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Exposure to Industrial Air Toxics and Risk of Breast Cancer in California: The Multiethnic Cohort Study

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Abstract

Objective: To estimate breast cancer risk associated with residential exposure to industrial air pollutants.

Methods: We analyzed 53,313 women in the California Multiethnic Cohort (1993–1996) for associations between 15 industrial pollutants identified from the EPA Toxic Release Inventory and breast cancer incidence. TRI sites were linked to geocoded residential histories using a quadratic decay model, estimating 5-year lagged annual exposures. Cox proportional hazards models estimated risk per interquartile range increase, with analyses stratified by race/ethnicity and hormone receptor status.

Results: Increased risk was associated with exposure to dichloromethane (HR=1.17, 95% CI: 1.05–1.29), tetrachloroethylene (HR=1.53, CI: 1.39–1.69), 1,1,1-trichloroethane (HR=1.77, CI: 1.65–1.91), diethanolamine (HR=1.06, CI: 0.98–1.15), lead (HR=1.02, CI: 1.00–1.03), and methyl ethyl ketone (HR=1.27, CI: 1.15–1.41). Formaldehyde was associated only with hormone receptor–negative tumors (HR=1.44, CI: 1.15–1.73).

Conclusion: Residential exposure to certain industrial pollutants may increase breast cancer risk.

Key words: breast cancer, air pollution, industrial pollution, toxic release inventory

SMART learning outcomes:

- Identify residential exposures to industrial air pollutants among women in the California Multiethnic Cohort from 1993–2016

- 23 • Discuss that several industrial pollutants (i.e., dichloromethane, tetrachloroethylene,
24 1,1,1-trichloroethane, diethanolamine, lead, and methyl ethyl ketone) were associated
25 with breast cancer risk
- 26 • Learn that formaldehyde exposure was specifically associated with hormone receptor–
27 negative breast cancer, highlighting potential etiologic heterogeneity by tumor subtype.
- 28

1. Introduction

Breast cancer is the most commonly diagnosed cancer globally and the leading cause of cancer deaths among women.¹ There is a growing literature on breast cancer risk due to environmental chemical agents, including phenols, organic solvents, and air pollution.^{2,3} Studies investigating occupational exposures to chemical agents have reported mixed results. Several studies reported increased risk of breast cancer in women with occupational exposure to any chemicals, organic solvents, polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOC), and heavy metals,⁴⁻¹⁵ while others investigating occupational exposure to organic solvents and PAHs had null findings.¹⁶⁻¹⁹ However, the occupational literature is limited due to low statistical power, resulting from a limited sample size of women in many of the older occupational cohort studies.

In addition to occupational exposure to chemicals, there is evidence to support that residential proximity to industrial pollution sources increases breast cancer risk. A study evaluating residential proximity to various industrial facilities found excess risk of breast cancer among women living in close proximity to industrial sites releasing organic solvents.²⁰ There was also evidence of an association between mammographic density, one of the strongest risk factors for breast cancer, and residential proximity to industries releasing inorganic compounds, organic solvents, and phenols.²¹ These studies focused on the type of industrial facility and common byproducts, but did not measure emission levels of individual chemicals in the nearby environment.

Studies investigating ambient exposure to specific agents found positive associations with breast cancer and residential exposure to certain VOCs, organic solvents, chlorinated hydrocarbons, aromatic hydrocarbons, PAHs, aldehydes and epoxides.²²⁻²⁵ Since industrial agents vary by location, there is limited overlap in the chemicals studied across the literature;

this, coupled with the sometimes-contradictory results, warrant additional studies to understand associations between residential exposure to specific chemicals and breast cancer risk. In this study, we used the EPA Toxics Release Inventory to examine the association between industrial pollution and breast cancer incidence, focusing on 15 chemical agents commonly released in Los Angeles County during 1987-2012. We selected agents which have been found to be associated with breast cancer or animal mammary tumors in previous studies, are established or suspected carcinogens according to the International Agency for Research on Cancer (IARC), or are endocrine disruptors.^{23,26-29}

2. Methods

2.1 Study Population

The Multiethnic Cohort (MEC) is a large prospective cohort with men and women aged 45-75 years at recruitment representing five racial and ethnic groups (African American, Japanese American, Latino, Native Hawaiian, and White) residing in Hawaii (HI) or California (CA). This racially and ethnically diverse cohort was enrolled from 1993 through 1996, and completed a mailed self-administered questionnaire at baseline to collect demographics, diet, lifestyle factors, anthropometrics, reproductive and medical histories, medication use and family history of cancer.³⁰

Participants were followed for incident diagnosis of breast cancer through linkage with the CA and HI cancer registries. For this study, we included 56,950 female participants from the Southern California MEC cohort who had no history of breast cancer prior to cohort entry and had home addresses available, which were geocoded into latitude and longitude coordinates (n = 1,049 missing home addresses were excluded). Residential addresses were obtained and regularly updated through periodic mailings of newsletters, follow-up questionnaires and

linkages to administrative databases and registries.^{31,32} After exposure lagging by 5 years (as described below) and removing individuals whose exposure period was less than the lag time (N = 3,637), there were 53,313 participants left for our study population (Figure 1). This study population was followed from the time of study entry (1993-1996) until the incidence of invasive breast cancer, death, or the end of the study (December 31, 2013), whichever came first (mean $\pm$ SD follow-up time = 16.7 $\pm$ 5.4 years).

2.2 Exposure Assessment

The Toxic Release Inventory (TRI) program was established in 1986 to monitor and document industrial management of toxic chemicals. It reports detailed information on 787 chemicals and 33 chemical categories released by over 23,000 facilities through various processes including disposal, recycling, energy recovery and treatment. Reporting releases to the TRI is mandatory for facilities covered by the North American Industry Classification System (NAICS), with 10 or more full-time employees, who are involved in the manufacturing, importing, processing, or usage of TRI-listed chemicals exceeding Environmental Protection Agency (EPA) established thresholds during a calendar year. The TRI keeps a comprehensive record of air, water, and land releases for all listed chemicals. Air releases are further categorized as "stack emissions" (releases occurring through a confined air stream and easier to track) and "fugitive emissions" (releases not occurring through a confined air stream) which together make up 85% of all releases in California. Data on the annual air releases in pounds for the selected chemicals of interest were obtained from the TRI database. The chemicals included in this analysis were selected by first calculating the top 50 chemicals released in Los Angeles County (by poundage) between 1987-2012 and then reduced to established or suspected IARC carcinogens, mammary gland carcinogens in animal bioassays, and suspected endocrine disruptors (N = 26).^{23,26-29} We excluded traffic-related agents as TRI emissions would account for

a small proportion of subjects' exposures to these agents (benzene, ethylbenzene, toluene, xylene).³³ We then reviewed maps and emissions data to examine the distribution of the chemicals in the Los Angeles air basin throughout the study period and excluded chemicals that did not have sufficient exposure contrasts in the study period (2-methoxyethanol, ammonia, ethylene oxide, isopropyl alcohol, phosphoric acid, trichloroethylene, vinyl acetate). We utilized ArcGIS 10.2 (ESRI, Redlands) to visualize the information geographically for the 15 agents included in this analysis. This involved mapping the ambient air release data at the location of each facility using the latitude and longitude values provided by the EPA.

This method has been described previously.³⁴ Briefly, MEC participants were linked to the location of each release site through ArcGIS by using their geocoded baseline and follow-up addresses within a specific buffer size. If a residential address did not link to any facilities, we considered the participants unexposed during the follow-up period. For successful links, we assigned the annual release of each chemical from the facility to the participants. Then, we calculated the straight-line distance between the residential address and TRI sites.

We implemented quadratic decay models to estimate exposures following the analytical approach described by Conley.³⁵ We examined various distance thresholds around the facilities to ensure consistency in effect estimates across different distances and chose a 3 km threshold for our study as it was the smallest threshold that provided sufficient statistical power for estimating effects for most pollutants.

The quadratic decay model uses a modified equation (Equation 1) from Cutter et al.³⁶ In this model, K_{ir} represents the impact of site i on residence r and v_i is the volume of releases from site i . Additionally, d_{ir} is the straight-line distance between site i and residence r and T is the

threshold distance.³⁵ Calculation of a residence's exposures only included the sites that were within the threshold distance from residence r .

$$K_{ir} = v_i \left(1.0 - \left(\frac{d_{ir}^2}{T^2} \right) \right) \quad [1]$$

We computed a set of cumulative exposures for each year within the cohort's exposure window (1993-2013), lagged by 5 years; longer lagging was not possible due to sparse data. Average exposures were computed as a weighted mean of yearly exposure estimates for all geocoded addresses in participant's residential history from the time of enrollment until the event (breast cancer, censor, death, or the end of the study: December 31, 2013, whichever came first).

2.3 Statistical Analyses

We utilized Cox proportional hazard models to evaluate the relationship between time-dependent exposure to industrial pollutants and breast cancer risk. Results are reported per interquartile range (IQR) increase in exposure. To minimize the impact of outliers, we restricted the analysis to exposures at or below the 99th percentile. We generated risk-set based estimates using a counting process within the Cox model to calculate both crude and adjusted hazard ratios. Covariates were selected based on subject-matter knowledge and known associations with breast cancer risk.²⁴ We adjusted for the following characteristics collected at cohort entry (see Table 1 for detail on covariate levels): age at cohort entry, race/ethnicity, body mass index, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity, energy intake, alcohol use, smoking, educational attainment, neighborhood socioeconomic status (SES; baseline and end of follow-up). Multiple imputations were used to estimate missing values for

covariates with more than 500 missing observations. To account for TRI sites located near major roadways, we adjusted for cumulative monthly NO_x exposure using land use regression models.³¹

We performed stratified analyses by racial and ethnic groups and used a global simultaneous test based on the Wald test to check for heterogeneity in effects. We also evaluated associations between breast cancer and exposure quartiles based on the air toxics exposure distribution in the exposed group. Furthermore, we conducted stratified analyses by breast cancer subtype: hormone receptor-positive breast cancer defined as being positive for the estrogen receptor and/or the progesterone receptor (ER+ or PR+) and hormone receptor-negative breast cancer defined as being negative for both the estrogen and progesterone receptors (ER- and PR-). The number of premenopausal cases (N=5) was too small to conduct meaningful statistical analyses.

We also conducted a series of sensitivity analyses. First, we conducted analyses stratified by moving status, where non-movers were defined as having the same address throughout the study period while movers had more than one address. Additionally, to examine whether the exposed population living close to releasing facilities was unique compared to the overall cohort population, we repeated all analyses among the exposed subgroup only i.e. all women who lived within a 3 km radius of any releasing facility. Finally, we reran the main models as a complete case analysis, including only participants with no missing covariate data. Spatial joining and mapping were completed in ArcGIS 10.2 (ESRI, Redlands) and data management and statistical analyses were completed using SAS 9.4.

3. Results

Participant characteristic information is displayed in Table 1. A majority of the study population was Latino or African American, had two or more children, did not have a family

history of breast cancer, and had never used estrogen. At baseline, 36.3% were alcohol drinkers and 14.1% were smokers, 52.5% completed less than high school, and 25.3% resided in the lowest neighborhood SES quintile.

Correlations for all agents among the study population are shown in Table S1. There was a moderate correlation ($r=0.416$) between methyl tert-butyl ether and n-hexane while correlations between other agents were low. Median exposure levels, range and interquartile range among exposed women are shown in Table S2. Exposure levels varied considerably by race and ethnicity, with African American women having the lowest median exposure and Latino women having the highest median exposure levels in most comparisons.

Adjusted results from the quadratic decay model found elevated hazards of breast cancer among individuals exposed to dichloromethane (Hazard Ratio (HR) = 1.17; 95% Confidence Interval (CI): 1.05, 1.29), tetrachloroethylene (HR = 1.53; 95% CI: 1.39, 1.69), 1,1,1-trichloroethane (HR = 1.77; 95% CI: 1.65, 1.91), diethanolamine (HR = 1.06; 95% CI: 0.98-1.15), lead (HR = 1.02; 95% CI: 1.00, 1.03), and methyl ethyl ketone (HR = 1.27; 95% CI: 1.15, 1.41) as well as a slightly decreased hazard with exposure to lead compounds (HR = 0.98; 95% CI: 0.95, 1.00) (Table 2).

When stratified by hormone receptor status (Table 3), the adjusted hazard ratio for formaldehyde was elevated only among females with hormone receptor-negative breast cancer (HR = 1.44; 95% CI: 1.15, 1.73) and not among those with hormone receptor-positive breast cancer (0.93; 95% CI: 0.71, 1.22). For all other pollutants, point estimates were similar across hormone receptor status, with overlapping confidence intervals.

Analyses stratified by racial and ethnic group are shown in Table S3. Hazard ratios were generally similar across racial and ethnic groups with three exceptions. 1,1,1-

Trichloroethane displayed significant heterogeneity (P value for heterogeneity (P-het): <0.0001); the highest hazard ratio was among Japanese American women (HR = 3.17; 95% CI: 2.61, 7.23) and the lowest among White women (HR = 1.60; 95% CI: 1.39, 2.04). Additionally, heterogeneity was notable for formaldehyde (P-het: 0.0134) where the highest hazard ratio was among African American women (HR = 1.45; 95% CI: 1.10-1.38) and the lowest among Latino women (HR = 0.46; 95% CI: 0.26-0) and for phenol where the highest hazard ratio was among African American women (HR = 2.01; 95% CI: 1.40-2.88) and lowest among White women (HR = 0.83; 95% CI: 0.54-1.27). The associations with breast cancer risk were largely similar in movers and non-movers (Table S4), with overlapping confidence intervals.

In the quartile analysis, the positive associations between formaldehyde, tetrachloroethylene, 1,1,1-trichloroethane, diethanolamine, methyl ethyl ketone, and breast cancer appeared to be driven by exposure at the highest quartile (Table S5). The subgroup analyses limiting to exposed women showed similar results, but the hazard ratios were higher and moved away from the null. Most notably, these analyses no longer showed a slight negative effect with exposure to lead compounds (Tables S6-S9). The complete case analysis, restricted to women with no missing covariate information, yielded similar point estimates and overlapping confidence intervals (Table S10).

4. Discussion

In this multi-ethnic cohort study, we found associations between exposure to several industrial air toxics and breast cancer. The associations we found with dichloromethane and tetrachloroethylene support the findings of previous studies on ambient industrial pollutants and breast cancer risk^{20,23} and the associations with lead are consistent with findings from occupational studies.^{9,37} The association we found with 1,1,1-trichloroethane was not seen in previous occupational studies of the agent,^{6,10} while to our knowledge naphthalene and

diethanolamine have not been previously examined in relation to breast cancer. The discrepancies may be attributed to exposure measurement, as this is one of the few studies that investigated residential exposure to various chemicals released by industrial facilities at an individual level, rather than occupational or municipality-level exposures. Alternatively, discrepancies may be due to differing exposure distributions based on the location and demographics of the cohort.

The associations we found with dichloromethane (methylene chloride) partially support the findings of the Sister Study.²³ Our study found dichloromethane increased the risk of breast cancer overall, as well as hormone receptor-positive and hormone receptor-negative breast cancer, while the Sister Study found slight positive associations with overall breast cancer and positive associations with ER+ but did not find associations with ER- breast cancer.²³ These discrepancies may be due to the difference in exposure classifications with the Sister Study utilizing census-tract average exposures while our study used a quadratic decay model to estimate exposures from industrial releases near the home. Additionally, the Sister Study is comprised of sisters of women with breast cancer so they may have greater underlying genetic susceptibility. Dichloromethane is classified by IARC as probably carcinogenic to humans (Group 2A) and has been found to induce mammary gland tumors in mice and rats following both gavage and topical exposure.^{38,39} Human in-vitro and animal in-vivo studies have produced evidence that dichloromethane metabolism via glutathione S-transferase theta 1 (*GSTT1*) results in the formation of genotoxic reactive metabolites.³⁹ Dichloromethane is not produced in California, but it is used widely by industries and consumers. The major use categories of dichloromethane in California are paint removers, aerosols, degreasers, and polyurethane foam manufacturing; additionally it is used in the manufacturing of pharmaceuticals, electronics, chemicals, and pesticides.⁴⁰

Supporting our results for tetrachloroethylene, one previous study reported a positive association with occupational exposure and breast cancer.⁹ Tetrachloroethylene, which is used primarily as a solvent in dry cleaning and degreasing processes in California, is classified as a probable human carcinogen (Group 2A) by IARC.⁴¹⁻⁴³ Mechanistic studies of tetrachloroethylene have identified two major metabolic pathways: CYP450-mediated oxidation which results in a variety of oxidative metabolites, and glutathione conjugation which results in genotoxic metabolites.⁴³ In animals, one study reported an increased incidence of mammary gland fibroadenoma in rats exposed to tetrachloroethylene through inhalation and exposure to tetrachloroethylene through inhalation and gavage resulted in increased liver tumor incidence in rats and mice.⁴²

1,1,1-trichloroethane has been classified as a probable human carcinogen (Group 2A) by IARC.⁴⁴ Industrially, 1,1,1-trichloroethane is used as a solvent and degreasing agent and as a chemical intermediate in the production of vinylidene chloride. Additionally, 1,1,1-trichloroethane is used in consumer goods including household cleaning products, glues, and aerosol sprays.⁴⁵ Researchers reported elevated odds ratios among occupationally exposed workers with > 10 years of 1,1,1-trichloroethane exposure with wide confidence intervals.¹⁰ Mechanistic evidence for carcinogenesis is limited, but studies of rodents and human in-vitro cells suggest that 1,1,1-trichloroethane may induce oxidative stress, chronic inflammation, and alter cell proliferation.⁴⁴

In the TRI, lead (elemental lead) and lead compounds (any chemical containing lead) are tracked separately. Lead compounds encompass a diverse group of chemicals, and their carcinogenicity varies across the class; inorganic lead compounds are classified as probably carcinogenic to humans (Group 2A), while organic lead compounds are not classifiable as to their carcinogenicity to humans (Group 3).⁴⁶ Lead is classified as a possible human carcinogen

(Group 2B) by IARC.⁴⁷ Since lead was removed from automotive gasoline in 1992, the main sources of lead exposure in California are ore and metals processing, waste incinerators, and gasoline emissions from piston-engine aircrafts. There is also lead in soil from historic use and these particles can be resuspended in the air.⁴⁸ Studies show that exposure to lead can induce chromosomal aberrations. Studies provided evidence for lead inhibiting DNA repair, causing adverse effects on gap junctions, altering gene expression, interacting with binding sites on DNA-associated protein, and causing changes in the p53 tumor suppressor protein.⁴⁹

Methyl ethyl ketone is a suspected endocrine disruptor but information on its carcinogenicity is lacking.²⁷ In California, the primary emission sources of methyl ethyl ketone are manufacturers of millwork, veneer, plywood, wood furniture, and rubber and plastic footwear. Methyl ethyl ketone is also present in cigarette smoke, gasoline, and motor vehicle exhaust.⁵⁰ To our knowledge, this is the first study to examine and report an association between methyl ethyl ketone exposure and breast cancer risk.

The heterogeneity of risk estimates by racial and ethnic groups needs to be interpreted cautiously as they may not be meaningful and may reflect random variation. Our analyses were based on the overall IQR while race-specific IQRs varied widely for some of the chemicals. This may have been due, for example, to industry locations near ethnic enclaves and the concentrated presence of industrial air toxics in certain areas, combined with the distinct clustering of minority neighborhoods in LA.⁵¹ For example, African American participants predominantly resided in southwest LA (Inglewood), while Japanese American participants were more dispersed across Los Angeles, but they also clustered in certain neighborhoods such as northeast LA (Monterey Park) and in some west side neighborhoods (Torrance and South Bay). While White and Latino MEC participants lived throughout the LA basin, White participants concentrated more to the west and Latino participants to the east of downtown Los Angeles.⁵¹

Strengths of this study include the prospective cohort study design, and access to detailed residential histories for all participants living in CA, including whether they relocated during the study period. With the detailed questionnaire information, we were able to adjust for a large number of risk factors for breast cancer that might be confounders. Furthermore, the MEC is unique with its racial and ethnic diversity and representation of minoritized population groups. A potential limitation of our study is that TRI reporting requirements only apply to facilities with 10 or more employees that manufacture or process at least 25,000 pounds or use an excess of 10,000 pounds of a listed chemical annually, thus, it might not capture all emissions.⁵² Furthermore, estimating air toxics exposures based on distance from emission sources may introduce nondifferential exposure misclassification, as we are not able to account for wind patterns, topography, or other physical barriers that influence pollutant dispersion.⁵³ To mitigate the influence of extreme outliers, we excluded exposures above the 99th percentile; this decision removed the most highly exposed individuals, potentially limiting our ability to characterize risks at the upper end of the exposure distribution. Additionally, our application of a 5-year exposure lag to account for disease latency is a simplification. This approach does not fully address the current understanding of breast cancer etiology, which emphasizes specific and critical windows of susceptibility across the life course (e.g., prenatal development, puberty, pregnancy, and menopausal transition), potentially leading to nondifferential exposure misclassification by not being able to focus on these highly vulnerable developmental periods.⁵⁴ Finally, differences in mammography uptake by racial/ethnic groups may introduce residual confounding, potentially differentially depressing point estimates for breast cancer risk in groups with lower screening uptake and high exposure.

In conclusion, our study highlights the impact of exposure to ambient industrial pollutants that are considered air toxics on breast cancer risk. Our results largely confirmed occupational

312 studies as well as some previous environmental exposure studies and also suggested a few
313 associations previously not observed in humans.

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Figure 1. Flow chart of Multiethnic Cohort female study participants for analysis

Table 1. Characteristics of study population at baseline, before multiple imputations

Characteristics	Total, N (%) (N=53313)
Race and ethnicity	
African American	18556 (34.8)
Japanese American	5712 (10.7)
Latino	20869 (39.1)
Native Hawaiian	62 (0.1)
White	8114 (15.2)
Age at cohort entry	
44-49 years old	7325 (13.7)
50-54 years old	7722 (14.5)
55-59 years old	10226 (19.2)
60-64 years old	10045 (18.8)
65-69 years old	9127 (17.1)
70+ years old	8868 (16.6)
Family history of breast cancer in mother or sisters	
Yes	5292 (9.9)
No	43820 (82.2)
Missing	4201 (7.9)
Menopausal status	
Pre-Menopause	5638 (10.6)
Natural Menopause	25827 (48.4)
Surgical Menopause (oophorectomy with or without hysterectomy)	7801 (14.6)
Other Surgery that causes periods to stop (hysterectomy, endometrial ablation)	10579 (19.8)
Period stopped but reason unknown (including women with aged 65+ at baseline)	2759 (5.2)
Missing	709 (1.3)
Age at menarche	
≤ 12 years old	25175 (47.2)
13-14 years old	20173 (37.8)
> 14 years old	6938 (13.0)
Missing	1027 (1.9)
Menopausal hormone therapy	
Never estrogen use, with or without past or current progesterone use	28542 (53.5)
Past estrogen use, with or without past progesterone use	9257 (17.4)
Current estrogen use alone	6223 (11.7)

Current estrogen use with progesterone - past or current	5967 (11.2)
Missing	3324 (6.2)
Age at first live birth	
No children	6225 (11.7)
15-20 years old	19300 (36.2)
21-30 years old	23105 (43.3)
> 30 years old	3023 (5.7)
Missing	1660 (3.1)
Parity	
0 children (nulliparous)	6087 (11.4)
1 child	6074 (11.4)
2-3 children	20355 (38.1)
4 or more children	19878 (37.3)
Missing	919 (1.7)
BMI at baseline	
Underweight (<18.5 kg/m ²)	816 (1.5)
Normal (18.5-24.9 kg/m ²)	17985 (33.7)
Overweight (25-29.9 kg/m ²)	18731 (36.1)
Obese (>30 kg/m ²)	14910 (28.0)
Missing	871 (1.6)
Alcohol Drinker	
Yes	19328 (36.3)
No	31631 (59.3)
Missing	2354 (4.4)
Smoker	
Current smoker	7501 (14.1)
Former smoker	15213 (28.5)
Never smoker	29147 (54.7)
Missing	1452 (2.7)
Moderate and vigorous physical activity, MET-hours/day	
0	4116 (7.7)
Quartile 1, <0.4	17858 (33.5)
Quartile 2, 0.4-<0.7	4016 (7.5)
Quartile 3, 0.7-<1.2	11854 (22.2)
Quartile 4, 1.2-<13.3	13448 (22.2)
Missing	2021 (3.8)
Energy intake, kcal/day	
Quintile 1, 425.2-<1190.5	10420 (19.5)
Quintile 2, 1190.5-<1575.2	10095 (18.9)
Quintile 3, 1575.2-<1996.0	10038 (18.8)
Quintile 4, 1996.0-<2667.1	10018 (18.8)

Quintile 5, 2667.1-<7401.3	10387 (19.5)
Missing	2355 (4.4)
Education	
< High school	21407 (50.3)
High school graduate	12958 (30.5)
College	4292 (10.1)
Graduate school	3864 (9.1)
Neighborhood socioeconomic status at baseline	
Quintile 1 – Low	9932 (23.4)
Quintile 2	10955 (25.8)
Quintile 3	8636 (20.3)
Quintile 4	7797 (18.3)
Quintile 5 – High	5201 (12.2)
Ambient nitrogen oxides (NOx) level, Mean (Standard Deviation) ^a	1.33 (0.2)

^a Average per 50 ppb NOx during the follow-up period

Table 2. Hazard ratios and 95% confidence intervals for the association between one interquartile range (IQR) increase in industrial toxic exposure and breast cancer risk, with 5-year exposure lagging, using the quadratic decay model (N=53313) ^a

Industrial Pollutant	CAS Registry Number ^b	N cases ^c	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) ^d
Mammary carcinogens in animal bioassays				
Dichloromethane ^{e,f}	75-09-2	2210	1.13 (1.09, 1.16)	1.17 (1.05, 1.29)
Styrene ^{e,f}	100-42-5	2223	1.03 (1.02, 1.04)	1.02 (0.98, 1.07)
Group 1 carcinogens				
Formaldehyde	50-00-0	2236	0.86 (0.80, 0.93)	1.02 (0.83, 1.25)
Group 2A carcinogens				
Lead compounds ^g	N420	2233	0.96 (0.95, 0.97)	0.98 (0.95, 1.00)
Tetrachloroethylene ^e	127-18-4	2207	1.60 (1.56, 1.65)	1.53 (1.39, 1.69)
1,1,1-Trichloroethane	71-55-6	2200	1.94 (1.90, 1.99)	1.77 (1.65, 1.91)
Group 2B carcinogens				
Diethanolamine ^e	111-42-2	2238	1.07 (1.04, 1.09)	1.06 (0.98, 1.15)
Di(2-ethylhexyl) phthalate ^e	117-81-7	2238	0.98 (0.92, 1.04)	1.06 (0.86, 1.30)
Naphthalene ^e	91-20-3	2229	1.04 (1.02, 1.06)	1.01 (0.95, 1.07)
Lead ^e	7439-92-1	2210	1.00 (0.99, 1.00)	1.02 (1.00, 1.03)
Suspected endocrine disruptors				
Ethylene glycol	107-21-1	2232	0.97 (0.96, 0.98)	0.97 (0.94, 1.00)
Methyl ethyl ketone	78-93-3	2207	1.29 (1.25, 1.33)	1.27 (1.15, 1.41)
Methyl tert-butyl ether	1634-04-4	2230	1.11 (1.05, 1.18)	0.93 (0.77, 1.12)
N-Hexane	110-54-3	2229	0.99 (0.97, 1.02)	0.96 (0.90, 1.03)
Phenol	108-95-2	2235	0.94 (0.89, 0.98)	1.03 (0.88, 1.19)

^aThe exposed group is defined as women living within the 3km buffer of the facilities; the unexposed group is defined as women living outside of the 3km buffer of the facilities.

^bChemical Abstracts Service Registry Number

^c The number of cases included in the adjusted model

^d Adjusted for race/ethnicity, age at cohort entry, BMI, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity (hour/day), energy intake (kcal/day), alcohol use (non-drinker/drinker), smoking (never/former/current smoker), education, neighborhood socioeconomic status at baseline, and ambient average nitrogen oxides level during follow-up period.

^eSuspected endocrine disruptor

^fGroup 2A chemical classified by IARC

^gTotal lead compounds with inorganic lead compounds were classified as Group 2A chemicals; organic lead compounds were classified as Group 3 chemicals by IARC

Table 3. Hazard ratios and 95% confidence intervals of breast cancer associated with one interquartile range (IQR) increase in industrial toxic exposure by hormone receptor status, with 5-year exposure lagging, using the quadratic decay model (N=53313) ^a

Industrial Pollutant	Hormone Receptor-Negative (ER- and PR-)				Hormone Receptor-Positive (ER+ or PR+)			
	CAS Registry Number ^b	N cases ^c	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) ^d	N cases ^c	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) ^d	P value for heterogeneity
Mammary carcinogens in animal bioassays								
Dichloromethane ^{d,e}	75-09-2	370	1.24 (1.16, 1.34)	1.34 (1.11, 1.57)	1576	1.11 (1.06, 1.15)	1.15 (1.01, 1.30)	0.362
Styrene ^{d,e}	100-42-5	373	1.09 (1.06, 1.11)	1.08 (1.00, 1.17)	1580	1.02 (1.01, 1.04)	1.01 (0.97, 1.07)	0.196
Group 1 carcinogens								
Formaldehyde	50-00-0	374	1.33 (1.20, 1.47)	1.44 (1.15, 1.73)	1593	0.76 (0.69, 0.84)	0.93 (0.71, 1.22)	0.038
Group 2A carcinogens								
Lead compounds ^f	N420	373	0.95 (0.93, 0.97)	0.97 (0.91, 1.03)	1590	0.96 (0.95, 0.97)	0.98 (0.95, 1.00)	0.753
Tetrachloroethylene ^d	127-18-4	367	1.86 (1.74, 1.99)	1.66 (1.44, 1.88)	1573	1.48 (1.42, 1.53)	1.44 (1.28, 1.63)	0.056
1,1,1-Trichloroethane	71-55-6	367	1.95 (1.84, 2.06)	1.78 (1.59, 1.96)	1571	1.90 (1.84, 1.95)	1.74 (1.59, 1.91)	0.778
Group 2B carcinogens								
Diethanolamine ^d	111-42-2	374	1.04 (0.97, 1.12)	1.05 (0.83, 1.27)	1594	1.07 (1.04, 1.10)	1.06 (0.97, 1.17)	0.85
Di(2-ethylhexyl) phthalate ^d	117-81-7	374	0.98 (0.84, 1.14)	1.07 (0.56, 1.59)	1594	0.94 (0.87, 1.02)	1.03 (0.80, 1.33)	0.904
Naphthalene ^d	91-20-3	373	0.97 (0.92, 1.03)	0.95 (0.76, 1.13)	1586	1.06 (1.04, 1.08)	1.02 (0.95, 1.09)	0.362
Lead ^d	7439-92-1	372	1.00 (0.99, 1.01)	1.02 (0.98, 1.06)	1578	0.99 (0.99, 1.00)	1.02 (1.00, 1.04)	0.849
Suspected endocrine disruptors								
Ethylene glycol	107-21-1	373	0.98 (0.95, 1.00)	0.98 (0.90, 1.06)	1589	0.96 (0.95, 0.98)	0.96 (0.92, 1.00)	0.795
Methyl ethyl ketone	78-93-3	364	1.59 (1.48, 1.70)	1.55 (1.33, 1.77)	1577	1.25 (1.21, 1.30)	1.24 (1.10, 1.40)	0.059
Methyl tert-butyl ether	1634-04-4	371	1.48 (1.32, 1.66)	1.27 (0.88, 1.65)	1589	1.15 (1.07, 1.22)	0.96 (0.77, 1.19)	0.219
N-Hexane	110-54-3	373	1.04 (0.99, 1.09)	1.02 (0.86, 1.18)	1588	1.02 (1.00, 1.05)	0.98 (0.91, 1.06)	0.843
Phenol	108-95-2	373	0.89 (0.78, 1.01)	1.00(0.61, 1.39)	1592	0.96 (0.91, 1.02)	1.04 (0.88, 1.24)	0.714

^a The exposed group is defined as women living within the 3km buffer of the facilities; the unexposed group is defined as women living outside of the 3km buffer of the facilities.

^b Chemical Abstracts Service Registry Number

^c The number of cases included in the adjusted model

^d Adjusted for race/ethnicity, age at cohort entry, BMI, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity (hour/day), energy intake (kcal/day), alcohol use (non-drinker/drinker), smoking (never/former/current smoker), education, neighborhood socioeconomic status at baseline, and ambient average nitrogen oxides level during follow-up period.

^e Suspected endocrine disruptor

^f Group 2A chemical classified by IARC

^g Total lead compounds with inorganic lead compounds were classified as Group 2A chemicals; organic lead compounds were classified as Group 3 chemicals by IARC

466 **Figure 1.** Flow chart of Multiethnic Cohort female study participants for analysis

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