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

Kerryn W. Reding1,2, Michael T. Young3, Adam A. Szpiro3, Claire J. Han1, Lisa A. DeRoo4, Clarice Weinberg5, Joel D. Kaufman3, and Dale P. Sandler5

Abstract

Background: Some but not all past studies reported associations between components of air pollution and breast cancer, namely fine particulate matter (PM2.5) and nitrogen dioxide (NO2). 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 to 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 NO2, PM2.5, and PM10.

Results: Although breast cancer risk overall was not associated with PM2.5 (HR = 1.03; 95% confidence intervals (CI), 0.96–1.11), PM10 (HR = 0.99; 95% CI, 0.98–1.00), or NO2 (HR = 1.02; 95% CI, 0.97–1.07), the association with NO2 differed according to ER/PR subtype (P = 0.04). For an interquartile range (IQR) difference of 5.8 parts per billion (ppb) in NO2, the relative risk (RR) of ER+/PR− breast cancer was 1.10 (95% CI, 1.02–1.19), whereas there was no evidence of association with ER−/PR+ (RR = 0.92; 95% CI, 0.77–1.09; Pinteraction = 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 NO2.

Impact: Though these results suggest there is no substantial increased risk for breast cancer overall in relation to air pollution, NO2, a marker of traffic-related air pollution, may differentially affect ER+/PR− breast cancer. Cancer Epidemiol Biomarkers Prev; 24(12): 1–3. ©2015 AACR.
Results were unchanged when we adjusted for geography using splines. In subset analyses, (i) we examined the effect of air pollution separately for breast cancer subtypes, stratifying by estrogen receptor/progesterone receptor (ER/PR) and stage, calculating RR and 95% CI using polytomous logistic regression; and (ii) 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 interquartile range (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 that affect estrogen, such as polycyclic aromatic hydrocarbons (PAH). PAHs have estrogenic properties, as shown by PAH binding to ER$\beta$ to induce transcriptional targets (8). Thus, there is biologic plausibility for a differential role of air pollution by hormone receptor status. However, Liu and colleagues 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$_2$; ref. 4).

This analysis using a prospective, large national sample that 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 affect 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.

### Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control subjects ($N = 47,591$)</th>
<th>Case subjects ($N = 1,749^*$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at enrollment, SD</td>
<td>55.1 9.0</td>
<td>58.5 8.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Non-Hispanic white</th>
<th>Non-Hispanic black</th>
<th>Hispanic</th>
<th>Other</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>40.46 85.0</td>
<td>4.32 9.1</td>
<td>1.576 3.3</td>
<td>1.231 2.6</td>
<td>6 0.0</td>
</tr>
<tr>
<td>SD</td>
<td>85.0</td>
<td>113</td>
<td>53</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>RR b,c,d</td>
<td>1.03</td>
<td>0.99</td>
<td>0.96</td>
<td>1.09</td>
<td>1.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Less than high school</th>
<th>Completed high school</th>
<th>Bachelor’s degree</th>
<th>Graduate degree</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>494 1.0</td>
<td>6,735 14.2</td>
<td>16,183 34.0</td>
<td>11,398 24.0</td>
<td>8 0.0</td>
</tr>
<tr>
<td>RR b,c,d</td>
<td>1.09</td>
<td>1.09</td>
<td>1.09</td>
<td>1.09</td>
<td>1.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>RR b,c,d</th>
<th>95% CI</th>
<th>Mean</th>
<th>SD</th>
<th>RR b,c,d</th>
<th>95% CI</th>
</tr>
</thead>
</table>

| 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 |
| PM$_{10}$ | 22.2 | 5.8 | 22.2 | 5.8 | 0.99 | 0.98–1.00 | 22.6 | 6.1 | 1.02 | 0.96–1.09 |
| NO$_2$    | 10.1 | 4.7 | 10.1 | 4.7 | 1.02 | 0.97–1.07 | 10.4 | 4.7 | 1.10 | 1.02–1.19 |

*Excluding in situ breast cancer cases.

**Table 2. The risk of invasive breast cancer associated with PM$_{2.5}$, PM$_{10}$, and NO$_2$**

<table>
<thead>
<tr>
<th>Air pollution</th>
<th>Control ($N = 47,591$)</th>
<th>All cases ($N = 1,749^*$)</th>
<th>ER$^+/PR^+$ breast cancer ($N = 497$)</th>
<th>ER$^-/PR^+$ breast cancer ($N = 223$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
</tbody>
</table>

*Estimated using Cox proportional hazards.

**Estimated using polytomous logistic regression.

*Test of interaction in the polytomous regression model.
Disclosure of Potential Conflicts of Interest

J.D. Kaufman is a consultant/advisory board member for Health Effects Institute, Diesel Exhaust Epidemiology Panel. No potential conflicts of interest were disclosed by the other authors.

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