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Particulate Matter and Traffic-related Exposures in Relation to Breast Cancer Survival

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Abstract

Background: While particulate matter (PM) has not been consistently associated with breast cancer risk, two studies have reported harmful associations for breast cancer survival. We examined PM exposures and breast cancer survival in two US-based prospective cohort studies.

Methods: The Nurses' Health Study (NHS) and NHSII are cohorts with detailed data on medical history, lifestyle factors, and causes of death. Women with Stage I-III breast cancer (n=8,936) were followed through June 2014. Residential PM was estimated using spatio-temporal models. We performed Cox regression to estimate hazard ratios (HR) of breast cancer specific-mortality and all-cause mortality for 10 $\mu g/m^3$ increases in post-diagnosis PM.

Results: There were 1,211 breast cancer specific deaths. Overall, PM was not associated with breast cancer specific mortality ($PM_{2.5}$: HR=1.09 95% CI 0.87, 1.36; $PM_{2.5–10}$: HR=1.03 95% CI 0.85, 1.24; PM_{10}: HR=1.05, 95% CI 0.89, 1.24), but was associated with modest increases in all-cause mortality ($PM_{2.5}$: HR=1.12 95% CI 0.96, 1.30; $PM_{2.5–10}$: HR=1.12 95% CI 1.00, 1.24; PM_{10}: HR=1.09, 95% CI 1.01, 1.18). However, among participants with Stage I disease $PM_{2.5}$ was associated with higher breast cancer specific-mortality (HR=1.64 95% CI 1.11, 2.43).

Conclusions: PM was not associated with breast cancer specific death overall; however, higher PM was associated with all-cause mortality. Higher $PM_{2.5}$ was associated with higher breast cancer mortality among Stage I breast cancer patients even after adjustment.

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Impact: Studies on ambient PM and breast cancer survival demonstrate that $PM_{2.5}$ may have broader health effects than previously recognized and warrants further research on breast tumor progression.

Keywords

breast cancer; breast cancer survival; breast cancer mortality; air pollution; particulate matter; mortality; epidemiology

Introduction

Among women, breast cancer is the most commonly diagnosed cancer, excluding non-melanoma skin cancer, and a leading cause of cancer death.(1,2) In the United States, several million women at any given time are living with breast cancer.(2) While the global burden of breast cancer mortality has decreased over time in most high-income countries, there is a growing burden of breast cancer mortality in developing countries.(3–5) There is also wide international variation in air pollution, with high and increasing levels of particulate matter (PM) less than 2.5 microns in diameter ($PM_{2.5}$) observed in parts of Latin America, Asia, and Africa.(6) The International Agency for Research on Cancer (IARC) recently declared that outdoor air pollution and PM are human carcinogens, mainly based on evidence with lung cancer incidence (7) and several cohort studies have since reported generally null associations between PM and breast cancer incidence (8–11); however, research on PM after diagnosis in relation to breast cancer survival is limited.

There is convincing evidence that PM induces systemic inflammation, oxidative stress, and epigenetic changes,(12–15) which are hypothesized to be underlying mechanisms that may drive breast tumor progression.(16–19) To date, one study using California Surveillance Epidemiology and End Results (SEER) registry data reported that county-based $PM_{2.5}$ levels at diagnosis were associated with higher breast cancer mortality rates, particularly among breast cancer patients with localized disease.(16) In a smaller study within a northern Italian province, a similar association between $PM_{2.5}$ and breast cancer specific mortality was reported;(20) however, these studies did not account for important clinical and lifestyle predictors of breast cancer mortality, particularly post-diagnostic lifestyle factors such as body mass index (BMI), weight gain, physical activity, and aspirin use that are relevant to breast cancer survival (21–23), or have updated PM exposure. These findings have yet to be validated in broader geographic settings and potential confounding factors remain to be considered, particularly related to lifestyle and clinical factors.

Given the nationwide geographic scope of the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) and the ability to account for individual-level clinical and lifestyle factors, we investigated associations between PM exposures and distance to major roadways in relation to breast cancer survival among women with Stage I-III disease residing across the conterminous United States. We hypothesized that exposure to $PM_{2.5}$, which has a host of biologic effects and a longer atmospheric half-life,(12,24) following a diagnosis would be associated with higher breast-cancer specific death and overall mortality, particularly among women with localized, Stage I disease as observed in the California SEER study.

Methods

Study Population

The NHS cohort was established in 1976, enrolling 121,700 married, female nurses between the ages of 30–55 years who resided in 11 states (California, Connecticut, Florida, Massachusetts, Maryland, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas).(25) The NHSII cohort was established in 1989, enrolling 116,430 female nurses between the ages of 25–42 years residing in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina and Texas), without a prior history of cancer, excluding non-melanoma skin cancer. Briefly, participants in both cohorts completed baseline and subsequent biennial questionnaires that were mailed to their residential addresses to collect information on medical history, anthropometrics, reproductive history, lifestyle factors, and medications.(26)

Participants with self-reported breast cancer gave consent for study staff to review medical records to confirm the diagnosis. In this study, we included participants without a previous report of cancer and with confirmed Stage I-III primary breast cancer diagnosed between 1988–2008 who had PM exposure data (NHS n=6,499; NHSII n=2,437); the large majority of participants in these cohorts have information on stage, 92% in NHS and 87% in NHSII. Return of the questionnaires implied informed consent, and all participants or next-of-kin provided written approval to obtain medical records. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health and those of participating registries as required.

Endpoints: Breast cancer death, all-cause mortality and distant recurrence

The primary outcome of interest was death due to breast cancer (n=1,211: NHS n=899; NHSII n=312). Deaths were reported by next-of-kin, the post office, or by searches of the National Death Index for nonresponders; it has been estimated that ascertainment of vital status using the National Death Index in this cohort was 98% (27,28). The date and cause of death were confirmed by study physicians using information from medical records, the National Death Index, tumor registries and death certificates. As secondary analyses, we examined associations with all-cause mortality (n=2,614 deaths from to all-causes: NHS n=2,241; NHSII n=373) and breast cancer recurrence. A participant was considered to have distant recurrence if she reported 1) a distant metastasis to the lung, liver, brain or bone on a supplemental questionnaire sent to women with breast cancer, or 2) another cancer in the lung, liver, or brain on the main questionnaires that was confirmed by medical record review to be a metastasis and not a primary cancer. For women who died from breast cancer without reporting recurrence, we included them as having recurred two years before death for those with at least two years of follow-up or as having recurred at the time of death for those with less than two years of follow-up.

Exposures: Particulate Matter (PM) and Distance to Roadways

As part of the questionnaire mailing process, residential addresses were updated biennially in both cohorts. By the mid-1990s, participants resided in all 50 states.(29) Study

participants' residential addresses were geocoded and linked to predicted estimates of PM and to proximity to various-sized roadways over the course of the study.

i. Particulate matter: PM is classified into the following three size fractions: particles less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$), particles less than 10 microns (PM_{10}), and particles between 2.5–10 microns ($PM_{2.5–10}$) (24). PM comes from various sources and the varying contribution of these sources is different across regions of the United States. We defined the regions based on the Census Bureau designated regions: Northeast, Midwest, South, and the West.(30)

Predictions of monthly average $PM_{2.5}$ and PM_{10} were generated using spatio-temporal models that accounted for spatial and meteorological variation over time.(31) The monthly estimates were linked with participants' residential addresses between 1988 through 2007.(31) As $PM_{2.5}$ data were not directly measured before 1999, we derived $PM_{2.5}$ levels before 1999 from the PM_{10} levels before 1999 using the 1999 ratio of $PM_{2.5}$:PM_{10}.(31) $PM_{2.5–10}$ was calculated as the difference between PM_{10} and $PM_{2.5}$ estimates. We evaluated the models for predictive accuracy using a 10-set cross-validation approach; cross-validation correlation coefficients were high for $PM_{2.5}$ ($R^2 = 0.77$) and moderate for PM_{10} (R^2=0.58) and $PM_{2.5–10}$ (R^2=0.46).(31) Because PM predictions were not available after 2007, we carried forward the 2007 average PM levels for subsequent years of follow-up. In the current study, the primary exposure of interest was two-year average PM that was updated every questionnaire cycle from the report of diagnosis until the year of an endpoint or the end of follow-up.

ii. Distance to Roadways: A secondary exposure of interest was proximity of each residential address to various types of major roadways as a proxy for traffic-related exposures. Distance (in meters) from each residential address to nearest roadways was calculated using GIS software and the ESRI StreetMap Pro 2007 road network. Distances were calculated from three different types of roadways U.S. Census Feature Class Code roadways: A1 (primary roads, typically interstate highways, with limited access, division between opposing directions of traffic, and defined exits); A2 (primary major, non-interstate highways and major roads without access restrictions); and A3 (smaller, secondary roads, usually with more than two lanes).

Covariates

We considered the following demographic and clinical predictors of breast cancer mortality in multivariable models stratified on time since diagnosis: age at diagnosis, calendar year of diagnosis, disease stage (I, II, III), grade (1, 2, 3, missing), treatment (radiation only, chemotherapy only, both radiation and chemotherapy, neither radiation or chemotherapy—of whom, 99% had surgery—or missing), hormonal treatment (yes, no, missing), estrogen receptor (ER) status (ER positive, ER negative, missing), race/ethnicity (White, Black, Hispanic, Other), region of residence at diagnosis (Northeast, Midwest, South, West), and Census tract-level median income based on values from the 2000 Census. We additionally considered individual level markers of socioeconomic status gathered from the main questionnaires in NHS (work status, marital status, and husband's education) and NHSII

(living arrangements, marital status and personal income). Stage and grade data were abstracted from review of medical records. Tumors ≤2.0 cm without lymph node involvement were classified as Stage I; Stage II tumors were ≤2.0 cm with 1–3 lymph nodes involved, 2.1–4.0 cm with <3 lymph nodes involved, or >4.0 cm without lymph node involvement; tumors of any size with ≥4 lymph nodes involved or tumors >4.0 cm with 1–3 lymph nodes involved were classified as Stage III tumors. Information on breast cancer treatment was self-reported at the time of giving permission to obtain medical records. Information on ER status was obtained from pathology reports and tissue microarrays (TMA).(32,33)

We considered the following pre- and post-diagnosis lifestyle factors: pre-diagnosis body mass index (BMI), weight change between the cycle of diagnosis compared to the cycle after the diagnosis (stable weight change within 5%, moderate weight gain of 5-<10%, large weight gain ≥10%, moderate weight loss 5-<10%, large weight loss of ≥10%), pre- and post-diagnosis smoking status (never, past, current, missing), pre- and post-diagnosis physical activity categories (<3, 3 to <9, 9 to <15, 15 to <24, ≥24 MET-hours/week, missing), and post-diagnosis aspirin use (nonuser, current user, and missing). The post-diagnosis variables were updated every two years or as they became available.

Statistical Analysis

We conducted Cox proportional hazards models for time-varying covariates (34) to estimate Hazard Ratios (HRs) and 95% confidence intervals (CI) for each 10 $\mu g/m^3$ increase in updated PM exposures and by categories of proximity to A1, A1-A2, and A1-A3 roadways (≥250 meters, 150–249 meters, 50–149 meters, <50 meters). Person-time started at the questionnaire date when the participant reported her diagnosis and ended at the date of the endpoint (breast cancer death, death, or distant recurrence), or end of follow-up (June 2014). Violation of the proportional hazards assumption was tested using the likelihood ratio test (LRT). We considered adjustment for the aforementioned covariates and allowed the baseline hazard to vary by time since diagnosis to finely control for confounding. Four models are presented showing adjustment for age and diagnosis date in Model 1, additional adjustment for demographic factors (i.e. race/ethnicity, region, Census-tract median income) and pre-diagnosis lifestyle factors (i.e. physical activity and BMI) in Model 2, additional adjustment for clinical information in Model 3 (i.e. stage, ER status, treatment, hormone treatment, and grade), and adjustment for post-diagnosis factors in Model 4 (weight change, physical activity, and aspirin use) given previous findings with their associations with breast cancer survival.(21–23,35) Estimates from the cohorts were meta-analyzed to present pooled estimates. Statistically significant heterogeneity between the estimates across cohorts was assessed using the Q statistic. We assessed whether associations differed by stage, ER status, grade, region of residence, aspirin use, and BMI categories using likelihood ratio tests. In sensitivity analyses, we restricted to women who did not move to another state after diagnosis.

All analyses were conducted in SAS version 9.4 (Cary, NC).

Results

Among the 8,936 participants with Stage I-III breast cancer diagnosed between 1988–2008 (NHS n=6,499; NHSII n=2,437), there were 1,211 confirmed breast-cancer specific deaths over follow-up (NHS n=899; NHSII n=312) and 2,614 deaths from to all-causes (NHS n=2,241; NHSII n=373). The median date of diagnosis for NHS was 1998 and for NHSII was 2001. The proportion of cases alive after five-years since diagnosis in NHS was 89% and in NHSII was 93%. The median follow-up time in NHS was 13.25 years (standard deviation [SD]=6.4) and in NHSII was 12.0 years (SD=5.2). Among those who died from breast cancer, the average time from diagnosis to breast-cancer specific death was 6.6 years in NHS (IQR 3.0, 9.4) and 5.9 years in NHSII (IQR 2.6, 8.3). In NHS, the annual average levels of $PM_{2.5}$, $PM_{2.5–10}$, and PM_{10} at diagnosis were 13.3 $\mu g/m^3$ (SD=3.5), 8.9 $\mu g/m^3$ (SD=4.8), and 22.2 $\mu g/m^3$ (SD=6.9), respectively. In NHSII, the annual average levels of $PM_{2.5}$, $PM_{2.5–10}$, and PM_{10} at diagnosis were 12.9 $\mu g/m^3$ (SD=3.1), 8.4 $\mu g/m^3$ (SD=4.7), and 21.3 $\mu g/m^3$ (SD=6.2), respectively. Age-standardized characteristics are presented in Table 1. Overall, no consistent patterns were observed across cohorts between breast cancer mortality predictors and calendar-year adjusted $PM_{2.5}$ quintiles at diagnosis.

After adjustment for demographic, clinical, and pre- and post-diagnostic lifestyle factors, none of the PM exposures were statistically significantly associated with breast cancer specific-death overall (Table 2). The pooled HR of breast cancer specific-death for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.09 (95% CI 0.87, 1.36), $PM_{2.5–10}$ was 1.03 (95% CI 0.85, 1.24) and PM_{10} was 1.05 (95% CI 0.89, 1.24). The proportional hazards assumption was not violated in the models with LRT p-values >0.05. The change in estimates from Model 1 to Model 2 in NHSII was driven by pre-diagnosis physical activity and BMI. The strongest contributors to the change in estimates from Model 2 to Model 3 for NHS were stage, ER status and hormonal therapy. No significant heterogeneity was found between cohorts, and adjusting for individual-level markers of socioeconomic status did not materially change the estimates or conclusions. Proximity to A1-A3 roadways was not associated with breast cancer mortality (see Table S1). However, the associations between $PM_{2.5}$ and breast cancer survival differed by disease stage at diagnosis (Table 3). Among women with Stage I breast cancer, the HR of breast cancer specific-death for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.69 (95% CI 1.16, 2.47) in the pooled multivariable model that did not adjust for post-diagnostic lifestyle factors. The associations were null among women with Stage II or III breast cancer (Table 3). After multivariable adjustment that accounted for post-diagnostic lifestyle factors, the pooled HR among Stage I participants was similar (HR=1.64, 95% CI 1.11, 2.43) and remained null among women with Stage II and III disease (Table 3). Similar patterns were observed for PM exposures and breast cancer recurrence (see Table S2) and when we restricted to women who did not move (see Table S3). The associations between PM exposures and breast cancer mortality did not differ by grade, ER status, region of residence at diagnosis, aspirin use, or BMI (see Table S4).

Among women diagnosed with breast cancer in the NHS who died over follow-up (n=2,241), the five most common causes of death were breast cancer (40.1% of deaths), dementia (5.7%), unknown causes (4.8%), lung cancer (4.4%), and myocardial infarction (3.3%). The remaining deaths were due to other cancers (9.6%), cardiovascular diseases

(6.3%), respiratory conditions (4.4%), Parkinson's disease (0.7%), and other causes (20.8%). Among the NHSII breast cancer participants who died over follow-up (n=373), the five most common causes of death were breast cancer (83.9%), lung cancer (1.6%), unknown causes (1.1%), ovarian cancer (0.8%), and lymphomas (0.8%). The remaining deaths were due to other cancers (2.4%), cardiovascular diseases (1.9%), respiratory conditions (0.5%), and other causes (7.0%). There was no statistically significant heterogeneity across cohorts for PM exposures and all-cause mortality. The pooled HRs of all-cause mortality for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.12 (95% CI 0.96, 1.30), $PM_{2.5–10}$ was 1.12 (95% CI 1.00, 1.24) and PM_{10} was 1.09 (95% CI 1.01, 1.18) (Table 4).

Discussion

We observed moderate positive associations between $PM_{2.5}$ and breast cancer specific-mortality only among women with Stage I breast cancer, but not among those with Stage II or III disease. The hazard of breast-cancer specific death for women with Stage I breast cancer was 1.64 times higher (95% CI 1.11, 2.43) per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The associations were specific to $PM_{2.5}$ and were not found for larger PM size fractions. Similar to a previous study of all-cause mortality in the NHS (36), we observed modest associations between PM exposures and all-cause mortality among women diagnosed with breast cancer.

Our observed HRs of breast cancer specific mortality were attenuated compared to those reported in the California SEER study(16) and the Varese, Italy cancer-registry study,(20) and we did not observe associations among Stage II or Stage III patients. The California SEER study reported an 86% higher rate of overall breast cancer death (95% CI 1.12, 3.10) for each 5 $\mu g/m^3$ increase in $PM_{2.5}$ and a weaker association for a 10 $\mu g/m^3$ increase in PM_{10} (HR=1.13 95% CI 1.02, 1.25),(16) while we did not find an association with PM exposures and overall breast cancer specific mortality ($PM_{2.5}$ HR=1.04 95% CI 0.84, 1.28; PM_{10} HR=1.02 95% CI 0.89, 1.18). The California SEER study observed positive associations for a 5 $\mu g/m^3$ increase in $PM_{2.5}$ among breast cancer patients with localized disease (HR=2.13 95% CI 1.15, 3.95), regional disease (HR=2.07 95% CI 1.11, 3.84) and distant stage disease (HR=1.62 95% CI 1.05, 2.51); however, we only observed positive associations for $PM_{2.5}$ among Stage I breast cancer patients (HR=1.64 95% CI 1.11, 2.43) and not among Stage II (HR=0.88 95% CI 0.60, 1.30) or Stage III (HR=1.08 95% CI 0.69, 1.70) participants. Of note, the California SEER registry data could not consider important clinical (e.g. treatment, grade, and estrogen receptor status) or pre- or post-diagnosis lifestyle factors (e.g. body mass index, physical activity, and aspirin use) as we have done in the current study that may contribute to the observed differences across studies. Similarly, in a population-based cancer registry cohort in Varese, Italy, an elevated HR of breast cancer specific death was also observed (HR=1.72 95% CI 1.08, 2.75) comparing women residing in the highest quartile of $PM_{2.5}$ ($\geq$26.5 $\mu g/m^3$) to the lowest quartile of $PM_{2.5}$ ($<$21.1 $\mu g/m^3$) after adjusting for age, stage, grade, diagnosis date, and screening participation.(20)

The associations between PM and breast cancer mortality were specific to $PM_{2.5}$. $PM_{2.5}$ has an atmospheric half-life ranging from days to weeks (24) and comes primarily from combustion sources, organic compounds, and metals, which can penetrate the small airways and alveoli deep in the lung.(15) In the United States, approximately 80% of $PM_{2.5}$

composition consists of sulfates, nitrates, ammonium, elemental carbon, organic carbon, Na^+, and silicon and the remaining ~20% is a catch-all category consisting largely of many minerals and metals (e.g., lead, cadmium, vanadium, nickel, copper, zinc, manganese, and iron).(24,37) On the other hand, $PM_{2.5–10}$ does not penetrate as deep into the lung as $PM_{2.5}$, has a shorter atmospheric half-life ranging from minutes to days, and comes from the breaking of large crustal material as well as ocean spray and organic materials.(24) The biological effects of exposure to $PM_{2.5}$ go beyond the lungs, inducing systemic inflammation, oxidative stress, and epigenetic changes, though no studies have examined the influence of $PM_{2.5}$ on breast tissue.(12–15,38–43)

Inflammation may be a key driver of the actions of $PM_{2.5}$ on breast tumor progression. Epidemiologic studies of aspirin and other non-steroidal anti-inflammatory drug use after a breast cancer diagnosis reported improved breast cancer survival suggesting the importance of inflammatory processes after diagnosis.(44,45) Similarly, protein expression of cyclooxygenase-2 (COX-2), a marker of inflammation and target for aspirin, in breast tissue specimens was associated with worse breast cancer prognosis.(46) In human lung cells, benzo[a]pyrene, a major component of air pollution, induced COX-2 expression at the RNA and protein levels.(47) Although we did not observe differences in the associations of PM and breast cancer mortality among aspirin users and among non-users, the role of air pollution and inflammation in the breast remains to be elucidated and other biological mechanisms may be at play. Early-life exposures to ambient total suspended particles—particles of larger size—and traffic emission estimates were associated with differential epigenetic methylation patterns for a few genes within breast tissue in the Western New York Exposures and Breast Cancer study and the Long Island Breast Cancer Study Project case-control study.(48,49) To date, no studies have explored whether ambient $PM_{2.5}$ influences molecular changes in breast tissue.

This study has several limitations. Exposure measurement error is often a challenge. Instead of collecting personal exposure data, which is not feasible for a decades-long large epidemiologic scale, we used predictions from spatio-temporal modeling. The PM data are subject to Berkson error as the PM monitors measure only part of the true exposure that results in imprecision, as well as classical error, which usually results in attenuated estimates.(50,51) Despite the limitations inherent in the exposure assessment, the PM predictions were more strongly correlated with personal PM exposure than PM values from a nearest monitor(52) and have been shown to be associated with various outcomes such as mortality,(36) lung cancer,(29) and coronary heart disease.(53,54) While missing data is often a limitation in epidemiologic studies, the missing data of the covariates in this study was not related to ambient particulate matter exposure. Residual confounding cannot be fully ruled out, though we adjusted in stages to demonstrate the influence of individual-level demographic factors, pre-diagnosis lifestyle factors, clinical factors, and post-diagnosis lifestyle factors as well as markers of socioeconomic status. Additionally, the participants of this study were predominately white and results of this study may not be generalizable to other populations if there is reason to believe that the associations would be different by race/ethnicity. Although, the overall 5-year survival proportion in NHS and NHSII were similar to overall 5-year survival in SEER from corresponding years (55).

There are also several strengths of this study. We used a high-resolution spatio-temporal model of PM estimates across a large geographic area of the contiguous United States that were updated from 1988–2007. The PM estimates that have been associated with mortality, respiratory and cardiovascular diseases in these cohorts.(29,36,53,54,56–58) The NHS and NHSII participants reside across the United States, making this the most geographically expansive study of PM and breast cancer survival to date, as far as the authors are aware. The large size of the study allowed for stratified analyses to explore the associations separately by stage and other potential effect modifiers. Furthermore, the wealth of longitudinal data on lifestyle, clinical factors, and demographics allowed for finer control of potential confounding that was not feasible in previous registry-based studies.

In conclusion, $PM_{2.5}$ was associated with worse breast cancer prognosis only among women with locally-spread breast cancer, but not advanced tumors—even after consideration of important clinical and pre- and post-diagnostic lifestyle factors. This study confirms in a large geographic context that even after adjustment for lifestyle and clinical factors that $PM_{2.5}$ was associated with worse breast cancer specific mortality among women with localized disease, demonstrating that air pollution may have broader health effects than previously recognized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list:

PM	Particulate matter
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
HR	Hazard Ratio
CI	Confidence Interval
IARC	International Agency for Research on Cancer
$PM_{2.5}$	Particulate matter less than 2.5 microns in diameter
SEER	Surveillance Epidemiology and End Results

BMI	Body mass index
PM_{10}	Particles less than 10 microns
$PM_{2.5–10}$	Particles between 2.5–10 microns
GIS	Geographic Information Systems
ESRI	Environmental Systems Research Institute
ER	Estrogen receptor
TMA	Tissue microarray
MET	Metabolic Equivalent of Task
SD	Standard deviation
IQR	Interquartile range
LRT	Likelihood Ratio Test
COX-2	Cyclooxygenase-2
RNA	Ribonucleic acid

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Table 1

Age-standardized characteristics by year-adjusted $PM_{2.5}$ quintiles at breast cancer diagnosis in NHS (n=6,499) and NHSII (n=2,437)

	NHS					NHSII				
	1st (n=1,323)	**2nd (n=1,320)**	**3rd (n=1,263)**	**4th (n=1,290)**	**5th (n=1,303)**	**1st (n=473)**	**2nd (n=490)**	**3rd (n=498)**	**4th (n=494)**	**5th (n=482)**
Average age at diagnosis ± SD[a]	64.5±8.3	64.4±8.3	64.4±8.3	64.5±8.3	64.4±8.3	47.1±5.7	47.0±5.8	47.1±5.7	47.1±5.7	47.0±5.9
Stage at diagnosis, %										
- I	64	63	62	63	61	52	56	52	54	50
- II	28	27	29	28	29	34	33	33	35	36
- III	9	10	9	9	10	14	11	15	11	15
Radiation and/or Chemotherapy, %										
- Chemotherapy only	13	12	14	13	12	22	21	20	20	17
- Radiation only	29	31	29	29	28	10	11	11	13	11
- Radiation & Chemotherapy	17	19	18	17	19	37	42	39	40	42
- Neither	21	19	20	20	21	9	8	8	5	7
- Missing	20	19	19	20	21	23	19	23	22	23
Hormone treatment, %										
- Yes	59	60	60	61	62	52	58	54	54	52
- No	21	20	20	19	17	21	19	19	19	21
- Missing	20	20	20	20	21	27	22	27	27	27
Estrogen receptor status, %										
- Positive	74	75	77	75	72	70	72	70	72	70
- Negative	17	17	15	17	18	23	23	22	22	23
- Missing	8	8	8	8	9	7	5	8	6	7
Grade, %										
- 1	18	17	17	17	18	15	17	18	17	15
- 2	32	34	32	33	32	42	37	36	34	42
- 3	25	24	24	22	23	32	36	34	33	33
- Missing	26	26	28	28	28	12	10	12	15	10
Pre-menopausal, %	8	7	7	8	6	68	68	68	64	66
White, %	97	99	98	97	94	94	96	97	96	89
Region of residence, %										

	NHS					NHSII				
	1st (n=1,323)	2nd (n=1,320)	3rd (n=1,263)	4th (n=1,290)	5th (n=1,303)	1st (n=473)	2nd (n=490)	3rd (n=498)	4th (n=494)	5th (n=482)
- Northeast	30	61	62	52	41	32	42	39	33	27
- Midwest	5	7	16	26	28	16	26	35	40	35
- West	29	14	9	7	23	31	12	10	7	25
- South	36	18	13	15	7	22	20	16	20	13
BMI at diagnosis, %										
- <21 kg/m^2	11	9	9	10	8	15	15	16	15	15
- 21 - <23 kg/m^2	16	15	15	14	15	17	18	18	15	21
- 23 - <25 kg/m^2	20	17	18	17	17	20	17	20	17	17
- 25 - <30 kg/m^2	31	32	33	34	33	24	28	26	28	22
- 30 - <35 kg/m^2	12	15	14	15	15	14	12	11	11	13
- 35+ kg/m^2	5	6	7	6	7	8	8	7	11	9
- Missing BMI	5	5	3	4	5	0	2	2	2	3
Physical activity >9 MET hours/week, %	49	48	49	48	47	63	57	55	54	55
Never smoked, %	43	40	41	41	44	59	61	61	60	64
Post-diagnostic factors										
Weight change, %										
- Stable within <5%	59	60	59	58	60	57	56	55	56	54
- Moderate gain of 5-<10%	15	15	14	15	14	17	19	19	15	17
- Large gain ≥10%	7	7	8	8	8	9	9	11	14	12
- Moderate loss of 5-<10%	9	11	12	13	12	10	10	9	9	11
- Large loss of ≥10%	9	7	7	6	6	6	6	6	7	6
Used Aspirin, %	40	39	40	39	41	23	25	21	20	19
Physical activity (MET hours/week), %										
- <3	27	26	27	27	28	17	16	21	23	21
- 3-<9	24	25	20	24	23	17	24	23	24	21
- 9-<15	12	11	13	14	14	14	14	12	15	16
- 15-<24	13	17	15	14	16	18	15	16	15	14
- ≥24	23	22	25	22	19	34	31	27	24	28
Average Census-tract median income ($) ±SD	58,482 ±24,460	65,799 ±25,924	67,601 ±26,768	65,092 ±27,834	60,057 ±23,230	63,493±23,350	66,521±23,985	69,128 ±27,119	67,736 ±25,252	64,035 ±26,274

Abbreviations: PM, Particulate matter; NHS, Nurses' Health Study; BMI, body mass index; MET, metabolic equivalent

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Values are means ± SD, or percentages and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

[a] Value is not age adjusted.

Table 2

HRs (95% CI) of breast cancer specific death for 10 μg/m^3 increases in post-diagnosis PM among Stage I-III participants (n=6,499 for NHS; n=2,437 for NHSII)

	$PM_{2.5}$	$PM_{2.5-10}$	PM_{10}	Events/ Person-years
NHS				*899/81,443*
Model 1[a]	1.25 (0.99, 1.58)	1.02 (0.88, 1.18)	1.07 (0.95, 1.19)	
Model 2[b]	1.14 (0.90, 1.46)	1.04 (0.86, 1.26)	1.06 (0.93, 1.20)	
Model 3[c]	1.14 (0.89, 1.46)	0.97 (0.80, 1.17)	1.02 (0.90, 1.16)	
Model 4[d]	1.03 (0.80, 1.32)	0.97 (0.80, 1.17)	0.99 (0.87, 1.13)	
NHSII				*312/27,902*
Model 1[a]	1.45 (0.94, 2.22)	1.07 (0.83, 1.38)	1.13 (0.93, 1.37)	
Model 2[b]	1.46 (0.94, 2.26)	1.15 (0.85, 1.56)	1.19 (0.95, 1.49)	
Model 3[c]	1.24 (0.79, 1.94)	1.17 (0.85, 1.61)	1.15 (0.91, 1.44)	
Model 4[d]	1.33 (0.84, 2.10)	1.19 (0.86, 1.63)	1.18 (0.93, 1.49)	
p-value for cohort heterogeneity[d]	*0.33*	*0.28*	*0.20*	
Pooled Estimates				*1,211/109,345*
Model 1[a]	1.29 (1.05, 1.59)	1.03 (0.91, 1.17)	1.08 (0.98, 1.19)	
Model 2[b]	1.21 (0.98, 1.50)	1.07 (0.91, 1.26)	1.09 (0.97, 1.22)	
Model 3[c]	1.16 (0.94, 1.44)	1.02 (0.87, 1.20)	1.05 (0.94, 1.17)	
Model 4[d]	1.09 (0.87, 1.36)	1.03 (0.85, 1.24)	1.05 (0.89, 1.24)	

Abbreviations: HR, hazard ratio; PM, Particulate matter; NHS, Nurses' Health Study; BMI, body mass index; MET, metabolic equivalent; ER, estrogen receptor

[a]Model 1 adjusted for age and diagnosis date.

[b]Model 2 adjusted for age, diagnosis date, demographics such as race/ethnicity (White, Black, Hispanic, Other), region of residence at diagnosis (Northeast, Midwest, South, West), and Census-tract median income as well as the following pre-diagnostic lifestyle factors: physical activity (<9 MET-hours/week, ≥9 MET-hours/week, missing) and BMI (<21, 21-<23, 23-<25, 25-<30, 30-<35, 35+ kg/m^2, missing).

[c]Model 3 adjusted for the same covariates as model 2 and also includes stage (I, II, III), ER status (ER+, ER−, missing), treatment (radiotherapy only, chemotherapy only, radiation and chemotherapy, missing), hormones (yes, no, missing), and grade (1, 2, 3, missing).

[d]Model 4 adjusted for age, diagnosis date, race/ethnicity, region of residence at diagnosis, Census-tract median income, stage, ER status, treatments, hormones, grade, pre- to post-diagnosis weight change categories (stable, moderate gain, large gain, moderate loss, large loss, missing), post-diagnostic physical activity (<3, 3 to <9, 9 to <15, 15 to <24, 24+ MET-hours/week, missing), and post-diagnostic aspirin use (nonuser, current user, unknown).

Table 3

Adjusted HRs (95% CI) of breast cancer specific death for a 10 μg/m^3 increase in post-diagnosis PM stratified by stage at diagnosis

	$PM_{2.5}$	$PM_{2.5-10}$	PM_{10}	Events/ person-years
NHS				
Model 3[a]:				
Stage I	1.60 (1.05, 2.45)	0.95 (0.66, 1.35)	1.12 (0.89, 1.41)	293/52,795
Stage II	0.83 (0.54, 1.28)	0.85 (0.60, 1.20)	0.89 (0.71, 1.11)	329/22,457
Stage III	1.18 (0.73, 1.93)	1.13 (0.79, 1.61)	1.11 (0.86, 1.42)	277/6,192
p-value for interaction:	0.29	0.29	0.21	
Model 4[b]:				
Stage I	1.50 (0.97, 2.32)	0.93 (0.65, 1.33)	1.09 (0.86, 1.38)	293/52,795
Stage II	0.82 (0.52, 1.28)	0.86 (0.60, 1.22)	0.89 (0.70, 1.12)	329/22,457
Stage III	0.98 (0.59, 1.63)	1.06 (0.73, 1.53)	1.02 (0.79, 1.33)	277/6,192
p-value for interaction:	0.27	0.46	0.42	
NHSII				
Model 3[a]:				
Stage I	2.12 (0.90, 5.02)	1.43 (0.81, 2.52)	1.46 (0.96, 2.21)	94/15,004
Stage II	1.03 (0.46, 2.30)	1.24 (0.74, 2.07)	1.14 (0.77, 1.69)	112/9,484
Stage III	1.45 (0.59, 3.57)	0.96 (0.48, 1.92)	1.09 (0.68, 1.74)	106/3,403
p-value for interaction:	0.03	0.18	0.04	
Model 4[b]:				
Stage I	2.41 (0.98, 5.93)	1.40 (0.78, 2.51)	1.50 (0.97, 2.32)	94/15,004
Stage II	1.13 (0.51, 2.52)	1.18 (0.69, 2.03)	1.13 (0.75, 1.69)	112/9,484
Stage III	1.59 (0.58, 4.30)	1.07 (0.52, 2.20)	1.17 (0.70, 1.95)	106/3,403
p-value for interaction:	0.047	0.14	0.03	
Pooled Estimates				
Model 3[a]:				
Stage I	1.69 (1.16, 2.47)	1.09 (0.74, 1.61)	1.20 (0.96, 1.50)	387/67,799
Stage II	0.87 (0.60, 1.28)	0.97 (0.69, 1.38)	0.95 (0.76, 1.18)	441/31,941
Stage III	1.24 (0.81, 1.90)	1.09 (0.80, 1.50)	1.10 (0.89, 1.38)	383/9,595
Model 4[b]:				
Stage I	1.64 (1.11, 2.43)	1.07 (0.73, 1.56)	1.21 (0.90, 1.61)	387/67,799
Stage II	0.88 (0.60, 1.30)	0.94 (0.70, 1.27)	0.94 (0.76, 1.16)	441/31,941
Stage III	1.08 (0.69, 1.70)	1.06 (0.76, 1.48)	1.05 (0.83, 1.33)	383/9,595

Abbreviations: HR, hazard ratio; PM, Particulate matter; NHS, Nurses' Health Study; BMI, body mass index; MET, metabolic equivalent; ER, estrogen receptor

[a]Model 3 adjusted for age, diagnosis date, race/ethnicity, region of residence at diagnosis, and Census-tract median income as well as pre-diagnostic physical activity and BMI, and the following clinical factors: ER status, treatment, hormones, and grade.

[b]Model 4 adjusted for age, diagnosis date, race/ethnicity, region of residence at diagnosis, Census-tract median income, ER status, treatments, hormones, grade, pre- to post-diagnosis weight change categories, post-diagnostic physical activity, and post-diagnostic aspirin use.

Table 4

HRs (95% CI) of all-cause mortality for a 10 μg/m^3 increase in post-diagnosis PM among Stage I-III participants (n=6,499 for NHS and n=2,437 for NHSII).

	$PM_{2.5}$	$PM_{2.5-10}$	PM_{10}	Events/ Person- years
NHS				*2,241/81,443*
Model 1[a]	1.29 (1.11, 1.51)	1.03 (0.94, 1.13)	1.08 (1.00, 1.16)	
Model 2[b]	1.21 (1.03, 1.41)	1.13 (1.00, 1.26)	1.12 (1.03, 1.21)	
Model 3[c]	1.19 (1.02, 1.40)	1.10 (0.98, 1.23)	1.10 (1.01, 1.19)	
Model 4[d]	1.12 (0.95, 1.32)	1.11 (0.99, 1.25)	1.09 (1.00, 1.18)	
NHSII				*373/27,902*
Model 1[a]	1.21 (0.81, 1.79)	1.10 (0.87, 1.38)	1.10 (0.92, 1.32)	
Model 2[b]	1.21 (0.81, 1.81)	1.11 (0.84, 1.47)	1.11 (0.91, 1.36)	
Model 3[c]	1.07 (0.71, 1.61)	1.12 (0.84, 1.49)	1.08 (0.87, 1.32)	
Model 4[d]	1.09 (0.72, 1.66)	1.15 (0.86, 1.54)	1.10 (0.89, 1.37)	
p-value for cohort heterogeneity[d]	*0.91*	*0.81*	*0.90*	
Pooled Estimates				*2,614/109,345*
Model 1[a]	1.28 (1.11, 1.48)	1.04 (0.96, 1.13)	1.08 (1.01, 1.15)	
Model 2[b]	1.21 (1.04, 1.40)	1.12 (1.01, 1.25)	1.12 (1.03, 1.21)	
Model 3[c]	1.17 (1.01, 1.36)	1.10 (0.99, 1.22)	1.10 (1.02, 1.18)	
Model 4[d]	1.12 (0.96, 1.30)	1.12 (1.00, 1.24)	1.09 (1.01, 1.18)	

Abbreviations: HR, hazard ratio; PM, Particulate matter; NHS, Nurses' Health Study; BMI, body mass index; MET, metabolic equivalent; ER, estrogen receptor

[a]Model 1 adjusted for age and diagnosis date.

[b]Model 2 adjusted for age, diagnosis date, race/ethnicity, region of residence at diagnosis, and Census-tract median income as well as pre-diagnostic lifestyle factors including physical activity, BMI, and smoking (never, current, past, missing).

[c]Model 3 adjusted for the same covariates as model 2 and also includes clinical factor such as stage, ER status, treatment, hormones, and grade.

[d]Model 4 adjusted for age, diagnosis date, race/ethnicity, region of residence at diagnosis, Census-tract median income, stage, ER status, treatments, hormones, grade, pre- to post-diagnosis weight change categories, post-diagnostic physical activity, post-diagnostic aspirin use, and post-diagnostic smoking (never, current, past, missing).