentially stable, with 50% of women reporting living at their baseline address at the time of enrollment for at least 10 years. Although a prior study in this population found that the main associations between the air pollutants and breast cancer varied geographically (9), the focus of the current study was on the role of familial risk, and we have no biological reason to believe that the role of familial risk on these associations would vary by region of the United States. In addition, exploring regional heterogeneity in the present study would have been hampered by small sample sizes in certain groups when stratifying across both BOADICEA and region. Including an underpowered analysis where we are also not able to further examine the composition of the air pollution risks identifying chance findings or results that cannot be adequately contextualized. The Sister Study collects extensive covariate information, so we were well equipped to adjust for well-measured potential socioeconomic, lifestyle, and reproductive factors. However, we cannot exclude the possibility of residual confounding by other factors, including correlated air pollutants or neighborhood level socioeconomic factors. We were also only able to consider air pollution exposure in one year. It is possible that there are other etiologically relevant periods of exposure to air pollution, such as hypothesized susceptible windows of exposure including adolescence and the reproductive years (41, 42), during which familial risk may modify associations.

Our work suggests underlying familial risk may be an important factor in the relationship between air pollution and breast cancer risk. Prior research on air pollution and breast cancer had mostly been conducted in populations with average familial risk or without considering the spectrum of familial risk so this work provides new information about the role of air pollution in breast cancer risk. Our results also suggest a need for studies considering gene-by-air pollution interactions to identify potential single-nucleotide polymorphisms or high-risk variants that are relevant to breast cancer risk associated with air pollution. Such research may help elucidate mechanisms underlying these relationships. Future work could also examine other (noncriteria) air pollutants or air pollution composition or consider whether there are windows of exposure to air pollution that are particularly relevant.

Authors' Disclosures

D.B. Bookwalter reports other support from National Institute of Environmental Health Sciences during the conduct of the study. J.D. Kaufman reports grants from NIH and US Environmental Protection Agency during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

N.M. Niehoff: Conceptualization, formal analysis, methodology, writing–original draft. **M.B. Terry:** Resources, methodology, writing–review and editing. **D.B. Bookwalter:** Resources, methodology, writing–review and editing. **J.D. Kaufman:** Resources, writing–review and editing. **K.M. O'Brien:** Validation, methodology, writing–review and editing. **D.P. Sandler:** Resources, data curation, methodology, writing–review and editing. **A.J. White:** Conceptualization, resources, supervision, methodology, project administration, writing–review and editing.

Acknowledgments

This work was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences, project numbers Z01-ES044005 (to N. Niehoff, K. O'Brien, D. Sandler, and A. White) and Z1AES103332 (to N. Niehoff and A. White). The authors appreciate the helpful feedback of Drs. Hannah Jahnke and Thanh Hoang from the National Institute of Environmental Health Sciences.

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Received September 29, 2021; revised November 18, 2021; accepted December 3, 2021; published first December 14, 2021.

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