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Breast Cancer Risk in Relation to Ambient Air Pollution Exposure at Residences in the Sister Study Cohort

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Abstract

Background—Some but not all past studies reported associations between components of air pollution and breast cancer, namely fine particulate matter ≤ 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2). It is yet unclear whether risks differ according to estrogen receptor (ER) and progesterone receptor (PR) status.

Methods—This analysis includes 47,591 women from the Sister Study cohort enrolled from August 2003-July 2009, in whom 1,749 invasive breast cancer cases arose from enrollment to January 2013. Using Cox proportional hazards and polytomous logistic regression, we estimated breast cancer risk associated with residential exposure to NO_2, $PM_{2.5}$, and PM_{10}.

Results—While breast cancer risk overall was not associated with $PM_{2.5}$ (Hazards ratio [HR] = 1.03; 95% CI: 0.96–1.11), PM_{10} (HR = 0.99; 95% CI: 0.98–1.00), or NO_2 (HR = 1.02; 95% CI: 0.97–1.07), the association with NO_2 differed according to ER/PR subtype (p = 0.04). For an interquartile range (IQR) difference of 5.8 parts per billion (ppb) in NO_2, the relative risk (RR) of ER+/PR+ breast cancer was 1.10 (95% CI: 1.02–1.19), while there was no evidence of association with ER−/PR− (RR=0.92; 95% CI: 0.77–1.09; $p_{interaction}$=0.04).

Conclusions—Within the Sister Study cohort, we found no significant associations between air pollution and breast cancer risk overall. But we observed an increased risk of ER+/PR+ breast cancer associated with NO_2.

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Conflict of Interest:

For co-author Dr. Joel D Kaufman

Entity: Health Effects Institute, Diesel Exhaust Epidemiology Panel

Relationship: Myself

Compensation: Compensated

Type: Minor ($10,000 or less).

Impact—Though these results suggest there is no substantial increased risk for breast cancer overall in relation to air pollution, NO_2, a marker of traffic related air pollution, may differentially affect ER+/PR+ breast cancer.

Keywords

Air pollution; Breast cancer risk; Particulate matter; Nitrogen dioxide; Cancer survival

Introduction

Several studies suggest an association between breast cancer risk and exposure to ambient fine-particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2), a marker of traffic-related air pollution (1–3). Most notably, a 2010 case-control study reported a 1.3-fold increased risk of breast cancer (95% CI of OR: 1.0–1.7) for every 5 ppb increase in NO_2 assessed via a land-use regression spatial model (3). The California Teachers Study recently reported an increased risk for ER−/PR− breast cancer associated with endocrine disruptors present in ambient air, namely cadmium compounds and inorganic arsenic (4). However, to date, relatively few studies have investigated the link between air pollution and breast cancer subtypes. This analysis sought to investigate breast cancer risk in relation to primary components of air pollution, namely $PM_{2.5}$, PM_{10}, and NO_2, and potential risk differences by breast cancer subtype.

Materials and Methods

The Sister Study, a cohort of 50,884 U.S. women between ages 35–74 whose sister had breast cancer (5), enrolled participants from 8/2003–7/2009, who were followed for a mean of 4.95 years. 2,089 breast cancer cases arose between enrollment and 1/2013, (of which 316 were *in situ)*, with a mean time to breast cancer of 3.96 years. Air pollution exposure was not ascertained on 1,234 women (24 invasive and 6 *in situ*; 1,204 non-cases) predominantly because they lived outside the conterminous U.S., resulting in 1,749 invasive breast cancers and 47,591 non-cases for this analysis. Annual averages of air pollution concentration outside the residence were estimated at each participant's home from a validated regionalized universal kriging model derived from regulatory monitors and a large suite of geographic covariates using previously described methods (6). For primary analyses, air pollution estimates were based on annual average concentrations at baseline home addresses, derived using monitoring data from 2006 ($PM_{2.5}$ and NO_2) and 2000 (PM_{10}). The cross-validated R^2 for $PM_{2.5}$ NO_2, and PM_{10} were 0.88, 0.85, and 0.53, respectively (6). HR and 95% CI were estimated using Cox proportional hazards models. Known breast cancer risk factors were considered for inclusion in the model if the factor was associated with both air pollution and breast cancer. Race, educational attainment, smoking status, and menopausal hormone therapy met these criteria. Results were unchanged when we adjusted for geography using splines. In subset analyses, (1) we examined the effect of air pollution separately for breast cancer subtypes, stratifying by ER/PR and stage, calculating RR and 95% CI using polytomous logistic regression; and (2) we examined residential air pollution concentrations derived from 1990's estimates among those who had lived long-term at their

current residence (i.e., excluding those who changed residences) in order to investigate associations of long-term air pollution with breast cancer.

Results

Breast cancer cases were more likely White, highly educated, and users of menopausal hormone therapy (Table 1). There was no association between invasive breast cancer overall and $PM_{2.5,}$ $PM_{10,}$ or NO_2 (Table 2). However, the risk associated with NO_2 differed when stratified by ER/PR ($p = 0.04$). NO_2 was associated with a 1.10-fold increased risk of ER +/PR+ breast cancer (95% CI: 1.02–1.19 per IQR of 5.8 ppb) but not with ER−/PR− breast cancer (RR = 0.92; 95% CI: 0.77–1.09). We observed a borderline increased risk of breast cancer *in situ* in relation to NO_2 (HR = 1.10; 95% CI: 0.99–1.24 per IQR of 5.8 ppb) (data not shown).

Discussion

Our analysis did not suggest an association between air pollution and overall invasive breast cancer risk. Multiple studies (2, 3), but not all (4, 7), found that exposure to traffic-related air pollutants, particularly NO_2, increased breast cancer risk. A potential explanation for differences among studies could be differing proportions of ER/PR subtypes, if as our data suggest, NO_2 is only associated with ER+/PR+ breast cancer. NO_2 probably serves as a marker for traffic-related pollution rather than a causal factor *per se* (3). As such, it may serve as a proxy for components of air pollution which affect estrogens, such as polycyclic aromatic hydrocarbons (PAH). PAHs have estrogenic properties, as shown by PAH binding to ER-β to induce transcriptional targets (8). Thus, there is biological plausibility for a differential role of air pollution by hormone receptor status. However, Liu et al reported that estrogen disruptors in ambient air were not associated with ER+/PR+, but rather with ER −/PR− breast cancer (their analysis did not report on NO_2) (4).

This analysis using a prospective, large national sample which systematically evaluated air pollution using state-of-the-art spatial modeling is able to rule out a strong relationship between air pollution and breast cancer risk. One limitation is that air pollution exposure earlier in life could impact breast cancer risk; however, our analysis of long-term air pollution exposure showed results were unchanged. Replication of these results is needed before firm conclusions can be drawn regarding ER+/PR+ breast cancer risk in relation to traffic-related air pollution.

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Table 1

Characteristics of the study population

Characteristic	Control subjects (N=47,591)		Case subjects (N=1,749)[a]	
	mean	**(SD)**	**mean**	**(SD)**
Age at enrollment	55.1	(9.0)	56.9	(8.9)
	n	**(%)**	**n**	**(%)**
Race/Ethnicity				
Non-Hispanic White	40,750	83.5	1,528	86.4
Non-Hispanic Black	4,318	8.9	113	6.4
Hispanic	2,433	5.0	71	4.0
Other	1,236	2.5	55	3.2
Unknown	7	0.0	0	0.0
Education				
Less than high school	605	1.3	15	0.9
Completed high school	6,882	14.2	245	13.9
Associate or technical degree	16,473	33.9	545	30.8
Bachelor's degree	13,058	26.9	490	27.7
Graduate degree	11,542	23.8	472	26.7
Unknown	11	0.0	1	0.0
Body Mass Index				
<18.5	568	1.2	17	0.9
18.5–24.9	18,171	37.4	639	36.1
25.0–29.9	15,334	31.6	571	32.3
30.0–39.9	12,101	24.9	450	25.5
≥ 40.0	2,375	4.9	91	5.2
Unknown	17	0.0	0	0.0
Smoking				
Never smoker	26,183	53.9	920	52.0
Former smoker	18,251	37.6	716	40.5
Current smoker	4,070	8.4	131	7.4
Unknown	67	0.1	1.0	0.1
Physical Activity (in Met-hours/week)				
1st Quintile	9,634	19.8	341	19.3
2nd Quintile	9,627	19.8	360	20.4
3rd Quintile	9,628	19.8	363	20.5
4th Quintile	9,631	19.8	353	20.0
5th Quintile	9,628	19.8	338	19.1
Unknown	423	0.9	13	0.7
Hormone Replacement Therapy				
No, has never taken	43,396	89.4	1,523	86.1
Yes, is taking or took in the past	4,962	10.2	238	13.5

Characteristic	Control subjects (N=47,591)		Case subjects (N=1,749)[a]	
	mean	(SD)	mean	(SD)
Unknown	213	0.4	7	0.4

[a]. excluding in situ breast cancer cases

Table 2

The risk of invasive breast cancer associated with $PM_{2.5}$, PM_{10}, and NO_2

	Breast Cancer						Breast Cancer Subtype								
Air pollution	**Control (N = 47,591)**		**All Cases (N = 1,749)**		**HR[a,b,c]**	**95% CI**	**ER+/PR+ (n = 947)**		**RR[b,c, d]**	**95% CI**	**ER−/PR− (n = 223)**		**RR[b,c, d]**	**95% CI**	**p-value[e]**
	Mean	*SD*	*Mean*	*SD*			*Mean*	SD			*Mean*	SD			
$PM_{2.5}$	*10.5*	*2.4*	*10.5*	*2.4*	1.03	0.96–1.11	*10.4*	*2.4*	1.00	0.91–1.09	*10.5*	*2.5*	0.99	0.81–1.20	0.99
PM_{10}	*22.2*	*5.8*	*22.2*	*6.0*	0.99	0.98–1.00	*22.2*	*6.1*	1.02	0.96–1.09	*21.9*	*5.4*	0.96	0.83–1.10	0.69
NO_2	*10.1*	*4.7*	*10.3*	*4.7*	1.02	0.97–1.07	*10.4*	*4.7*	**1.10**	**1.02–1.19**	*9.8*	*4.5*	0.92	0.77–1.09	0.04

[a]. Estimated using Cox proportional hazards.

[b]. Units representing an increase in the IQR difference: $PM_{2.5}$ = 3.6 μg/m^3; PM_{10} = 5.8 μg/m^3; NO_2 = 5.8 parts per billion (ppb).

[c]. Models adjusted for: age at diagnosis, race, educational attainment, smoking status, menopausal hormone therapy.

[d]. Estimated using polytomous logistic regression.

[e]. Test of interaction in the polytomous regression model.

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