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Metallic Air Pollutants and Breast Cancer Risk in a Nationwide Cohort Study

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Abstract

Background—Toxic metals show evidence of carcinogenic and estrogenic properties. However, little is known about the relationship between airborne metals and breast cancer. We evaluated the risk of breast cancer in relation to exposure to toxic metallic substances in air, individually and combined, in a U.S. wide cohort.

Methods—We recruited Sister Study participants (n=50,884), breast cancer-free women who had a sister with breast cancer, from 2003–2009. The 2005 Environmental Protection Agency National Air Toxic Assessment's census-tract estimates of metal concentrations in air (antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium) were matched to participants' enrollment residence. We used Cox regression to estimate the association between quintiles of individual metals and breast cancer incidence and weighted quantile sum regression to model the association between the metal mixture and breast cancer.

Results—2,587 breast cancer cases were diagnosed during follow-up (mean=7.4 years). In individual chemical analyses comparing the highest to lowest quintiles, postmenopausal breast cancer risk was elevated for mercury (hazard ratio [HR]=1.3, 95% confidence interval [CI]: 1.1–1.5), cadmium (HR=1.1, 95%CI: 0.96–1.3), and lead (HR=1.1, 95%CI: 0.98–1.3). The weighted quantile sum index was associated with postmenopausal breast cancer (odds ratio (OR)=1.1, 95%CI: 1.0–1.1). Consistent with the individual chemical analysis, the most highly weighted chemicals for predicting postmenopausal breast cancer risk were lead, cadmium, and mercury. Results were attenuated for overall breast cancer.

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Data and code are available for replication upon request (www.sisterstudy.niehs.nih.gov)

Conclusions—Higher levels of some airborne metals, specifically mercury, cadmium, and lead, were associated with a higher risk of postmenopausal breast cancer.

Keywords

breast cancer; metals; air pollution; cadmium; lead; mercury; mixtures

Introduction

Exposure to exogenous sex hormones (for example, hormone therapy) is an established risk factor for breast cancer[1]. However, little is known about the impact of environmental exposures with endocrine disrupting properties. [2] In addition, there has been increasing concern about health effects of environmental exposure to chemical mixtures. In particular, there has been a call for a better understanding of whether environmental endocrine disruptors, which may be biologically active even at low levels, act together to influence cancer risk.[3]

Exposure to metals from industrial and agricultural activities show some evidence of an association with breast cancer risk.[4] The general population is exposed to metals largely from their diet, water and the air,[5] as well as from cigarette smoking.[6] Metals have a long half-life[7] and can accumulate in breast tissue.[8] Metals have estrogenic properties,[9] and as such, are sometimes referred to as “metalloestrogens”.[4] In addition to possible endocrine disrupting effects, some metals have also been classified as known or suspected carcinogens.[10,11] Exposure to airborne metals is of interest, as recent studies have demonstrated an association between other measures of indoor and outdoor air pollution and breast cancer risk.[12–17] In the California Teacher’s Study, the authors observed an elevated risk of hormone receptor-negative breast cancer associated with airborne cadmium and arsenic levels in a select subgroup.[18] However, the association with other airborne metals and breast cancer risk has not been explored.

Individuals are often exposed to multiple environmental chemicals simultaneously and thus it is important to examine the relationship between chemical mixtures and disease risk.[19] Metal exposures often arise from similar sources, and thus exposure to certain metals may be correlated.[20] Therefore, our study objective was to evaluate the association between breast cancer risk and airborne exposure to metals, including antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium, considering the metals individually and as a mixture.

Methods

Study population

The NIEHS Sister Study is a nationwide prospective cohort study of 50,884 women that was designed to investigate environmental and lifestyle risk factors for breast cancer and has been described previously.[21] Briefly, during 2003–2009, women ages 35–74, who had a sister with breast cancer, were recruited throughout the US. Study participants completed an extensive computer-assisted telephone interview and self-completed questionnaires.

Participants are contacted annually and complete detailed follow-up questionnaires every 2–3 years. Response rates have remained >90% throughout follow-up.[21,22]

The Sister Study was approved by the institutional review boards of the NIH. Written informed consent was obtained from all participants. The results shown here include breast cancer cases diagnosed prior to July 31st, 2015 (Sister Study Data Release 5.02).

Outcome assessment

Study participants self-report their breast cancer diagnoses during follow-up surveys and annual health updates. Breast cancer incidence was defined as either ductal carcinoma *in situ* (DCIS) or invasive disease. We requested medical records and pathology reports to confirm diagnoses and obtain additional information regarding the tumor including estrogen receptor (ER) and progesterone receptor (PR) status and tumor staging. Medical records were successfully obtained for approximately 81% of cases. In the event that medical records are not available, self-reported data was used, which we have found to have a very high agreement with medical record information among those for whom both information sources were available.[23]

Exposure data

The Environmental Protection Agency (EPA) National Air Toxics Assessment (NATA) is a database that provides nationwide modeled airborne concentration information on hazardous air toxics (https://www.epa.gov/national-air-toxics-assessment). We used the 2005 NATA data release as it fell within the recruitment years for the NIEHS Sister Study (2003–2009). The 2005 NATA assessed emissions for 177 toxic substances in air using the National Emissions Inventory, a compilation of information on emissions from major point sources (factories, incinerators), non-point sources (dry cleaners, small manufacturers) and both on-road and non-road mobile sources (cars, trucks, and boats).[24] The model also incorporates supplementary information including secondary formation of toxics and background concentrations from long-range transport from distant sources or persistent from past years.[24] From these data, we used two validated air dispersion models that estimate concentrations for all ambient toxic pollutants in air. The HEM-3 (AERMOD version) model is used for point, on-road mobile, and non-road mobile sources and the ASPEN model is used for non-point sources.[24] The 2005 NATA database includes census-tract level concentrations ($\mu g/m^3$) for the metals antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium. The NATA data were linked to each study participant's geocoded baseline residence at the census-track level and categorized in quintiles.

Covariates

We obtained covariates, including demographics, socioeconomic status, and reproductive history, from the baseline interview. We assessed menopausal status and age at menopause at baseline and updated with subsequent follow-up questionnaires by asking about the timing of their last period or history of hysterectomy/oophorectomy. A trained examiner measured height and weight during a home visit.

Statistical Analysis

Overall breast cancer (n=2,587), including both invasive breast cancer and ductal carcinoma *in situ* (DCIS), was the main outcome of interest. We considered whether associations varied by invasive/DCIS status, menopausal status, or tumor ER status. Confounders were identified using a directed acyclic graph (Supplemental 1).[25] We adjusted all models for race (non-Hispanic white, other), education (≤high school or equivalent, some college, 4-year degree or higher), annual household income (<$50,000, $50,000-$99,999, $100,000+), marital status (never married, living as married/married, separated/divorced/ widowed), parity (continuous), census-track level median income (<$50,000, $50,000-$99,999, $100,000+), and geographic region (Northeast, South, Midwest, West). Missing values for covariates were minimal (<4%) and thus a complete case analysis was used.

Individual chemical analysis—To evaluate the association between quintiles of individual airborne metal levels and breast cancer risk, we used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). We explored restricted quadratic splines in modeling the relationship between metals and breast cancer risk; quintiles appeared to capture the associations well. Age was the time scale for the Cox model with follow-up accruing from age at baseline to age at breast cancer diagnosis or censoring (defined as the age of last follow-up or death). Trend tests were done using the p-value of a chi-square test using both the ordinal and continuous variable characterization in the adjusted Cox model. We considered overall breast cancer, pre vs postmenopausal breast cancer, ER+ vs ER- breast cancer and by breast cancer stage (stage 0 and 1 vs stage 2–4).

When evaluating the association between individual metals and the risk of an outcome such as ER subtype, we censored cases without the breast cancer subtype of interest at the time of diagnosis. We restricted ER analyses to invasive breast cancer cases as ER status is less frequently available for *in situ* disease. We tested heterogeneity by ER tumor status using a joint Cox model.[26] In analyses evaluating premenopausal breast cancer as an outcome, only women who were premenopausal at baseline were eligible. Premenopausal women were followed from age at baseline to age at premenopausal breast cancer diagnosis or censoring (including age at menopause). In analyses evaluating postmenopausal breast cancer as an outcome, women who were postmenopausal were eligible. They were followed from either age at baseline or age at menopause, whichever was later, to age at postmenopausal breast cancer diagnosis or censoring.

We evaluated the assumption of proportional hazards for the Cox model visually using log–log survival plots and via an interaction term in the model between each covariate and survival time (using an α=0.05). There was no evidence of time-variant associations. We evaluated effect measure modification on the multiplicative scale for length of time in baseline residence, current smoking status, BMI, geographic region, and number of first degree relatives with a family history of breast cancer using cross product terms and a likelihood ratio test.

We conducted the following sensitivity analyses for a select group of airborne metals: (1) we excluded person–time and cases diagnosed in 2003–2004 prior to exposure assessment in

2005, (2) we limited to women who did not report moving during the follow-up period, and (3) we investigated potential confounding by airborne polycyclic aromatic hydrocarbon (PAH) and benzene levels.

Weighted quantile sum analysis—The weighted quantile sum approach was used to estimate a weighted linear index to estimate the combined association of correlated compounds (10 airborne metals) scored as ordinal variables (quintiles) on breast cancer risk.

The dataset was randomly divided into a training and validation dataset (40% training, 60% validation). We empirically determined weights through bootstrap sampling (n=100) of the training set. The weights are constrained to sum to 1 and to range between 0 and 1, which functions to reduce dimensionality and address collinearity between metals. The unknown weights, w, are estimated in order to maximize the likelihood for b=1 to B using the following equation: $g(\mu) = \beta_0 + \beta_1\left(\sum_{i=1}^{c} w_i q_i\right) + z'\ \phi\ \big|_b$ with the constraints that $\sum_{i=1}^{c} w_i\big|_b = 1$, $0 \le w_i \le 1$ for i=1 to c and $\beta_1 > 0$ Where w_i is the weight for the ith metal q_i and $\sum_{i=1}^{c} w_i q_i$ is a weighted index for a set of c airborne metals, and the final constraint forces the detection of metals with a positive associations. The z term represents the vectors of covariates; ϕ is the coefficients of the covariates. The outcome of breast cancer is binary, so we used a logit link (g). We estimated weighted quantile sum as $\sum_{i=1}^{c} w_i q_i$, where $w_i = \frac{1}{n_b}\sum_{j=1}^{n_b} w_{ij}$ and n_b is the number of bootstrap samples where β_1 is statistically significant. The weighted quantile sum index is then tested in the validation dataset using the equation $g(\mu) = \beta_0 + \beta_1 WQS + z'\phi$.

Weights were calculated separately for overall breast cancer, postmenopausal and ER+ breast cancer and were used to calculate weighted quantile sum indices specific to each outcome. The weighted quantile sum method is limited by being constrained to associations that are all in the same direction and thus we did not estimate an association for either ER- or premenopausal breast cancer by this method as we observed individual chemicals to have both positive and negative associations with those outcomes.

We specifically selected the weight quantile sum method for this analysis because it can be used to estimate an overall mixture effect which is useful for understanding the combined impact of airborne metals while also identifying the bad actors driving the overall association. Additionally, prior simulation studies have shown it to have a good sensitivity and specificity compared to other mixtures analytic approaches.[27,28]

We performed descriptive analyses and individual metal analyses using SAS version 9.3 software (SAS Institute, Inc., Cary, NC). We performed weighted quantile sum analysis using the R package gWQS.[29]

Results

There were 2,587 breast cancer cases diagnosed during an average of 7.4 years of follow-up. Descriptive characteristics of the Sister Study cohort are shown in Table 1. The study population is composed largely of non-Hispanic White postmenopausal women. Airborne metal concentrations were highest for lead, followed by manganese, nickel, chromium, and arsenic (Supplemental Figure 2). Lower concentrations were estimated for selenium, cadmium, mercury, cobalt, and antimony. Airborne metal levels were only moderately correlated, with correlation coefficients (r) ranging largely from 0.2–0.5 (Supplemental Table 1).

Airborne metal concentrations were consistently higher for non-white study participants compared to white women (eTable 2). Women with higher educational attainment and annual household income tended to live in census tracks with higher concentrations of metals. Women who were married or living as married had lower air metal levels as did women with fewer children.

When considering the metals individually, comparing the highest to the lowest quintile, we observed a higher risk of overall breast cancer for mercury (Q5 vs. Q1, HR=1.2, 95% CI: 1.0–1.4; p_{trend}=0.03) and possibly cadmium (Q5 vs. Q1, HR=1.1, 95% CI: 0.96–1.3; p_{trend}=0.2) and lead (Q5 vs Q1, HR=1.1, 95% CI: 0.93–1.2; p_{trend}=0.5) (Table 2). Higher risk of breast cancer was also observed for other metals, including antimony (Q4 vs. Q1, HR=1.1, 95% CI: 1.0–1.3; p_{trend}=0.9); however, these trends were largely non-monotonic and observed associations did not persist into the 5th quintile. Higher levels of mercury was associated with postmenopausal (Q5 vs. Q1, HR=1.3, 95% CI: 1.1–1.5; p_{trend}=0.02), but not premenopausal breast cancer (Q5 vs. Q1, HR=0.92, 95% CI: 0.68–1.3 p_{trend}=0.8). HRs for postmenopausal breast cancer were also elevated for cadmium (Q5 vs Q1, HR=1.1, 95% CI: 0.96–1.3; p_{trend}=0.1), and lead (Q5 vs. Q1, HR=1.1, 95% CI: 0.98–1.3; p_{trend}=0.07). Inverse trends were observed for lead and nickel with premenopausal breast cancer although estimates of association were imprecise. Associations for invasive breast cancer and ductal carcinoma *in situ* were not statistically different. Trend tests for models using metal concentrations in the continuous form are shown in the supplemental materials (eTable 3).

Associations for metallic air toxics appeared to be stronger for ER+ disease compared to ER- (eTable 4). When we estimated relative HRs using the joint Cox model comparing the risk of ER+ breast cancer to ER-, the associations were largely in the positive direction, but these associations appeared to be driven by inverse associations with ER- breast cancer. The association between airborne metals and breast cancer stage was not consistent across the metals, although there was some evidence that mercury may be more strongly associated with early stage breast cancer (p *for trend*=0.05) (eTable 5).

In subgroup analyses, we observed that associations were stronger in women who were overweight/obese with a BMI ≥ 25 (eTable 6). The association with airborne metals also appeared to be higher in current smokers, especially cadmium (Q5 vs Q1, HR=2.1, 95% CI: 1.2–3.5) and selenium (Q5 vs Q1, HR=1.7, 95% CI: 1.0–2.8) (eTable 7). Associations did not vary by family history of breast cancer or by residential geographic region. Although

statistical interactions were not evident, results tended to be more pronounced in women who had lived in their baseline residence for more than 10 years (eTable 8).

In our sensitivity analyses, results did not materially change when we excluded person–time and cases diagnosed in 2003–2004, which was prior to exposure assessment in 2005 (eTable 9) or when we limited to women who did not report moving during the follow-up period (eTable 10). We also observed little evidence of confounding by airborne polycyclic aromatic hydrocarbon (PAH) and benzene levels (eTable 11).

The weighted quantile sum index was associated with postmenopausal breast cancer (OR=1.06, 95% CI:1.00, 1.13) but an association was less evident for overall breast cancer (OR=1.02, 95% CI: 0.98–1.08) or ER+ breast cancer (OR=1.03, 95% CI: 0.97–1.09). A quintile increase in the weighted quantile sum index estimated a 6% higher odds of postmenopausal breast cancer.

The estimated weights for each metal are shown in eTable 12. If all metals in the index received equal weights, the weight for each metal would be 0.1. Weights greater than 0.1 signify increased contribution to the weighted index than expected; higher weights indicate stronger associations with breast cancer. The most heavily weighted metals for postmenopausal breast cancer were cadmium (weight=0.23), lead (weight=0.22), and mercury (weight=0.21).

Discussion

In this large U.S.-wide prospective study, we evaluated the association between air toxic metals and breast cancer risk and observed that women who had higher census-track airborne metal concentrations at their residence were at an increased risk of postmenopausal breast cancer. In individual chemical analysis, we found higher levels of cadmium, lead, and mercury to be related to postmenopausal breast cancer. These findings were consistent with our weighted quality sum analysis which found an overall increase in risk for postmenopausal breast cancer and that the association was driven by cadmium, lead and mercury. This is to our knowledge the first prospective nationwide study to consider the association between these metallic air toxics and breast cancer.

Associations tended to be most evident for postmenopausal breast cancer, with results that were attenuated for overall breast cancer. Our finding of an increase in risk of postmenopausal breast cancer for higher airborne concentrations of metals is biologically plausible as metals are capable of activating estrogen receptor α,[30] inducing the proliferation of estrogen-dependent breast cancer cells,[9,30–32] and increasing the expression of estrogen-regulated genes.[30,31,33]. Metals have been classified as known and suspected carcinogens.[10,11] Other breast cancer risk factors, such as obesity, which can lead to local estrogen production as well as higher circulating estrogen levels,[34] have also been shown to have differential associations with breast cancer based on menopausal status at diagnosis.[35,36]

Women who had lived in their baseline residence for a longer period of time at enrollment tended to have a higher risk associated with airborne metals. However, these women were also more likely to be postmenopausal at diagnosis. Thus, the observed higher risk for

postmenopausal breast cancer may, in part, reflect a longer duration of exposure, and thus potentially more accurate exposure classification, at the baseline residence. We did not observe associations with ER+ breast cancer, except for an elevated risk in relation to higher mercury levels. The lack of association with other metals, such as cadmium and lead, may be due at least in part to decreased power as the individual HRs tended to be positive but attenuated relative to the associations observed for postmenopausal breast cancer.

Despite the biologic plausibility of an association between metals and breast cancer risk, previous studies using biomarkers for exposure assessment have been inconclusive. There is some evidence that metal concentrations, including cadmium, mercury, and lead, are higher in breast cancer tumor tissue than in tissue from normal controls.[8,37] Most prior epidemiologic research on metals and breast cancer risk has focused on cadmium.[38] Findings from cadmium studies have been inconclusive; case–control studies with urinary cadmium measurements have reported strong positive associations[38–42] whereas two prospective cohort studies did not observe an association.[43,44] To the best of our knowledge, no prior epidemiologic study has considered the association between mercury and breast cancer. There has been one study evaluating the association between urinary lead and breast cancer risk in a case–control study; they found no evidence of an association.[45] A recent systematic review concluded there may be an association between breast cancer risk and arsenic exposure in select subgroups.[46] Many of the prior studies were retrospective with samples collected after cancer diagnosis, thus the findings may also be influenced by reverse causation. Additionally, these studies of cadmium and lead have largely relied on urine markers, which may be influenced by kidney dysfunction which is prevalent in older adults.[47] Our results may also differ from prior studies due to differences in route of metal exposure; biomarkers measure exposure from multiple exposures, including from diet, tobacco smoke and water, whereas our study only considered airborne metal concentrations.

These results for a positive association between airborne pollutants and breast cancer risk are consistent with a prior study in the Sister Study cohort which reported an elevated risk of ER+PR+ breast cancer in relation to NO_2 levels.[14] A recent study of European cohorts found an association between breast cancer and the nickel component of PM10.[15] The California Teachers Study reported an elevated association for ER-PR- breast cancer and arsenic and cadmium in residentially-stable non-smokers.[18] We did not observe these associations, although we also observed an association for cadmium with postmenopausal breast cancer. However, our study differed from the California Teachers Study in important ways. First, we used an updated version of the NATA database which incorporates substantial changes in methodology.[24] Additionally, our study population is distributed across the U.S. rather than being limited to a single state. Air pollution sources and thus, resulting pollutant mixtures, may vary by geographic region and thus could explain the differing associations with breast cancer between our two study populations.[48]

The EPA National Air Toxics Assessment database relies on reported information to model airborne concentrations at the census-track level. Therefore, all women who live within the same census track are given the same exposure and, thus, this approach is less precise than data resulting from other approaches such as a land-use regression model that utilizes monitored data and estimates exposure at the residential level. EPA conducts validation

studies for the model, comparing modeled estimates to monitored ambient levels. However, as hazardous air pollutants are rarely monitored, these monitored levels are not considered good comparison group for a modeled yearly average. An independent validation study in California found good agreement between monitored data and certain air toxics in the 2005 NATA data release, although the modeled estimates tended to underestimate monitored data.[49] Despite this, NATA is the only nationwide, publicly available dataset of hazardous air pollutants.

We used the 2005 NATA data, rather than including prior data releases, because of the substantial changes in the methodology between versions.[24] As such, a limitation of this study is that we are only considering levels at the enrollment residence, which may not represent the most relevant exposure window. For example, early life exposure to metals may be particularly relevant for breast cancer incidence[50] as has been observed for other environmental exposures.[51] The studies on urinary cadmium levels, with higher risks observed in case–control studies[38] but null associations in cohort studies with longer follow-up time periods,[43,44] suggest that recent exposure may be an important time period as well. Approximately 80% of our study population remained in this baseline residence throughout the follow-up period suggesting that these exposure estimates may also reflect airborne metal levels up until diagnosis and a sensitivity analysis limiting to participants who have not moved during follow-up produced largely similar results.

An important strength of this study is the consideration of multiple metals simultaneously to better estimate the risk associated with metals overall and to adjust for any collinearity between metals. Many studies on environmental chemicals tend to neglect to consider the impact of multiple exposure sources. There is no current gold-standard in statistical mixtures approaches.[19] The weighted quality sum method has been previously shown to be highly sensitive and specific across a range of chemical correlations.[28] The method provides a summary measure of the association as well as identifies “bad actors” that most strongly contribute to the index. A limitation of the method is that it cannot incorporate associations that are in different directions and thus we were unable to reliably estimate the weighted quality sum for either premenopausal or ER- breast cancer for which both positive and negative, but imprecise, associations with individual chemicals were observed. Another limitation of the weighted quality sum approach is that it relies on logistic regression and cannot incorporate the time-to-event data that is used in our individual models.

This study population is composed, based on enrollment criteria, of women who have a sister with breast cancer and although this does not alter our internal validity the magnitude of results may not be generalizable to all women. Women are exposed to metals from multiple sources but the air toxics used here do not consider exposure from other sources. Additionally, the census-track level estimates used here do not fully account for an individual’s airborne exposure, which will vary based on their activities, work environment and commuting practices. Tobacco smoke is a major source of some metals such as cadmium, lead, mercury and nickel as well as other carcinogens.[6] We found that associations tended to be more pronounced in women who reporting smoking, suggesting a possible synergistic effect. Estimates were also higher in women who were overweight or obese. Metals can accumulate in adipose tissue, especially in visceral fat,[52] although the impact of

these on breast cancer risk is uncertain. It is possible that these women may have a higher body burden of metals, resulting in constant low-dose exposure, as has been hypothesized for polycyclic aromatic hydrocarbons.[53] However, there also may be benefit for storing toxic compounds in body fat although weight loss may result in release of these toxins.[54]

This is the first study to consider a wide range of metallic air toxics, both individually and simultaneously, in a nationwide sample of US women at risk for breast cancer. We found a higher risk of postmenopausal breast cancer for increasing exposure to ambient metallic air toxics, especially mercury, cadmium, and lead. Given the high prevalence of exposure to metals and the persistently high incidence of breast cancer in the US, these findings warrant further investigation of the associations between toxic metals and breast cancer risk and support efforts to reduce the levels of airborne toxic metals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline study population characteristics, NIEHS Sister Study, 2003–2009.

Study Characteristics	N	%
Age		
≤45	6,424	13
46–50	7,439	16
51–55	9,387	20
56–60	9,479	20
61–65	7,142	15
≥65	7,924	17
Menopausal Status		
Premenopausal	16,749	35
Postmenopausal	31,031	65
Race		
Non-Hispanic White	40,636	85
Non-white	7,159	15
Education		
High school graduate or less	7,178	15
Some college	16,178	34
Four-year degree or more	24,439	51
Annual Household Income		
<$49,999	11,834	25
$49,999-$99,999	19,673	41
≥$100,000	16,288	34
Census-track median income		
<$49,999	15,727	33
$49,999-$99,999	28,110	59
≥$100,000	3,958	8.3
Parity		
Nulliparous	8,781	18
1	7,051	15
2	27,194	57
≥3	4,769	10
Marital		
Never married	2,594	5.4
Married or living as married	35,674	75
Divorced, widowed or separated	9,527	20
Geographic Region		
Northeast	8,102	17
Midwest	13,083	27
South	16,020	34
West	10,590	22

Study Characteristics	N	%
BMI		
< 18.5	527	1.1
18.5–24.9	17,736	37
25.0–29.9	15,076	32
≥30.0	14,440	30
Smoking Status		
Never or former smoker	43,810	92
Current smoker	3,982	8.3

Table 2.

Metallic air toxics and breast cancer risk overall and by menopausal status at diagnosis, NIEHS Sister Study, 2003–2009.

		Overall			Premenopausal BC		Postmenopausal BC	
Metals	**Person-years (n=356,888)**	**Cases (N=2,574)**	**Age-adjusted HR (95% CI)**	**Adjusted HR (95% CI)[a]**	**Cases (N=536)**	**Adjusted HR (95% CI)[a]**	**Cases (N=2,034)**	**Adjusted HR (95% CI)[a]**
Antimony								
Quintile 1	71,703	489	1 (referent)	1 (referent)	101	1 (referent)	388	1 (referent)
Quintile 2	71,685	509	1.1 (0.94, 1.2)	1.0 (0.91, 1.2)	95	0.81 (0.61, 1.1)	414	1.1 (0.95, 1.3)
Quintile 3	71,015	551	1.2 (1.0, 1.3)	1.1 (0.99, 1.3)	113	0.86 (0.65, 1.1)	436	1.2 (1.0, 1.4)
Quintile 4	70,629	557	1.2 (1.1, 1.3)	1.1 (1.0, 1.3)	130	0.95 (0.72, 1.2)	425	1.2 (1.0, 1.4)
Quintile 5	71,040	462	0.98 (0.86, 1.1)	0.95 (0.83, 1.1)	95	0.69 (0.51, 0.94)	367	1.0 (0.88, 1.2)
P for trend				0.9		0.1		0.5
Arsenic								
Quintile 1	71,697	486	1 (referent)	1 (referent)	78	1 (referent)	408	1 (referent)
Quintile 2	71,027	517	1.1 (0.97, 1.2)	1.1 (0.92, 1.2)	119	1.2 (0.90, 1.6)	398	1.0 (0.88, 1.2)
Quintile 3	72,117	515	1.1 (0.96, 1.2)	1.0 (0.90, 1.2)	120	1.1 (0.81, 1.5)	393	1.0 (0.87, 1.2)
Quintile 4	70,720	543	1.2 (1.0, 1.3)	1.1 (0.96, 1.3)	117	1.1 (0.81, 1.5)	424	1.1 (0.94, 1.3)
Quintile 5	71,318	513	1.1 (0.96, 1.2)	1.0 (0.90, 1.2)	102	0.97 (0.71, 1.3)	411	1.1 (0.90, 1.2)
P for trend				0.6		0.5		0.3
Cadmium								
Quintile 1	71,257	486	1 (referent)	1 (referent)	86	1 (referent)	400	1 (referent)
Quintile 2	71,461	518	1.1 (0.95, 1.2)	1.1 (0.93, 1.2)	101	1.0 (0.77, 1.4)	415	1.1 (0.92, 1.2)
Quintile 3	71,559	509	1.1 (0.95, 1.2)	1.0 (0.92, 1.2)	121	1.1 (0.84, 1.5)	387	1.0 (0.88, 1.2)
Quintile 4	71,464	522	1.1 (0.97, 1.3)	1.1 (0.94, 1.2)	110	0.94 (0.70, 1.3)	411	1.1 (0.96, 1.3)
Quintile 5	71,138	539	1.1 (1.0, 1.3)	1.1 (0.96, 1.3)	118	1.0 (0.78, 1.4)	421	1.1 (0.96, 1.3)
P for trend				0.2		0.9		0.1
Chromium								
Quintile 1	71,700	487	1 (referent)	1 (referent)	86	1 (referent)	401	1 (referent)
Quintile 2	71,093	552	1.2 (1.0, 1.3)	1.1 (0.98, 1.3)	111	0.95 (0.71, 1.3)	441	1.2 (1.0, 1.3)
Quintile 3	71,401	526	1.1 (0.99, 1.3)	1.1 (0.92, 1.2)	122	1.0 (0.76, 1.4)	402	1.1 (0.91, 1.2)

		Overall			Premenopausal BC		Postmenopausal BC	
Quintile 4	71,894	512	1.1 (0.95, 1.2)	1.0 (0.89, 1.2)	104	0.85 (0.63, 1.2)	406	1.1 (0.91, 1.2)
Quintile 5	70,792	497	1.1 (0.94, 1.2)	1.0 (0.88, 1.2)	113	0.92 (0.68, 1.2)	384	1.0 (0.88, 1.2)
P for trend				0.5		0.4		0.7
Cobalt								
Quintile 1	71,203	472	1 (referent)	1 (referent)	88	1 (referent)	383	1 (referent)
Quintile 2	70,913	549	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	114	1.1 (0.86, 1.5)	435	1.2 (1.0, 1.3)
Quintile 3	71,214	552	1.2 (1.1, 1.3)	1.2 (1.0, 1.3)	109	1.1 (0.79, 1.4)	442	1.2 (1.0, 1.4)
Quintile 4	71,663	508	1.1 (0.96, 1.2)	1.1 (0.94, 1.2)	104	0.97 (0.72, 1.3)	403	1.1 (0.95, 1.3)
Quintile 5	71,078	487	1.1 (0.93, 1.2)	1.0 (0.91, 1.2)	119	1.1 (0.83, 1.5)	367	1.0 (0.87, 1.2)
P for trend				0.9		0.9		0.9
Lead								
Quintile 1	71,804	471	1 (referent)	1 (referent)	88	1 (referent)	383	1 (referent)
Quintile 2	70,988	532	1.2 (1.0, 1.3)	1.1 (0.98, 1.3)	130	1.2 (0.87, 1.5)	402	1.1 (0.95, 1.3)
Quintile 3	71,320	535	1.2 (1.0, 1.3)	1.1 (0.98, 1.3)	110	0.89 (0.66, 1.2)	423	1.2 (1.0, 1.4)
Quintile 4	71,595	532	1.2 (1.0, 1.3)	1.1 (0.97, 1.3)	108	0.85 (0.64, 1.2)	422	1.2 (1.0, 1.4)
Quintile 5	71,172	504	1.1 (0.98, 1.3)	1.1 (0.93, 1.2)	100	0.82 (0.61, 1.1)	404	1.1 (0.98, 1.3)
P for trend				0.5		0.02		0.07
Manganese								
Quintile 1	71,881	504	1 (referent)	1 (referent)	84	1 (referent)	420	1 (referent)
Quintile 2	70,989	541	1.1 (0.98, 1.3)	1.1 (0.95, 1.2)	121	1.2 (0.92, 1.6)	418	1.0 (0.91, 1.2)
Quintile 3	71,612	499	1.0 (0.90, 1.2)	0.98 (0.87, 1.1)	103	1.0 (0.75, 1.4)	396	0.99 (0.86, 1.1)
Quintile 4	71,931	534	1.1 (0.96, 1.2)	1.1 (0.93, 1.2)	124	1.1 (0.83, 1.5)	408	1.0 (0.90, 1.2)
Quintile 5	70,466	496	1.0 (0.90, 1.2)	1.0 (0.88, 1.1)	104	1.0 (0.76, 1.4)	392	0.99 (0.86, 1.2)
P for trend				0.8		0.8		0.9
Mercury								
Quintile 1	71,272	466	1 (referent)	1 (referent)	89	1 (referent)	377	1 (referent)
Quintile 2	71,402	520	1.1 (1.0, 1.3)	1.1 (0.97, 1.3)	98	0.90 (0.67, 1.2)	421	1.2 (0.99, 1.3)
Quintile 3	71,553	513	1.1 (0.99, 1.3)	1.1 (0.95, 1.2)	100	0.86 (0.64, 1.2)	411	1.1 (0.98, 1.3)
Quintile 4	71,621	530	1.2 (1.0, 1.3)	1.1 (0.98, 1.3)	134	1.1 (0.83, 1.5)	395	1.1 (0.96, 1.3)
Quintile 5	71,032	545	1.2 (1.1, 1.4)	1.2 (1.00, 1.4)	115	0.92 (0.68, 1.3)	430	1.3 (1.1, 1.5)
P for trend				0.02		0.8		0.02

	Overall				Premenopausal BC		Postmenopausal BC	
Nickel								
Quintile 1	71,794	519	1 (referent)	1 (referent)	102	1 (referent)	416	1 (referent)
Quintile 2	71,577	518	1.0 (0.90, 1.1)	0.97 (0.85, 1.1)	115	0.89 (0.68, 1.2)	402	0.98 (0.85, 1.1)
Quintile 3	71,942	517	1.0 (0.90, 1.2)	0.95 (0.84, 1.1)	112	0.81 (0.61, 1.1)	405	0.99 (0.86, 1.2)
Quintile 4	70,716	518	1.0 (0.91, 1.2)	0.97 (0.85, 1.1)	99	0.73 (0.55, 0.98)	418	1.0 (0.90, 1.2)
Quintile 5	70,850	502	1.0 (0.88, 1.1)	0.94 (0.83, 1.1)	108	0.78 (0.59, 1.0)	393	0.99 (0.85, 1.1)
P for trend				0.5		0.04		0.8
Selenium								
Quintile 1	70,972	481	1 (referent)	1 (referent)	86	1 (referent)	395	1 (referent)
Quintile 2	71,162	537	1.1 (1.00, 1.3)	1.1 (0.97, 1.3)	112	1.1 (0.85, 1.5)	425	1.1 (0.95, 1.3)
Quintile 3	71,053	513	1.1 (0.96, 1.2)	1.0 (0.92, 1.2)	107	0.98 (0.73, 1.3)	404	1.1 (0.91, 1.2)
Quintile 4	71,887	523	1.1 (0.97, 1.2)	1.1 (0.92, 1.2)	118	1.1 (0.81, 1.4)	403	1.0 (0.90, 1.2)
Quintile 5	71,805	520	1.1 (0.96, 1.2)	1.1 (0.93, 1.2)	113	0.97 (0.72, 1.3)	407	1.1 (0.93, 1.3)
P for trend				0.5		0.7		0.5

[a]Adjusted for race (non-Hispanic white, other), education (≤high school or equivalent, some college, 4-year degree or higher), annual household income (<$50,000, $50,000-$99,999, $100,000+), marital status (never married, living as married/married, separated/divorced/ widowed), parity (continuous), census-track level median income (<$50,000, $50,000-$99,999, $100,000+) and geographic region (Northeast, South, Midwest, West)