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## Residential Exposure to Estrogen Disrupting Hazardous Air Pollutants and Breast Cancer Risk: the California Teachers Study

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### Abstract

**Background**—Some studies show increased breast cancer risk from exposure to xenoestrogens, but few have explored exposures via ambient air, which could impact large populations.

**Objectives**—This study explored the association between breast cancer risk and residential exposures to ambient estrogen disruptors among participants in a large cohort study, the California Teachers Study.

**Methods**—Participants consisted of 112,379 women free of breast cancer and living at a California address in 1995/1996. Eleven hazardous air pollutants (HAPs) from the U.S. EPA 2002 list were identified as estrogen disruptors based on published endocrine disrupting chemical lists and literature review. Census-tract estrogen disruptor concentrations modeled by the U.S. EPA in 2002 were assigned to participants' baseline addresses. Cox proportional hazards models were used to estimate hazard ratios associated with exposure to each estrogen disruptor and a summary measure of nine estrogenic HAPs among all participants and selected subgroups, adjusting for age, race/birthplace, socioeconomic status, and known breast cancer risk factors.

**Results**—5,361 invasive breast cancer cases were identified between 1995 and 2010. No associations were found between residential exposure to ambient estrogen disruptors and overall breast cancer risk or hormone-responsive-positive breast cancer risk, nor among targeted subgroups of participants (pre/peri-menopausal women, post-menopausal women, never smokers, non-movers, and never-smoking non-movers). However, elevated risks for hormone-responsive-negative tumors were observed for higher exposure to cadmium compounds and possibly inorganic arsenic among never-smoking non-movers.

**Conclusion**—Long-term low-dose exposure to ambient cadmium compounds or possibly inorganic arsenic may be a risk factor for breast cancer.

## INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, accounting for approximately 25% of the total cancer cases and 14% of total cancer deaths in 2012.<sup>1</sup> Although the etiology of breast cancer is not fully-understood, risk factors identified by epidemiological studies have shown increased risk from exposure to endogenous estrogens during a woman's life based on early onset of menarche, nulliparity, late age of first pregnancy, less breast feeding and late menopause, as well as from exposure to exogenous estrogens such as hormone replacement therapy.<sup>2</sup> Limited evidence is beginning to emerge suggesting that breast cancer risk may also be increased with exposures to environmental agents with potential estrogenic effects.<sup>3-6</sup> However, exposures to these environmental agents are primarily localized via ingestion or skin contact, and almost no studies to date have examined associations between breast cancer risk and exposure to environmental estrogens via ambient air, which could impact large populations.

The Clean Air Act Amendments of 1990 identified 189 air toxics or hazardous air pollutants (HAPs).<sup>7</sup> Subsequent to the passage of these Amendments, the U.S. Environmental Protection Agency (EPA) developed the National-Scale Air Toxics Assessment (NATA) program to evaluate health risks due to exposure to HAPs in the U.S. As part of the program, NATA has estimated annual concentrations for some HAPs triennially since 1996, using emissions data compiled by the National Emissions Inventory, dispersion models, meteorological data and release parameters (e.g. stack height, exit velocity, emission rates, etc.).<sup>8</sup> Some HAPs have potential endocrine disrupting effects on the estrogen system.<sup>9</sup> The purpose of this study was to use the NATA data to examine breast cancer risk due to exposure to those HAPs with estrogen disrupting properties among women in the California Teachers Study (CTS).

## METHODS

### Study Population

The CTS is a multi-institutional prospective cohort study consisting of 133,479 women who responded to a 1995-96 mailing to all active and retired female enrollees in the State Teachers Retirement System. For this analysis, CTS participants were excluded (in sequence) for the following reasons: lived outside California at baseline (n=8,867); asked to be removed from the study after joining (n=1); had unknown history of prior cancer (n=139), had a prior history of invasive or in situ breast cancer (n=6,211); or had an address that could not be geocoded (n=5,882). A total of 112,379 women were included in this study. The CTS was approved by the Institutional Review Boards at all participating institutions.

### Outcome Assessment

The CTS cohort is followed annually for cancer diagnosis through annual linkages with the California Cancer Registry (CCR). The CCR is a legally mandated statewide population-based cancer reporting system, modeled after the National Cancer Institute's Surveillance,

Epidemiology and End Results program; it maintains the highest standards for data quality and completeness and is estimated to be 99% complete [<http://www.ccrca.org/>]. Thus, as long as CTS participants remain California residents, cancer follow-up is essentially complete. Approximately 90% of the active cohort remained in California during the study period.

Incident cases of invasive breast cancer (ICD-O-3 site codes C500-C509, excluding those with histology codes of 9050-9055, 9140 and 9590-9992), diagnosed prospectively from baseline (1995/1996) through 2010, constitute the cases for the present analysis. Tumor estrogen receptor (ER) and progesterone receptor (PR) status was obtained from CCR records and cases were classified into two groups: hormone receptor positive (ER+ or PR+), and hormone receptor negative (ER- and PR-). 85% of the cases had ER and PR information during the follow-up period; the proportions of cases with this information ranged from 77% to 83% from 1995 to 2003, and ranged from 88% to 96% from 2004 to 2010.

### Covariate Information

Data on personal breast cancer risk factors were collected from the CTS baseline questionnaire and included information on: age at baseline (years), race/birthplace (white, non-white U.S. born, non-white foreign born, other/unknown); family history of breast cancer (no, yes, unknown); age at menarche (11, 12-13, 14 years, unknown/never); age at first full-term pregnancy (nulliparous, 24, 25-29, 30 years, unknown); breast feeding history (nulliparous, pregnant but no live birth, and among those with at least one live birth: never breastfed or breastfed <6, 6-11, 12 months, unknown); strenuous physical activity (lifetime average to age 54: 0-0.50, 0.51-2.00, 2.01-3.50, 3.51-5.00, >5.00 hours/week, unknown); body mass index (BMI 24.9, 25.0-29.9, 30.0 kg/m<sup>2</sup>, unknown); alcohol consumption (none, <20, 20 gram/day, unknown); menopausal status and hormone therapy (HT) use at baseline (premenopausal; among peri/post-menopausal: never used HT, former HT use, current estrogen use, current estrogen/progestin use; other/unknown); smoking exposure categories (no passive/active smoking, passive smoking only, former smoker, current smoker); and pack-years of smoking (never smoker, 10, 11-20, 21-30, 31 pack years, unknown).

Measures of neighborhood socioeconomic status (SES) were based on 2000 U.S. census block group data, which included: percentage of adults over age 25 years having completed a college degree or higher; percentage of adults without a high school degree; median family income; percentage of adults employed in managerial/professional occupations; and percentage of population below the poverty line. To address the high degree of collinearity between these measures, a composite measure of SES was created using principal components analysis based on the five individual variables described above. The loadings of the first principal component, categorized into quartiles, were then used in this analysis.

### Follow-up

State and national mortality files, as well as reports from relatives, were used to ascertain date and cause of death. To identify movers during the follow-up period, address changes were obtained by several methods including annual mailings, notifications of moves received

from participants, and linkages to nationwide consumer reporting companies and the U.S. Postal Service National Change of Address database.

Follow-up time was calculated as the number of days between the day when a participant completed her baseline questionnaire and the earliest of four dates: the date of her invasive breast cancer diagnosis; the date of her first non-California residential address lasting 4 months or longer; the date of her death; or December 31, 2010. Participants who were diagnosed with in situ breast cancer during the follow-up period were censored at the time of their diagnoses.

### Identification of Hazardous Air Pollutants with estrogen disrupting effects

A consolidated listing of 966 chemicals purported to be endocrine disrupting compounds (EDCs) was released in 2005 by the Institute of Environment and Health (IEH) of the University of Leicester. The list is based on original studies or reviews from peer-reviewed journals and various reports by national or international governmental and non-governmental organizations published between 2000 and 2002.<sup>9</sup> This list includes notes on which hormone systems can be affected for some chemicals. Another comprehensive list of 906 potential EDCs has been posted online by the Endocrine Disruptor Exchange Inc (Paonia, CO),<sup>10</sup> based on published peer-reviewed studies. A total of 436 chemicals are commonly identified by the two lists based on the Chemical Abstracts Service Registry Numbers, which are not available for all chemicals on the two lists. These two lists were used to identify EDCs among HAPs.

Directly measured concentrations of HAPs that are time and space representative are extremely limited. However, the U.S. EPA NATA has produced sophisticated, census-tract level modeled concentrations of a variety of HAPs over several time periods: 33 HAPs in 1996, 177 in 1999, 181 in 2002 and 178 in 2005, with significant improvements in methodology in the later years.<sup>8</sup> These modeled concentrations were calculated from information on 1) major stationary and area sources, based on estimated emissions from National Emissions Inventory; 2) onroad and nonroad mobile sources; and 3) estimated background HAP concentrations, and then summarized by census-tract level averages. More details can be found from the NATA 2002 website.<sup>11</sup>

Estimates of ambient HAP concentrations in 2002 were used as a proxy for participants' exposure during follow-up time in this study for the following three reasons. First, a study comparing modeled estimates of 12 HAPs in California with monitored concentrations provided by the California Air Resources Board demonstrated that, for most HAPs, modeled ambient concentrations agreed much better with monitored levels in 2002 and 2005 than in previous years.<sup>12</sup> Unfortunately, of the 12 HAPs for which modeled and monitored concentrations were compared, only one, styrene, was included in the 11 estrogen disrupting compounds chosen. (See below for criteria used to identify estrogen disruptors.) Second, the correlation between 2002 and 2005 of each of the chosen NATA-modeled estrogen disruptor concentrations was very high, with Spearman correlation coefficients of approximately 0.8 for dibutylphthalate, diesel emissions and dimethyl formamide, and above 0.9 for the other 8 chemicals. Finally, the year 2002 is closer to the midpoint of the follow-up period of this study (1995–2010) than is 2005.

The identification of the 11 estrogen disruptors among HAPs for this study was based on four criteria: 1) the pollutant was modeled by the EPA NATA in California in 2002; 2) the pollutant was listed by IEH<sup>9</sup> or TEDX as a potential EDC<sup>10</sup>; 3) the pollutant was reported to be a potential estrogen disruptor by IEH<sup>9</sup> or at least one published peer-reviewed study; and 4) participants' exposure to the pollutant had sufficient variability in California, with at least 25% of the participants having different assigned concentrations. The final included pollutants consisted of the following: inorganic arsenic compounds (including arsine), biphenyl, cadmium compounds, chlorobenzilate, bis(2-ethylhexyl) phthalate, dibutylphthalate, dimethyl formamide, 4-nitrophenol, styrene, diesel engine emissions and selenium compounds. Selenium compounds are reported to have anti-estrogenic effects, diesel emission is a mixture of estrogenic compounds and anti-estrogenic compounds, and the remaining 9 pollutants are reported to have potential estrogenic effects. eTable S1 in the supplemental material summarizes the exposure sources for the general population and the potential estrogen disrupting effects for these chemicals.

### Exposure assessment

Annual ambient concentrations of the 11 estrogen disruptors estimated by NATA at the census-tract level for 2002 were assigned to all CTS participants living in the corresponding tracts based on their baseline residential addresses. To estimate participants' total exposure to the 9 estrogenic HAPs, an exposure potential index (EPI) was calculated for each census tract and then assigned to participants within corresponding tracts. The following method was used to calculate the EPIs: 1) calculating a rank score for each of the 9 estrogenic HAPs across the 7049 California census tracts, where ties were replaced by the minimum rank, and then shifting and scaling the rank scores so that the rank scores for each HAP ranged from 0 to 1; 2). creating a summary EPI for each census tract by summing across the 9 rank scores, and then shifting and scaling the summary EPIs across the census tracts so that the EPIs ranged from 0 to 1.

### Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for each pollutant, and for the summary EPI of the 9 estrogenic HAPs. Age at the start and end of follow up (in days) was used to define time on study. Participants' assigned exposure was categorized into quintiles. Two types of models were used for the risk analysis. One adjusted for race/birthplace only and stratified by age; the other also stratified by age, but used backward selection, starting with all individual-level covariates and neighborhood SES and adjusting only for those covariates for which a *p*-value in the backward selection model was less than 0.15, with race/birthplace and the chemical of interest forced into the models. Risk analyses were run for all participants and for subgroups of menopausal status: pre/peri menopausal status or post menopausal status at baseline. To minimize unaccounted sources of exposure due to smoking and potential misclassification of residential exposures, risk analyses were also conducted among never smokers at baseline, women who did not change their residential addresses between 1995/1996 to 2010 (non-movers), and never smoking non-movers. Risk analyses were also conducted separately for subtypes of breast cancers based on hormone responsiveness. Results from these subgroup analyses are presented only for those compounds showing "results of interest" (i.e., the HR

for at least one quintile had a 95% CI that excluded one and a coherent pattern of HRs was observed for all the quintiles). Variables included in final models were enumerated in footnotes to tables presenting risk analysis results.

Pairwise Spearman correlation analysis was conducted between all compounds. For compounds showing “results of interest” in the risk analysis, model comparisons were performed to examine the potential impact of correlations between compounds on the risk analysis results, using the partial likelihood ratio to test two nested models: one with two compounds of high correlation compared to a nested model with one compound. For these tests, the quintile data were treated as variables with integer values one through five, and simple one-degree-of-freedom tests were used to compare models. All the data analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, NC, U.S.) and R 3.02 (R Development Core Team, Vienna, Austria).

## RESULTS

The median age of participants at baseline was 51 years, with a range of 22-104. Similar to the full CTS cohort, participants were predominantly white (86%), never smokers at baseline (66%) and without a family history of breast cancer (85%). A full description of the cohort can be found in eTable S2 of the supplemental materials. A total of 5,361 invasive breast cancer cases were diagnosed during the follow-up period, with 3,884 hormone-receptor-positive cases, 663 hormone-receptor-negative cases, and 814 with unknown tumor hormone responsiveness. Table 1 summarizes the number of outcomes for all participants and for targeted subgroups. While the majority of the cases were postmenopausal, residentially stable, and non-smokers at baseline, there were a substantial number of cases in all the targeted subgroups of interest.

Figure 1 shows the distributions of participants’ estimated exposures. All participants lived in census tracts with some estimated level of each estrogen disruptor, except for chlorobenzilate, for which 72% of the participants had an assigned exposure value of 0. While the inter-quartile range of participants’ exposure was narrow for all the pollutants, with the 75<sup>th</sup> percentile less than 15 times the 25<sup>th</sup> percentile, there was a wide range of estimated values for most chemicals. Medians and ranges of quintiles for all pollutants were presented in eTable S3 in the supplemental materials.

Table 2 presents the adjusted HRs for invasive breast cancer among all study participants for each of the estrogen disruptors and the summary EPI of the 9 estrogenic HAPs. Participants’ exposure was grouped into quintiles, with the lowest quintile as the reference group. HRs estimated by the models that adjusted for race/birthplace alone were quite similar to HRs estimated by the backward selection models that adjusted for more covariates. Slightly increased risk were observed among participants in the 2<sup>nd</sup> exposure quintile of biphenyl and cadmium compounds, in the 4<sup>th</sup> quintile of chlorobenzilate, and in the 2<sup>nd</sup> and 3<sup>rd</sup> quintiles of bis(2-ethylhexyl) phthalate.

The pattern of results was generally similar for pre/peri menopausal women, post-menopausal women, never smokers, and non-movers, and when restricted to subtypes of



invasive breast cancers defined by tumor hormone responsiveness. Although some marginal effects were observed among some of these subgroups of participants for some quintiles of exposures, no coherent pattern of risk were observed.

Subgroup analyses that were restricted to residentially stable non-smokers, who were supposed to have the best exposure assessment, however, did suggest some elevation in risk associated with cadmium and arsenic. Among this subgroup of the study population, there were elevated risks of hormone-receptor-negative breast cancer for exposures to inorganic arsenic compounds at the highest exposure quintile (HR=1.65; 95% CI=1.08-2.53), and for exposure to cadmium compounds at the two highest exposure quintiles (HR=1.58; 95% CI=1.05-2.40 for quintile 4, and HR=1.64; 95% CI=1.08-2.49 for quintile 5) (Table 3 and Figure 2). Elevated risks, however, were not observed for all breast cancers combined nor for the hormone-receptor-positive tumors. Risk analysis results for exposure to inorganic arsenic compounds and cadmium compounds for all strata defined by smoking status and residential stability were presented in eTable S4 in the supplemental materials.

Figure 3 shows a heat map of pairwise Spearman correlation coefficients ( $R_s$ ) for all compounds (except Chlorobenzilate, which had zero values for 72% of the estimated concentrations), where the compounds have been ordered to highlight the separation of inter-compound correlations into two distinct groups with significant within-group correlation but only modest between group correlation: the metal and non-metal compounds. Within the metal compounds, participants' estimated arsenic exposure was moderately correlated with estimated cadmium exposure ( $R=0.6$ ) and selenium exposure ( $R=0.5$ ), but not with other chemicals ( $R<0.3$ ). Participants' estimated cadmium exposure was also highly correlated with selenium exposure ( $R=0.8$ ). Model comparisons showed that adding selenium to an adjusted univariate model of hormone-receptor-negative breast cancer risk among residential stable non-smokers containing cadmium produced a model with little additional fit to the risk data ( $p=0.66$ ), while adding cadmium to an equivalent model containing selenium produced a model with a better fit to the risk data ( $p=0.045$ ), indicating that the risk elevations seen for cadmium were unlikely to be driven by the high degree of correlation with selenium. Similar analysis showed that adding arsenic to a model containing cadmium resulted in a model with little additional fit ( $p=0.71$ ), while adding cadmium to an equivalent model containing arsenic produced a model with a better fit ( $p=0.048$ ), indicating that the risk elevations observed for arsenic might be driven by its correlation with cadmium.

## DISCUSSION

Epidemiological studies showing positive associations between breast cancer risk and markers of air pollution are accumulating. Previous studies have shown increased breast cancer among women living close to industrial facilities or traffic emissions,<sup>13-15</sup> and have suggested that exposure to elevated levels of ambient particulate matter, nitrogen dioxide, carbon monoxide, sulfur dioxide or volatile organic compounds may be positively associated with increased breast cancer risk.<sup>13,16-18</sup> Although these studies might have captured proxies of exposures that may disrupt the estrogen system, this study, however, is the first to examine risks specifically focused on specific constituents that are estrogen disruptors in ambient air. In the present study, there was no evidence for overall increased breast cancer

risk among women living in neighborhoods with high levels of estrogen disruptors in the ambient air, with the exception of an increase in risk of hormone-receptor-negative breast cancer among residentially stable non-smokers for both cadmium and inorganic arsenic compounds.

There is some evidence in the literature that exposure to cadmium or inorganic arsenic compounds may be a risk factor for breast cancer. Higher cadmium concentrations were reported in breast tissue from breast cancer patients than from normal breast tissue.<sup>19,20</sup> Some epidemiologic studies have observed increased risk of overall breast cancer among women with higher urinary cadmium levels,<sup>3,21-23</sup> while one reported no association for dietary cadmium intake.<sup>24</sup> Several studies have reported elevated risks associated with cadmium that were confined to only ER+ tumors.<sup>21,25</sup> Julin et al,<sup>4</sup> however, reported increased risk for all breast cancer, ER+ tumors and ER- tumors associated with higher dietary cadmium exposure, though the ER- association was based on small numbers.

Epidemiological studies of arsenic exposure and breast cancer risk are fewer. A nested case-control study among nurses in the U.S. did not observe any increased risk of breast cancer among all or postmenopausal women with higher toenail arsenic levels.<sup>26</sup> One ecologic study in Australia observed an elevated incidence of breast cancer in regions with higher inorganic arsenic in soil or water,<sup>27</sup> while another ecologic study in Argentina did not find any association between breast cancer risk and arsenic concentrations in drinking water.<sup>28</sup>

Most breast cancer risk studies of cadmium and arsenic exposures have either relied upon body burden measurements or have focused on dietary sources, which are expected to contribute a much higher proportion of total exposure than those from ambient air.<sup>29</sup> However, both in vitro and in vivo studies show that cadmium and inorganic arsenic compounds are estrogenic,<sup>30,31</sup> and accumulating evidence has shown that endocrine disruptors act at low doses that may be environmentally relevant to human exposures.<sup>32</sup> Thus, there is some evidence to support the biological plausibility that long-term low-dose exposure to estrogen disrupting cadmium or inorganic arsenic compounds from ambient air could increase breast cancer risk.

While it is recognized that the etiology of breast cancer probably differs for the hormone-receptor defined subtypes of breast cancer, it is not entirely clear how these profiles differ. Exposures associated with reproductive history, such as early menarche, nulliparity and delayed childbearing, tend to be associated with hormone receptor-positive breast cancers, while the etiology of ER- tumors is largely unexplained.<sup>33</sup> The associations observed in the present study may seem counterintuitive with the widely accepted mechanism by which estrogens may cause breast cancer by binding with ERs.<sup>34</sup> The underlying mechanism by which arsenic or cadmium interacts with the estrogen pathway, however, remains unclear. Some in vitro and in vivo studies show cadmium and arsenic to mimic estrogen activity via the classic pathway mediated by ERs,<sup>35-37</sup> while more recent studies show that both arsenic and cadmium can induce basal-like cancer cell phenotypes in hormone-receptor-negative breast epithelial cell lines.<sup>38,39</sup> Additionally, evidence has supported mechanisms independent of ERs in estrogen-mediated breast cancer development through production of genotoxic estrogen metabolites (such as catechols and quinines), which can cause DNA



damage and/or form DNA adducts.<sup>34</sup> These observations provide some biologic rationale to support the findings in the present study implicating exposure to arsenic or cadmium for risk of hormone-receptor-negative breast cancer. It is worth noting that cadmium compounds cause lung cancer by causing genomic instability via DNA-repair inhibition and disturbance of tumor-suppressor proteins; and inorganic arsenic causes cancer in lung, skin and urinary bladder due to oxidative DNA damage, genomic instability, aneuploidy, etc.<sup>40</sup> It is possible that these mechanisms may increase risk for hormone-receptor-negative tumors but not for hormone-receptor-positive tumors.

There is also evidence that EDCs can produce a non-linear and potentially non-monotonic dose-response relationship (NMDRR). NMDRRs have been observed in some epidemiological studies that examined the association between body burden of environmental exposure to persistent organic pollutants or heavy metals and metabolic diseases or disorders among National Health and Nutrition Examination Survey participants.<sup>32</sup> While the present study yielded some evidence of potential non-monotonic dose-response relationships in the low-dose range, the effect sizes were generally close to unity. Since CTS participants' exposure levels from ambient air should be low enough to expect a monotonic dose-response curve if there in fact is one, suggestive NMDRRs observed between breast cancer risk and exposure to other chemicals examined in the present study were likely due to chance.

The backward selection models used in this study might result in some over adjustment, as not all variables associated with outcome might be confounders. Although alternative covariate selection methods, such as change-in-estimate approaches or those based on directed acyclic graphs, might perform better in terms of providing more parsimonious models, these methods were not explored due to the high similarity between the crude and adjusted results obtained in the risk analysis results. Another limitation in the present study was the inability to fully examine the effects of mixtures of estrogen disruptors. The creation of the summary EPI for 9 estrogenic compounds was designed to evaluate risks associated with a mixture of compounds that share similar mechanistic effects (i.e. estrogenic). But, similar to most epidemiological studies, the present study was not able to evaluate the potential interactions between different pollutants. An alternative way to examine the overall effect of multiple xenoestrogens on breast cancer would be to use biomarkers of total estrogenic activity to assess the total exposure. This approach, however, may present other limitations such as variations in individual metabolism, distinguishing endogenous and exogenous estrogens, and linking effects to exposure sources for the purpose of risk reduction. In addition, this study was not able to account for combined involvement of estrogen disruptors from dietary, household and cosmetic sources. However, this issue is not limited to the present study; rather it is common for all epidemiological studies examining health effects of xenoestrogens.<sup>6</sup> Furthermore, it is challenging to examine health risks of multipollutants that are highly correlated. Elevated health risk observed for one pollutant may be due to its high correlation with another pollutant. While in this study single-pollutant models yielded elevated risks for hormone-receptor-negative breast cancer for both arsenic and cadmium, comparisons of model fit for single pollutant versus two-pollutant models suggest that the elevated risks for exposure to cadmium compounds are unlikely due to its high correlation with other compounds, while the possibility that the risks for exposure to

arsenic compounds is due to its correlation with cadmium compounds could not be dismissed.

It is also worth noting that there are some sources of potential exposure misclassification in this study. First, breast cancer likely occurs in response to exposure over an extended period of time, and the use of NATA data for the year of 2002 assumed consistency of exposure over the period of observation, failing to account for changes in lifestyles or activities during different periods of life, and different temporal variations in ambient air concentrations in different geographic areas. For example, ambient arsenic concentrations modeled by NATA increased by >15% from 1999 to 2002 in about 80% of the California census tracts, while they decreased by >15% in about 10% of the census tracts; modeled ambient cadmium concentrations decreased by >15% from 1999 to 2002 in about 75% of California census tracts, while they increased >15% in 10% of the census tracts. However, it is not possible to distinguish whether these changes in modeled concentrations are due to real changes or changes in modeling methods and/or availability of emission data.<sup>8</sup> Second, participants' exposures were assigned based on residential addresses at baseline, failing to account for residential mobility and time spent at work. Third, participants resident within the same census tract were assumed to have uniform exposures when in fact they might have different exposures due to varying proximity to emission sources such as traffic or some toxics release facilities. Lastly, other sources of exposure, such as smoking and diet, may be more important than ambient air for estrogen disruptors such as cadmium and arsenic compounds for some participants. Risk analyses restricted to never smoking non-movers during the follow-up period were designed to partially reduce these sources of misclassification. Future studies with more sophisticated exposure assessment approaches to reduce potential exposure misclassification are needed to identify the true impact on breast cancer imposed by ambient estrogen disrupting pollutants.

## CONCLUSIONS

A significantly elevated incidence of hormone-receptor-negative breast cancer was observed among CTS participants who were residentially stable non-smokers and lived in neighborhoods characterized by higher exposure to cadmium compounds and possibly inorganic arsenic compounds in ambient air. No significant associations were generally evident for breast cancer risk and participants' exposure to other ambient estrogen disruptors. This study suggests that long-term low-dose exposure to cadmium and possibly inorganic arsenic compounds from ambient air may be a risk factor for hormone-receptor-negative breast cancer, although the underlying mechanisms require further exploration. Future studies with more sophisticated exposure assessment techniques are warranted to reduce potential exposure misclassification and to address the challenge of exposure to mixtures of estrogen disruptors.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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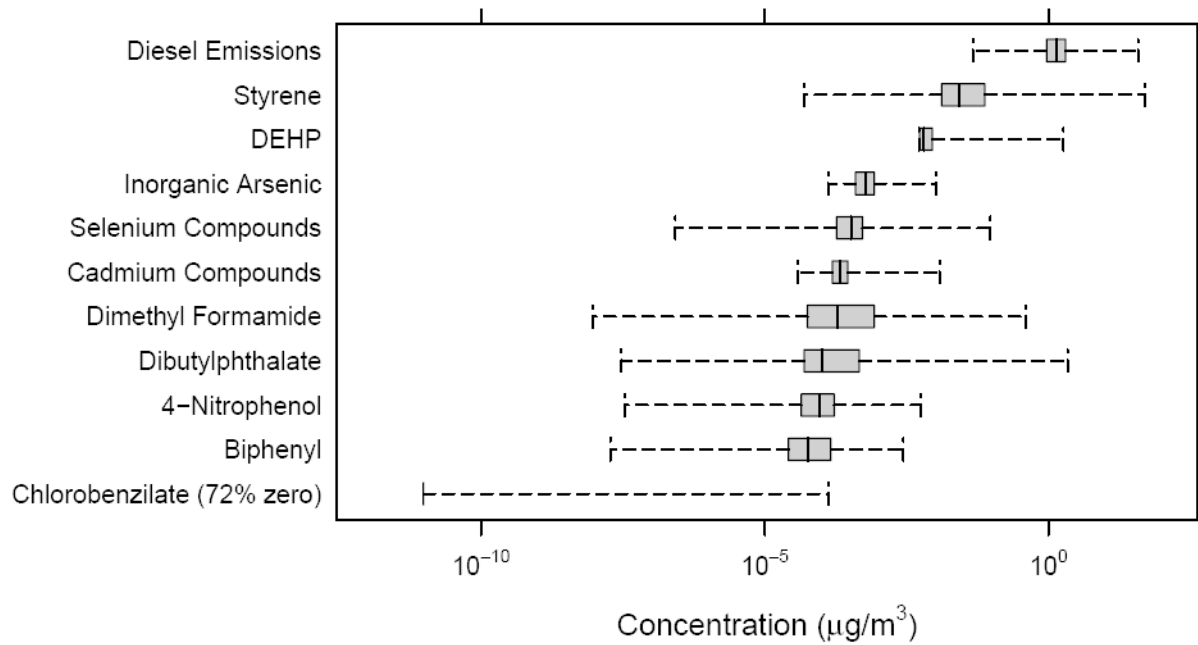
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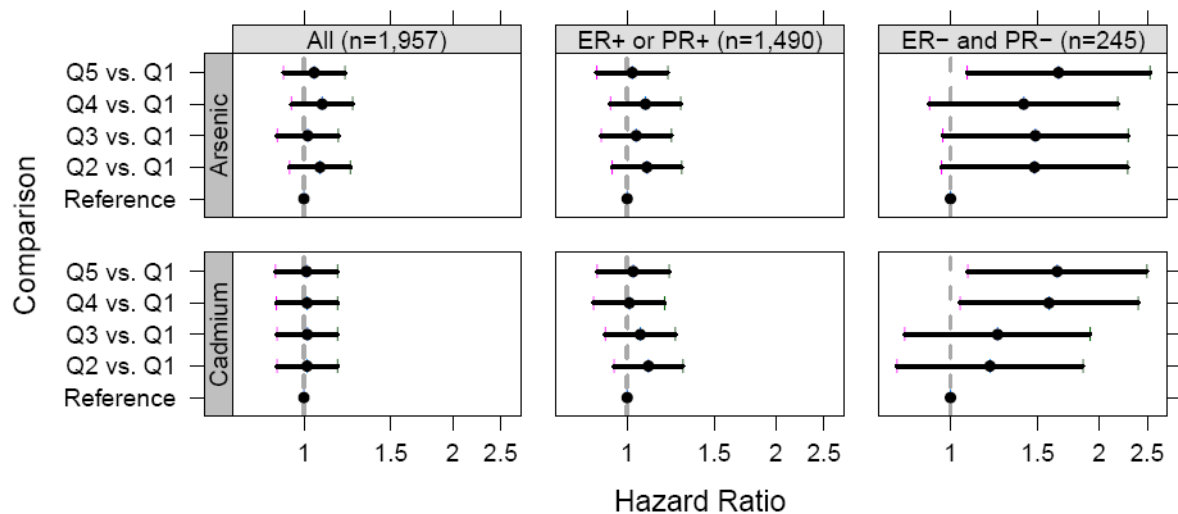
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**Figure 1.**

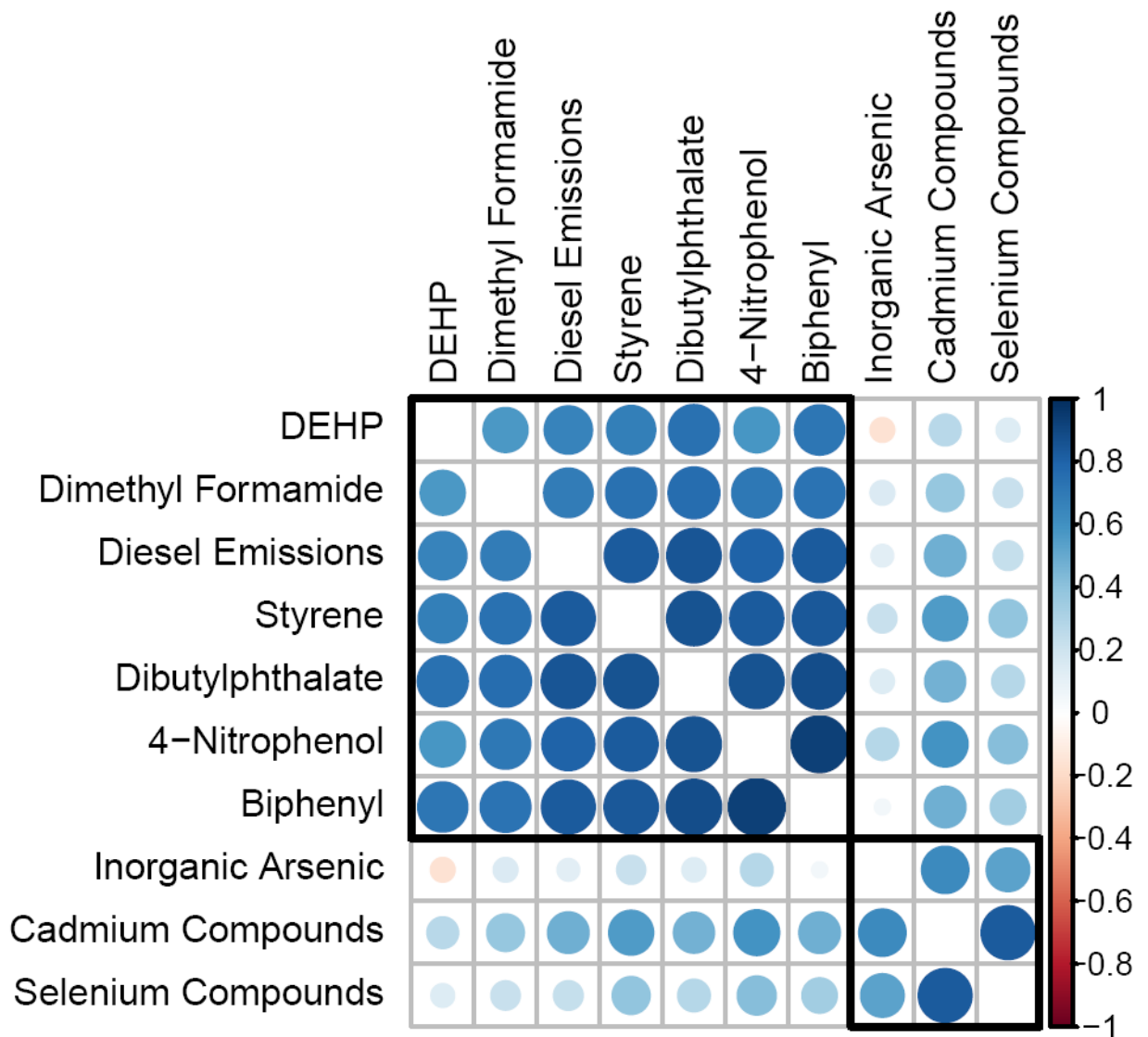
Distribution of concentrations for the eleven estrogen disruptors to which the study participants were exposed, shown on a log scale. Except for chlorobenzilate, the estimated concentration for each estrogen disruptor was greater than zero for every participant. For chlorobenzilate, 72% of the estimated exposure concentrations were zero and are not shown. The vertical line in the box represents the median, the box represents the interquartile (the 25<sup>th</sup> and the 75<sup>th</sup> percentiles) range, and the whisker bars represent the minimum and maximum values. DEHP is an abbreviation for bis(2-ethylhexyl) phthalate.





**Figure 2.**

Hazard ratios and 95% CIs for exposure to inorganic arsenic and cadmium compounds and breast cancer among residentially stable never smokers (n=38,426). For each panel, n indicates number of cases for that group of tumors. Risk models for all invasive breast cancer or ER+ or PR+ breast cancer were adjusted for age, race/birth place, family history of breast cancer, alcohol consumptions, body mass index (BMI), age at menarche, age at first full-term pregnancy, and menopausal status and hormone therapy use at baseline; and risk models for ER- and PR- breast cancer were adjusted for age, race/birthplace, family history of breast cancer, alcohol consumptions and BMI.



**Figure 3.**

Heat map of pairwise Spearman correlation coefficients for 10 estrogen disrupting compounds. For chlorobenzilate, 72% of the estimated exposure concentrations were zero and are not shown in the map.

Table 1

Selected characteristics of study participants

	Subjects with breast cancer		Subjects without breast cancer		Total	
	No.	%	No.	%	No.	%
All participants	5,361	100	107,018	100	112,379	100
Pre-/perimenopausal at baseline	1,433	27	46,413	43	47,846	43
Postmenopausal at baseline	3,443	64	51,980	49	55,423	49
Never smokers at baseline	3,143	59	71,206	67	74,349	66
Residentially stable <sup>a</sup>	3,291	61	55,702	52	58,993	53
Never smokers and residentially stable	1,957	37	36,778	34	38,735	35

<sup>a</sup>Did not move during follow-up, 1995/1996-2010

Unadjusted and adjusted hazard ratios for invasive breast cancer risk due to exposure to estrogen-disrupting hazard air pollutants among the full study population (n=112,379), with quintile 1 as the reference.<sup>a</sup>

**Table 2**

	model	Quintile 2		Quintile 3		Quintile 4		Quintile 5	
		HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Arsenic compounds (inorganic, including arsine)	A <sup>c</sup>	1.02	(0.94, 1.12)	1.01	(0.93, 1.10)	1.03	(0.95, 1.13)	1.04	(0.96, 1.13)
	B <sup>c</sup>	1.01	(0.93, 1.10)	1.00	(0.92, 1.09)	1.02	(0.94, 1.12)	1.03	(0.95, 1.13)
Biphenyl	A	1.11	(1.02, 1.21)	1.04	(0.95, 1.13)	1.05	(0.96, 1.14)	1.09	(1.00, 1.19)
	B	1.09	(1.00, 1.19)	1.02	(0.93, 1.11)	1.03	(0.94, 1.12)	1.06	(0.97, 1.16)
Cadmium compounds	A	1.10	(1.01, 1.20)	1.09	(1.00, 1.18)	1.01	(0.93, 1.10)	1.04	(0.95, 1.13)
	B	1.08	(1.00, 1.18)	1.07	(0.98, 1.16)	1.00	(0.92, 1.09)	1.03	(0.94, 1.13)
Chlorobenzilate	A					1.11	(1.01, 1.22)	1.00	(0.93, 1.07)
	B					1.10	(1.00, 1.21)	0.99	(0.93, 1.06)
DEHP	A	0.92	(0.84, 1.00)	0.90	(0.82, 0.98)	0.97	(0.89, 1.05)	0.94	(0.87, 1.02)
	B	0.91	(0.84, 0.99)	0.91	(0.83, 0.99)	0.97	(0.90, 1.06)	0.94	(0.87, 1.02)
Dibutylphthalate	A	1.04	(0.95, 1.13)	1.01	(0.93, 1.10)	1.05	(0.96, 1.14)	1.05	(0.96, 1.14)
	B	1.01	(0.93, 1.11)	0.98	(0.90, 1.07)	1.02	(0.93, 1.11)	1.03	(0.94, 1.12)
Dimethyl formamide	A	1.03	(0.95, 1.12)	1.08	(0.99, 1.18)	1.06	(0.98, 1.16)	1.02	(0.93, 1.11)
	B	1.02	(0.93, 1.11)	1.06	(0.97, 1.15)	1.05	(0.96, 1.14)	1.00	(0.92, 1.09)
4-Nitrophenol	A	1.07	(0.98, 1.17)	1.08	(0.99, 1.17)	1.05	(0.96, 1.14)	1.10	(1.01, 1.20)
	B	1.06	(0.97, 1.15)	1.05	(0.97, 1.15)	1.02	(0.93, 1.11)	1.07	(0.98, 1.17)
Styrene	A	1.03	(0.95, 1.13)	1.03	(0.94, 1.12)	1.04	(0.95, 1.13)	1.03	(0.94, 1.12)
	B	1.03	(0.94, 1.12)	1.01	(0.93, 1.10)	1.02	(0.94, 1.11)	1.02	(0.93, 1.11)
Selenium compounds	A	1.03	(0.95, 1.12)	1.00	(0.92, 1.09)	1.06	(0.98, 1.16)	1.00	(0.92, 1.09)
	B	1.01	(0.93, 1.10)	0.98	(0.90, 1.07)	1.05	(0.96, 1.14)	1.00	(0.92, 1.09)
Diesel engine emissions	A	1.03	(0.95, 1.12)	1.03	(0.95, 1.13)	1.07	(0.98, 1.16)	1.06	(0.97, 1.15)

model	Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
Exposure potential index of 9 estrogenic HAPs	B	1.02 (0.94, 1.11)	1.02 (0.93, 1.11)	1.05 (0.96, 1.14)	1.04 (0.95, 1.13)			
	A	1.08 (0.99, 1.17)	1.06 (0.97, 1.15)	1.07 (0.98, 1.16)	1.05 (0.96, 1.15)			
	B	1.07 (0.98, 1.16)	1.05 (0.96, 1.14)	1.05 (0.96, 1.14)	1.04 (0.95, 1.13)			

<sup>a</sup>No. of all invasive breast cancer cases combined: 5,361.

<sup>b</sup>DEHP: bis(2-ethylhexyl) phthalate;

<sup>c</sup>Model A: stratified by age at baseline and adjusted for race/birthplace only; Model B: stratified by age at baseline and adjusted for race/birthplace and the following covariates ascertained at baseline: family history of breast cancer, age at menarche, age at first full term pregnancy, the combined variable of menopausal status and hormone therapy use status, alcohol consumption, total pack years of smoking, strenuous physical activity and body mass index.

Adjusted hazard ratios (HR) for invasive breast cancer risk by hormone receptor status due to exposure to arsenic and cadmium compounds among never smoking residential stable participants

Estimated levels ( $\mu\text{g}/\text{m}^3$ , $10^{-4}$ )		all breast cancer <sup>a</sup> (n=1,957)		ER+ or PR+ <sup>b</sup> (n=1,490)		ER- and PR- <sup>c</sup> (n=245)	
	Median (range)	HR (95% CIs)		HR (95% CIs)		HR (95% CIs)	
Arsenic compounds (inorganic, including arsine)	Quintile 1	2.7 (1.3, 3.6)					
	Quintile 2	4.4 (3.6, 5.1)	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)		1.5 (1.0, 2.3)	
	Quintile 3	5.9 (5.1, 6.8)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)		1.5 (1.0, 2.3)	
	Quintile 4	7.9 (6.8, 9.5)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)		1.4 (0.9, 2.2)	
	Quintile 5	12(9.5, 110)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)		1.7 (1.1, 2.5)	
Cadmium compounds	Quintile 1	1.1 (0.4, 1.4)					
	Quintile 2	1.7 (1.4, 1.9)	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)		1.2 (0.8, 1.9)	
	Quintile 3	2.1 (1.9, 2.4)	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)		1.3 (0.8, 1.9)	
	Quintile 4	2.7 (2.4, 3.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)		1.6 (1.1, 2.4)	
	Quintile 5	4.1 (3.2, 120)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)		1.6 (1.1, 2.5)	

Note:

<sup>a</sup> all invasive breast cancer.

<sup>b</sup> ER+ or PR+: Tumor estrogen receptor (ER) or progesterone receptor (PR) positive.

<sup>a/b</sup> HRs and 95% CIs for both arsenic and cadmium compounds exposures were adjusted for age, race/birthplace, family history of breast cancer, alcohol consumption, body mass index (BMI), age at menarche, age at first full-term pregnancy, and menopausal status and hormone therapy use, all ascertained at baseline;

<sup>c</sup> ER- and PR-: ER and PR negative; HRs and 95% CIs for both arsenic and cadmium compounds exposure were adjusted for age, race/birth place, family history of breast cancer, alcohol consumption and BMI, all ascertained at baseline.