Exposure to Particle Radioactivity and Breast Cancer Risk in the Sister Study: A U.S.-Wide Prospective Cohort

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Introduction

Outdoor air pollution has been classified as a human carcinogen. The evidence for breast cancer risk is accumulating although the specific constituents driving the association are not well explored. Particulate matter can be a vector for radioactive isotopes, most of which arise from naturally occurring radon gas, which has been associated with a higher risk of breast and lung cancer. We evaluated the association between residential ambient particle radioactivity (PR), a radiometric characteristic of airborne particulate matter, and incident breast cancer.

Methods

The Sister Study cohort includes 50,884 U.S. women ages 35–74 who had a sister diagnosed with breast cancer but no breast cancer history themselves and who were enrolled between 2003–2009. Participants completed an enrollment questionnaire including educational attainment and self-reported race (American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, and White, with the option to select multiple categories) and ethnicity (Hispanic/Latina, with the option to provide country/region of origin). The cohort was approved by the institutional review board of the National Institutes of Health. We used data with follow-up through 23 September 2019 (data release 9.0).

We excluded women with a preenrollment breast cancer diagnosis or who were lost to follow-up (n = 363), and those outside the conterminous United States or who were missing covariates (n = 1,328) or PR data (n = 46), leaving 49,147 women for analysis. Incident breast cancer cases (invasive and ductal carcinoma in situ) were ascertained via self-report and confirmed with medical records.

Ambient PR exposure was estimated using a spatiotemporal ensemble model based on the U.S. Environmental Protection Agency’s Radiation Network (RadNet), a nationwide background environmental radiation monitoring network with gross beta particle activity data collected between 2001 and 2017 from 129 monitors. The multistage exposure model incorporates gross beta PR (PR-β) measurements from RadNet and predictors of emissions (e.g., ground-surface uranium, barometric pressure, soil characteristics, anthropogenic sources of radionucleotides) and transport of radon and its progeny [e.g., monthly average fine particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm (PM2.5), relative humidity, air mass sources]. In the first stage, nine base learning models were selected to characterize the complex associations between particulate radioactivity and its predictors. Stage two used a non-negative geographically and temporally weighted regression method to aggregate the predictions from the nine base learning models. This ensemble model had good accuracy, with a spatial cross-validation R² = 0.56. Estimated monthly levels of PR-β (mBq/m³), a measure of the particle-bound beta-emitting radionuclides, at a 32-km spatial resolution, were averaged to annual estimates at the geocoded enrollment address based on enrollment year.

As described previously, annual average PM with aerodynamic diameter ≤ 10 μm (PM10), PM2.5, and nitrogen dioxide (NO2) levels were estimated at participant residences using a validated regionalized kriging model with spatial smoothing. For PM2.5 and NO2, we used the 2006 annual average because it was a midpoint in the enrollment period (2003–2009). For PM10, we used the 2000 annual average based on data availability and because it predated enrollment.

We used Cox proportional hazards models with age as the time scale to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association with PR-β continuously [per interquartile range (IQR) 0.038 mBq/m³] and per 0.1 mBq/m³ increase] and in quintiles. We evaluated an a priori determined set of potential confounders; models were adjusted for self-reported race/ethnicity (non-Hispanic White, Black/African American including Black Hispanic, and Other, collapsed due to small numbers; “Other” included women who self-identified as non-Black Hispanic, Asian, Native Hawaiian/Pacific Islander, or American Indian/Alaska Native), because determinants of air pollutant exposure may vary by race/ethnicity, and education (high school or less, associate’s degree/technical degree/some college, bachelor’s degree or higher). We also considered a second model adjustment set that further adjusted for PM10 (micrograms per cubic meter, μg/m³), PM2.5, PM10 (μg/m³), and NO2 [parts per billion (ppb)]. Models were stratified by estrogen receptor (ER) status. We further stratified associations for an IQR increase and ER– breast cancer by race/ethnicity (non-Hispanic White and Black/African American including Black Hispanic). Associations were also stratified by years lived at the enrollment residence at the time of study baseline (<10 y, ≥10 y); heterogeneity was assessed using a likelihood ratio test of cross-product terms. For race-stratified analyses, we did not have the sample size necessary to produce stable estimates for other racial ethnic groups.
Results

With an average of 10 y of follow-up, 3,894 women were diagnosed with breast cancer. The median PR-β was 0.39 mBq/m³. Black women and those with lower educational attainment tended to have higher exposure (Table 1). PR-β varied by census region but did not correlate strongly with residential air pollutants (PM$_{2.5}$ r = 0.2, PM$_{10}$ r = 0.2, NO$_2$ r = -0.1).

PR-β was not associated with overall breast cancer risk. Patterns of association were similar with adjustment for residential air pollutants; estimates provided here are fully adjusted (Table 2). When considering the IQR, higher PR-β was suggestively positively related to ER− (HR$_{IQR}$ = 1.08; 95% CI: 0.96, 1.21) but inversely related to ER+ breast cancer risk (HR$_{IQR}$ = 0.96; 95% CI: 0.91, 1.00). Higher PR-β levels were associated with nonmonotonically higher HRs for ER− breast cancer in the second, third, and fourth but not the fifth quintiles (HR$_{Q2vsQ1}$ = 1.30 95% CI: 0.97, 1.75; HR$_{Q3vsQ1}$ = 1.26; 95% CI: 0.92, 1.72; HR$_{Q4vsQ1}$ = 1.34 95% CI: 0.98, 1.84; HR$_{Q5vsQ1}$ = 1.19 95% CI: 0.87, 1.62; p-trend = 0.4). This association for ER− cancers did not significantly vary for non-Hispanic White (case n = 418; HR$_{IQR}$ = 1.09, 95% CI: 0.97, 1.23) vs. Black/African American women (case n = 53; HR$_{IQR}$ = 1.00, 95% CI: 0.65, 1.54) (p-for-heterogeneity = 0.7), althoughCls were wide. Hrs for ER− cancers were elevated for women who reported living at their baseline residence for ≥10 y (case n = 276; HR$_{IQR}$ = 1.15, 95% CI: 0.99, 1.34) in comparison with <10 y (case n = 222; HR$_{IQR}$ = 1.01, 95% CI: 0.86, 1.18) (p-for-heterogeneity = 0.2).

Discussion

In this prospective study of U.S. women, higher estimated exposure to ambient PR-β was associated with an elevated risk of ER− breast cancer. This finding was robust to adjustment for several criteria air pollutants that were previously associated with breast cancer risk in this cohort. These results are intriguing, given the widespread nature of air pollution, limited research on PR, and lack of established risk factors for ER− breast cancer.

Experimental studies suggest that ionizing radiation exposure is more relevant to the development of ER− vs. ER+ tumors, and county-level estimates of residential radon have also been associated with ER− breast cancer. However, a nested case–control study within a large study of childhood cancer survivors did not observe differences in the radiation dose–response for ER+ and ER− cancers.

We employed a novel exposure model to estimate residential PR-β in a nationwide cohort, allowing us to consider a range of relevant exposure levels. We also had extensive covariate information to address potential confounding, including by residential air pollution exposure. A limitation is that we relied on ambient PR-β estimated for the home at the time of study enrollment as a proxy for long-term exposure, which could result in nondifferential misclassification and attenuation of relative risks. However, over 50% of participants reported living at their enrollment address for at least 10 y. Further, annual PR is a joint complex function of source radionuclides, atmospheric movement, and abundance of atmospheric aerosol (PM). Although long-term trends have been observed in PR, the spatial pattern of PR is relatively stable because the spatial patterns of key predictors (e.g., uranium, relative humidity) do not change remarkably from year to year. Therefore, we assumed that the spatial contrast in exposure was fairly stable in our population over time. The exposure model uses PM-bound gross beta activity as a surrogate measure for total PR; beta particles are relatively low energy but could be a proxy for alpha and gamma radiation, which may contribute to cancer risk. The ratio between beta particles and alpha particles was shown to be stable in a recent study. When inhaled, alpha particles can be diffused to blood and transported to other organs, supporting plausibility for our observed associations.

This study suggests a possible role of radioactive particles in the development of ER− breast cancer, although our data did not reflect a dose–response relationship. More research is needed to confirm these findings.
Table 2. The association between beta particle radioactivity exposure at the baseline address and breast cancer risk overall and by ER status with stratification by time spent at baseline address.

| All participants | n Person-years | Cases | Age-adjusted HR (95% CI) | A priori adjusted HR (95% CI) | Fully adjusted HR (95% CI) | Cases | Age-adjusted HR (95% CI) | A priori adjusted HR (95% CI) | Fully adjusted HR (95% CI) | Cases | Age-adjusted HR (95% CI) | A priori adjusted HR (95% CI) | Fully adjusted HR (95% CI) |
|------------------|----------------|-------|--------------------------|-------------------------------|--------------------------|-------|--------------------------|-------------------------------|--------------------------|-------|--------------------------|-------------------------------|--------------------------|
| Quintile 1<sup>a</sup> | 9,830 | 106,976 | 794 | 1.0 (Ref) | 1.0 (Ref) | 1.0 (Ref) | 611 | 1.0 (Ref) | 1.0 (Ref) | 1.0 (Ref) | 81 | 1.0 (Ref) | 1.0 (Ref) | 1.0 (Ref) |
| Quintile 2 | 9,829 | 106,905 | 798 | 1.01 (0.91, 1.11) | 1.01 (0.91, 1.11) | 0.99 (0.89, 1.09) | 582 | 0.96 (0.85, 1.07) | 0.96 (0.86, 1.08) | 0.94 (0.83, 1.05) | 103 | 1.28 (0.95, 1.71) | 1.26 (0.94, 1.68) | 1.30 (0.97, 1.75) |
| Quintile 3 | 9,829 | 107,514 | 753 | 0.95 (0.86, 1.05) | 0.95 (0.86, 1.05) | 0.94 (0.84, 1.04) | 533 | 0.88 (0.78, 0.98) | 0.98 (0.81, 1.07) | 0.87 (0.77, 0.98) | 101 | 1.25 (0.93, 1.67) | 1.22 (0.91, 1.64) | 1.26 (0.92, 1.72) |
| Quintile 4 | 9,829 | 107,876 | 791 | 1.00 (0.91, 1.10) | 1.00 (0.91, 1.10) | 1.00 (0.89, 1.11) | 565 | 0.93 (0.83, 1.04) | 0.95 (0.85, 1.06) | 0.94 (0.83, 1.07) | 111 | 1.37 (1.03, 1.82) | 1.34 (1.00, 1.79) | 1.34 (0.98, 1.84) |
| Quintile 5 | 9,830 | 107,418 | 754 | 0.95 (0.86, 1.04) | 0.95 (0.86, 1.05) | 0.96 (0.87, 1.07) | 536 | 0.87 (0.77, 0.98) | 0.89 (0.79, 1.00) | 0.91 (0.81, 1.03) | 102 | 1.26 (0.94, 1.68) | 1.24 (0.92, 1.66) | 1.19 (0.87, 1.62) |

<sup>a</sup> Adjusted for race (non-Hispanic White, Black/African American, other race including women who identified as non-Black Hispanic, Asian, Native Hawaiian/Pacific Islander, or American Indian/Alaska Native) and education (less than or equal to high school; associate’s degree/technical degree/some college; bachelor’s degree or higher), and criteria air pollutants (PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>).

<sup>e</sup> Adjusted for race (non-Hispanic White, Black/African American, other race including women who identified as non-Black Hispanic, Asian, Native Hawaiian/Pacific Islander, or American Indian/Alaska Native) and education (less than or equal to high school; associate’s degree/technical degree/some college; bachelor’s degree or higher), and criteria air pollutants (PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>).

<sup>p</sup> For trend — — — 0.3 0.3 0.6 — — 0.2 0.2 0.2 — — 0.1 0.2 0.4

IQR increase<sup>e</sup> 49,147 536,689 3,894 0.98 (0.94, 1.01) 0.98 (0.94, 1.02) 0.98 (0.95, 1.03) 282 0.94 (0.90, 0.98) 0.95 (0.91, 0.99) 0.96 (0.91, 1.00) 498 1.11 (1.00, 1.23) 1.10 (0.99, 1.22) 1.08 (0.96, 1.21) 1.13 (1.09, 1.17) 1.28 (1.07, 1.49) 0.97 (0.81, 1.16) 1.24 (1.02, 1.51) 1.28 (1.03, 1.57)

IQR increase 0.1 mBq/m³ 49,147 536,689 3,894 0.98 (0.94, 1.04) 0.95 (0.86, 1.04) 0.96 (0.87, 1.07) 282 0.85 (0.76, 0.95) 0.87 (0.78, 0.98) 0.89 (0.79, 1.01) 498 1.31 (1.09, 1.57) 1.29 (1.07, 1.51) 1.21 (0.91, 1.63) 1.35 (1.11, 1.64) 1.31 (1.08, 1.57) 1.29 (1.06, 1.56) 1.27 (1.04, 1.54) 1.28 (1.04, 1.55) 1.31 (1.08, 1.57)

Note: —, no data; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; IQR, interquartile range; PR, particle radioactivity; PR<sub>b</sub>, beta particle radioactivity; Ref, reference.

<sup>1</sup> PR<sub>b</sub> ranges: Quintile 1: 0.277–0.356 mBq/m³; Quintile 2: 0.357–0.378 mBq/m³; Quintile 3: 0.379–0.393 mBq/m³; Quintile 4: 0.394–0.403 mBq/m³; Quintile 5: 0.404–0.514 mBq/m³.

<sup>2</sup> IQR is 0.038 mBq/m³ for baseline address.

<sup>3</sup>n = 560 women were missing ER status.

<sup>4</sup> Adjusted for race (non-Hispanic White, Black/African American, other race including women who identified as non-Black Hispanic, Asian, Native Hawaiian/Pacific Islander, or American Indian/Alaska Native) and education (less than or equal to high school; associate’s degree/technical degree/some college; bachelor’s degree or higher), and criteria air pollutants (PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>).

<sup>5</sup> p For heterogeneity tests the null hypothesis that there is no difference in association by ER receptor status (IQR increase: p = 0.06, 0.1 mBq/m³ increase: p = 0.06, Quintiles: p = 0.19) and by time spent living in home (<10 y vs ≥10 y) (Overall, IQR increase: p = 0.9, 0.1 mBq/m³ increase: p = 0.9, Quintiles: p = 0.7) (ER+: IQR increase: p = 0.3, 0.1 mBq/m³ increase: p = 0.3, Quintiles: p = 0.9) (ER−: IQR increase: p = 0.2, 0.1 mBq/m³ increase: p = 0.2, Quintiles: p = 0.8).
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