Association between ambient air pollution and breast cancer risk: The Multiethnic Cohort Study

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Abstract

Previous studies using different exposure methods to assess air pollution and breast cancer risk among primarily whites have been inconclusive. Air pollutant exposures of particulate matter and oxides of nitrogen were estimated by kriging (NO_x, NO_2, PM_{10}, $PM_{2.5}$), land use regression (LUR, NO_x, NO_2), and California Line Source Dispersion Model (CALINE4, NO_x, $PM_{2.5}$) for 57,589 females from the Multiethnic Cohort, residing largely in Los Angeles County from recruitment (1993-996) through 2010. Cox proportional hazards models were used to examine the associations between time-varying air pollution and breast cancer incidence adjusting for confounding factors. Stratified analyses were conducted by race/ethnicity and distance to major roads. Among all women, breast cancer risk was positively but not significantly associated with NO_x (per 50 parts per billion (ppb)) and NO_2 (per 20 ppb) determined by kriging and LUR and with $PM_{2.5}$ and PM_{10} (per 10 μg/m^3) determined by kriging. However, among women who lived within 500 meters of major roads, significant increased risks were observed with NO_x (Hazard Ratio (HR)=1.35, 95% CI: 1.02-.79), NO_2 (HR=1.44, 95% CI: 1.04-.99), PM_{10} (HR=1.29, 95% CI: 1.07-.55) and $PM_{2.5}$ (HR=1.85, 95% CI: 1.15-2.99) determined by kriging and NO_x

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(HR=1.21, 95% CI:1.01-.45) and NO_2 (HR=1.26, 95% CI: 1.00-.59) determined by LUR. No overall associations were observed with exposures assessed by CALINE4. Subgroup analyses suggested stronger associations of NO_x and NO_2 among African Americans and Japanese Americans. Further studies of multiethnic populations to confirm the effects of air pollution, particularly near roadway exposures, on risk of breast cancer is warranted.

Keywords

air pollution; breast cancer; Multiethnic Cohort; epidemiology

Introduction

To date the strongest evidence of an association between exposure to ambient air pollution and risk of breast cancer is based on results from the European Study of Cohorts for Air Pollution Effects (ESCAPE) Project of European cohort studies[1] and case-control studies from Canada;[2–4] these studies used land use regression (LUR) modeling to estimate long-term exposure to NO_X and NO_2. In contrast, cohort studies in the U.S.[5, 6] and Denmark[7, 8], which used other air pollution assessment approaches such as dispersion modeling and kriging interpolation found largely null associations between risk of breast cancer and exposure to NO_X, NO_2, and particulate matter (PM). These inconsistent results may be due to several factors including the use of different exposure assessment methods each with known strengths and limitations in spatial and temporal resolution (discussed below). Furthermore, as each study typically uses only one method of exposure assessment, a comparison of results across different exposure methods (i.e. kriging, LUR, dispersion modeling) has not been conducted within a single study. Prior studies also lacked large numbers of nonwhites to examine whether associations between air pollution and breast cancer risk may vary by race/ethnicity. In the American Cancer Society study of air pollution and lung cancer, non-whites were particularly susceptible to the effects of air pollution[9] but it is not known whether this extends to studies of air pollution and breast cancer.

To address the research gaps noted above, we conducted a large prospective study of ambient air pollution and breast cancer risk within the California (CA) component of the Multiethnic Cohort (MEC) and used three exposure assessment approaches (kriging, LUR, and dispersion modeling). Kriging interpolation was used to estimate exposures of NO_x, NO_2, $PM_{2.5}$, and PM_{10} from largely regional sources based on continuously collected air monitoring data. A temporally adjusted LUR model was used to estimate NO_x and NO_2, traffic-related exposures from regional and local sources based on data from spatially dense air monitoring campaigns, land use factors, and traffic characteristics[10, 11]. The California Line Source Dispersion Model, version 4 (CALINE4), air dispersion model, was used to estimate NO_x and $PM_{2.5}$ from local traffic sources within 1500 meters of participants' residences, capturing a small fraction of total emissions, and incorporated data on meteorological conditions, traffic counts, and roadway networks. These three approaches had varying degrees of spatial and temporal resolution in exposure coverage. The temporally adjusted LUR model captured both high spatial and temporal resolution in contrast to

kriging interpolation with modest spatial and high temporal resolution, and CALINE4 with high spatial and modest temporal resolution. To our knowledge, this is the first prospective study to apply three commonly used methods towards assessment of long-term exposure to NO_x and risk of breast cancer in a large multiethnic population. In addition, exposure to NO_2 and $PM_{2.5}$ were estimated by two of the three assessment methods, providing additional information.

Methods

Study Subjects

The MEC is a large population-based prospective cohort designed to investigate the etiology of cancer among a multiethnic population of U.S. adults[12]. Briefly, from 1993 through 1996, 96,810 men and 118,441 women aged 45-75 years from five self-reported racial/ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites), residing in Hawaii (HI) or CA (primarily Los Angeles County), were enrolled into the MEC. At baseline, participants completed a twenty-six page mailed questionnaire with questions pertaining to demographic characteristics, anthropometrics, reproductive history, and other lifestyle factors. Participants were followed prospectively for diagnosis of incident invasive breast cancer through routine linkage with the CA and HI statewide cancer registries, which are a part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program, and for vital status through linkages to the National Death Index and death certificate files. For this study, eligible female MEC participants were those who completed a baseline questionnaire while living in Southern CA, and provided valid addresses that was geocoded at the parcel or street segment level across the study period (n=63,511). We excluded women with a breast cancer diagnosis prior to cohort entry if reported on baseline questionnaire or found through linkage with the tumor registry, and those with implausible dietary (n=5,858) or address data (n=64), leaving 57,589 women for analyses. This cohort was followed from the date of entry (1993-996) to the earliest date of diagnosis of invasive breast cancer, death, or December 31, 2010 (study end date), whichever came earlier (mean + SD follow-up time=14.7 + 4.3 years).

Study Characteristics and Breast Cancer Risk Factors at Baseline

Risk factors for breast cancer that we evaluated were first-degree family history of breast cancer (yes, no), age at menarche (12, 13-4, >14 years), age at first live birth (no children, <20, 21-30, >30 years), number of children (0, 1, 2-3, 4+), menopausal status (pre-menopause, natural menopause, oophorectomy, hysterectomy), use of hormone therapy (no estrogen use, past estrogen use, current estrogen use only, current estrogen use with past or current progesterone use), alcohol intake (non-drinker; drinker (>0 g/day)), and smoking status (never, former, current). Self-reported height and weight were used to calculate body mass index ((BMI) under <18.5 kg/m^2), normal (18.5-24.9 kg/m^2), and over (25-29.9 kg/m^2) weight, and obese (30 kg/m^2)). Energy intake (kilocalories per day; quintiles) was based on dietary information from a self-administered food frequency questionnaire. Physical activity was based on hours per day spent engaging in moderate or vigorous activities (categorized into 0 and quartiles of non-zero values)[12–14]. Education (high school graduate, some college, college graduate, graduate and professional school) refers to the highest level

attained. Missing categories were included as applicable and missing data for variables such as education, BMI, smoking status, and age at menarche were low (1.6%-2.7%).

Address History, Geocoding, and Contextual Data

The MEC actively maintains accurate and up-to-date addresses on all participants via periodic mailings of newsletters, follow-up questionnaires, and linkages to administrative data and registries. For the 57,589 female Southern CA MEC participants included in this study, there were 94,256 addresses recorded during the follow-up period. Residential addresses were geocoded to latitude and longitude coordinates of parcels or street segments whenever parcels could not be identified. Geocoded addresses from 1993 through 2010 were linked to 1990 (1993-996 addresses), 2000 (1997-2005 addresses), and 2010 (2006-2010 addresses) U.S. Census block groups. Each MEC participant was assigned a composite measure of neighborhood socioeconomic status (nSES)[15, 16] based on the Census block group of her residential history across the study period that was categorized into quintiles based on the nSES distribution of Los Angeles County block groups. Straight line distances were calculated from baseline residential addresses to different road classes as defined by the U.S. Census Topologically Integrated Geographic Encoding and Referencing (TIGER) files: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), and A3 (smaller, secondary roads, usually with more than two lanes).

Air Pollution Exposure Assessment

In brief, kriging interpolation was used to estimate largely regional air pollution exposures for nitrogen dioxide (NO_2), nitrogen oxides (NO_x), particulate matter with aerodynamic diameter less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$)[17]. Measured concentrations of NO_2, NO_x, PM_{10} in 1993-2010 and $PM_{2.5}$ in 2000-2010 were obtained from U.S. EPA routine air monitoring data. $PM_{2.5}$ concentrations in 1993-999 were estimated from a published spatiotemporal model that used PM_{10}, meteorological variables, and spatial effect as predictors[18]. The LUR model was used to estimate regional and local NO_2 and NO_x exposures based on air monitoring data from spatially dense air monitoring campaigns and incorporated data on land use and traffic characteristics; monthly scaling factors for temporal adjustment were applied based on routinely collected long-term air monitoring data nearest to the participant's home[10, 11]. We have shown strong correlations (R^2= 0.88-0.92) between measured and modeled NO_x[19]. The CALINE4 model was used to estimate local traffic exposures of NO_x and $PM_{2.5}$ within 1500 meters of a residential location based on traffic emissions, meteorological, and roadway data[20–22]. Additional detailed methods are described in the Supplemental Material and Supplemental Figure 1, including the distribution of study participants with available air pollutant data for each exposure assessment approach (Supplemental Table 1). A correlation matrix of air pollutants (Supplemental Table 2) showed weak correlation between kriging assessed regional pollutants (oxides and PM) and CALINE4 NOx (R^2<0.22). LUR modeled pollutants (oxides), representing regional and local pollutants, were modestly correlated with kriging and CALINE4 assessed pollutants (R^2=0.26-0.61).

Statistical Analysis

As air pollutant exposures varied over time and the duration of exposures differed across participants, we employed time-dependent approaches to assess air pollutant exposures and evaluate their effects on breast cancer risk. For every participant's residential history across the study period, we calculated a set of cumulative average exposures for a series of time intervals, which were defined as the time between month (Kriging and LUR)/year (CALINE4) of cohort entry and each month/year during the follow up until the censor month/year (i.e., time of breast cancer diagnosis, death, or study end). These series of average exposures entered into the Cox proportional hazard models as time-dependent variables via the counting process style of input. During the regression calculation, the average exposure across the time interval starting from entry time until the time of the event was used for risk calculations. The regression model used age at cohort entry (five-year age categories) as a strata variable and also adjusted for breast cancer risk factors at baseline and yearly estimates of nSES at baseline and at time of event. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for a standard size increase in an air pollutant were calculated to compare effect estimates derived from different exposure assessment approaches for a specific pollutant. We selected a standard size increase for each pollutant as follows. For NO_x, which was measured by all three methods, we chose 50 ppb, which was close to the IQR of krigged (50.2 ppb) and LUR (45.6 ppb) although it was almost 4 times higher than the IQR for CALINE4 NO_x (8.7 ppb). By selecting this common fixed unit, it allowed for comparison across the three exposure assessment methods. For the same reason, we chose 20 ppb for NO_2 as the IQR for NO_2 was 16.5 ppb and 18.6 ppb determined by kriging and LUR, respectively. For PM_{10} and $PM_{2.5}$, we chose 10 μg/m^3 as this was close to the IQR of krigged PM_{10} (8.9 μg/m^3) but was higher than the respective IQRs for krigged (3.8 μg/m^3) and CALINE4 $PM_{2.5}$ (2.5 μg/m^3). We also examined co-pollutant models in which kriging models of NO_x or NO_2 were adjusted for $PM_{2.5}$ and PM_{10}, and LUR models of NO_x or NO_2 were also adjusted for gaseous pollutants determined by kriging. As similar findings were observed (data not shown), single pollutant models are presented.

We checked the proportional hazard assumption in a model with all covariates by graphing Schoenfeld residuals against time and found no violation of this assumption. Stratified analyses were conducted by race/ethnicity and baseline nSES as associations may be stronger in nonwhites and by distance of the residential address at baseline to major roads (<200, 200-<500, 500-<1600, >1600m) as proximity to major roads has been found to influence risk in some air pollution studies of lung[23–25] and breast cancers[5]. In addition, we conducted analysis separately for risk of hormone receptor-positive (ER+ and/or PR+; ER+PR+) and hormone receptor-negative (ER− and PR−; ER−PR−) breast tumors as heterogeneity in breast cancer risk factors by hormone receptor subtypes is well recognized[26]. We conducted sensitivity analyses to examine risk patterns by follow-up time (<10 years vs   10 years) between air pollution exposure and breast cancer incidence. We tested for heterogeneity in associations by race/ethnicity and distance to a major road by including an interaction term for each pollutant with race/ethnicity and distance as applicable. All *P* values presented are two-sided with a significance level of 0.05. Analyses were performed using SAS 9.2 statistical software (SAS Institute, Cary, NC).

We conducted a meta-analysis of breast cancer risk in relation to LUR NO_x and NO_2 by including published studies that specifically conducted intensive field campaigns to capture LUR NO_x and NO_2 in urban areas. The specific LUR studies included in our meta-analyses were the 11 cohorts within the ESCAPE Project[1] that collected data on both NO_x and NO_2 and three Canadian case-control studies that assessed exposure to LUR NO_2. The published study-specific adjusted risk estimates[1] and MEC results were meta-analyzed according to the DerSimonian and Laird random effects model,[27] using comparable standardized units of exposure across studies. Between-study heterogeneity was tested by the Cochran's Q test and quantified by I^2. Meta-analysis was performed using STATA 11 (Stata-Corp, College Station, TX) and additional methods are described (Supplemental Material).

Results

The study population consisted of 57,589 women (36% African American, 10% Japanese American, 38% Latino, and 15% white) with racial/ethnic differences in the prevalence of obesity, smoking, parity, age at first birth, and other breast cancer risk factors (Table 1). African Americans (37%) and Latinos (27%) were more likely to live in the lowest SES neighborhoods (quintile 1) at baseline in comparison with Japanese Americans (5%) and whites (7%). The proportion of non-movers over the study period was highest in Japanese Americans (71%) but similar in other racial/ethnic groups (55% to 57%). Thirty percent of the residential addresses at baseline were within 500 meters of major roads, ranging from 23% among African Americans to 35% among Latinos.

Secular changes and spatial patterns of air pollutant exposure were captured in this study (Supplemental Figure 2). Using LUR NO_x as an example, we presented levels at three time points, baseline (1993), mid-study period (2003), and study end (2010) showing a steady decline in this pollutant so that the median levels in 2010 were about half of that in 1993 (Supplemental Figure 3). Similar patterns of declines were observed for the other pollutants we investigated although the magnitude of decline differed. These changing air pollutant levels were captured in our Cox proportional hazard models with time-varying exposures (see Statistical Analysis).

Among all women, a positive association with breast cancer was suggested for NO_x and NO_2 exposure assessed by kriging and LUR as well as PM_{10} and $PM_{2.5}$ exposure assessed by kriging (HR range=1.04-.12; p value range=0.15-0.62; Table 2). Although there was no formal statistical evidence of heterogeneity in effects by race/ethnicity, statistically significant positive associations were observed in African Americans and Japanese Americans but not for Latinos and whites. For example, for LUR NO_x, an increase in exposure by 50 ppb was associated with a 26% (95% CI: 1.01-.58) and 42% (95% CI: 1.05-.91) increased risk of breast cancer in African Americans and Japanese Americans, respectively. For CALINE4 NO_x, an increase in exposure by 50 ppb was associated with an increased risk of breast cancer in Japanese Americans (HR=1.97; 95% CI: 0.99-3.92) but a reduced risk (HR=0.62, 95% CI: 0.39-0.99) in Latinos (P heterogeneity = 0.05). Risk associations were generally similar by nSES or by smoking status (data not shown).

Risk of breast cancer was not significantly associated with residential distance to major roads. Compared with women who lived furthest away from major roads (>1600 meters (m)), those who lived 500 -<1600, 200-<500, and <200 m showed HRs of 1.07 (95% CI: 0.97-.18), 1.06 (95% CI: 0.94-.19), and 1.02 (95% CI: 0.80-.18), respectively (Supplemental Table 3). However, the risk patterns associated with krigged and LUR pollutants differed in analyses stratified by distance to major roads (i.e., <200, 200-<500, 500-<1600, >1600 m) (Supplemental Table 3). For krigged PM_{10} LUR NO_x and LUR NO_2, the respective HR was highest and statistically significant among those living closest (<200 m) to major roads; the HR was 1.39 (95% CI: 1.02-.90), for krigged PM_{10} and 1.39 (95% CI: 1.04-.86) for LUR NO_x, and 1.73 (95% CI: 1.19-2.52) for LUR NO_2. Risks associated with exposure to krigged NO_x and krigged $PM_{2.5}$ were also higher among those who lived 200-<500 m of major roads; the respective HRs were 1.49 (95% CI: 1.03-2.14) and 1.86 (95% CI: 1.02-3.41). When we combined categories for those living <200 m and 200-<500m of major roads, women who lived within 500 m to major roads (Table 3) showed statistically significant increased risks of breast cancer for all krigged (NO_x, NO_2, PM_{10}, $PM_{2.5}$) and LUR (NO_x, NO_2) pollutants but not for CALINE4 pollutants (NO_x, $PM_{2.5}$). Results by distance were largely the same in movers and non-movers (data not shown). In contrast, there were no significant increased risk associated with exposure to any of these air pollutants among women who lived >500 m of roadways.

In subgroup analyses by hormone receptor status (Table 4), increased risk of ER−PR− breast cancer was suggested with a per 10 μg/m^3 increase in krigged PM_{10} for all women (HR=1.25; 95% CI: 0.96-.63) with a larger effect estimate among Japanese Americans (HR=3.90; 95% CI: 1.34-1.39). Interestingly, in subgroup analyses by hormone receptor status and distance to major roads (data not shown), risk of ER+PR+ breast cancer was significantly increased in association with krigged NO_x (HR=1.54, 95% CI:1.07-2.21). Risk of ER−PR− breast cancer was borderline significantly increased in association with LUR NO_2 (HR=1.80, 95% CI: 0.97-3.34) and statistically significantly increased with krigging PM_{10} (HR=1.94, 95% CI:1.15-3.24) and $PM_{2.5}$ (HR=5.30, 95% CI: 1.24-22.64).

We did not find any differences in results by follow-up time (<10 years vs 10 years) between air pollutants and risk of breast cancer (data not shown). As an example, for LUR NO_x, the HR was 1.01 (95% CI: 0.87-.16) for <10 years vs 1.07 (95% CI: 0.85-1.35) for 10 years of follow-up.

The meta-analysis of the associations between LUR NO_x and breast cancer among 11 cohorts within the ESCAPE Project[1] and the MEC provide further evidence that NO_x exposure impacts breast cancer risk (per 20 μg/m^3 meta-analysis HR=1.023; 95 % CI: 1.002-1.046; I^2 =7.2, 11df; Supplemental Figure 4). The meta-analysis of the association between LUR NO_2 (per 10 μg/m^3) and breast cancer risk also showed an elevated risk that was not statistically significant (HR=1.020; 95 % CI: 0.991-1.049; I^2 =11.1, 14df; data not shown).

Discussion

To our knowledge, this is the first large multiethnic cohort to employ three exposure assessment approaches (kriging interpolation, LUR, and CALINE4 models, Supplemental Figure 1) to estimate NO_x and risk of breast cancer. In addition, exposure history to NO_2 and $PM_{2.5}$ was assessed by two of the three assessment approaches so that we comprehensively and prospectively evaluated the impact of both gaseous and particulate matter air pollutants on breast cancer risk in the MEC. Although our prior expectations were that temporally adjusted LUR would provide increased precision and variability of individual exposure, both LUR and kriging were positively but not significantly associated with breast cancer risk. Nevertheless, increased risks of breast cancer ($p<0.05$) were most prominent with exposure to LUR NO_x among Japanese Americans and African Americans, and while the effect estimates for NO_x based on LUR models had narrower confidence intervals than for NO_x from kriging or CALINE4 models all of these exposures were consistently positively associated with the outcome. Among women living close to major roads (<200 m and 200-<500 m), increased risk of breast cancer was significantly associated with krigged (NO_x, NO_2, PM_{10}, $PM_{2.5}$) and LUR (NO_x and NO_2) derived pollutant measures and displayed comparable effect sizes of NO_x and NO_2 measured by LUR and kriging. Results for CALINE4 models were less consistent as the stratified analysis by proximity to major roadways (<500 vs 500m) yielded nearly identical risk estimates, which may reflect the difficulty to refine exposures when assessing the impact of local traffic within 1500m (see below). Lastly, the meta-analysis of MEC results with those from ESCAPE, comprising 11 European cohorts[1] also indicated a positive association between LUR NO_x and breast cancer.

The significant associations and larger effect sizes seen for both particulate matter (PM_{10}, $PM_{2.5}$) and nitrogen oxides (NO_x, NO_2) determined by kriging and LUR models among women residing within 500 meters of major roadways are intriguing as the proximity to major roadways measure (<200, 200-<500, 500-<1600, >1600m) was not significantly associated with risk. Previous studies have examined proximity effects using buffers of 100 m[23, 24], 200 m[5], and 300 m[11]. We selected multiple cut points including <200 m, 200-<500 m, and <500 m as previous studies showed an impact zone of primary local traffic emission of approximately 300m in the daytime with good mixing[28] and a wider impact zone before sunrise with stable atmosphere[29]. In a study of predictors of intra-community variation in air pollution in Los Angeles County, Franklin and colleagues[30] found that compared with living at least 1,500m from a freeway, living within 250m of a freeway was associated with 41% to 75% increase in traffic-related air pollutants depending on the size of the urban area. These results support our finding of consistent positive HRs associated with krigged and LUR air pollutant exposure for those who lived <200 m and 200-<500 m (Supplemental Table 3). Our results are compatible with studies of lung cancer, coronary heart disease, and other health endpoints, which have identified the importance of near-roadway air pollution[31–33]. Few studies on air pollution and breast cancer have examined proximity to major roads, but results from the Nurses' Health Study also point to the importance of air pollution effects by proximity to major roads[5] with the suggestion of increased risk for women living <50m of the largest road type compared to those living > 200 m away. These findings support the

need for further investigations of near roadway exposures and breast cancer risk to understand whether air pollution composition, sources of exposure (e.g., vehicle vs non-vehicle) or some other factors are involved.

These findings in the MEC also support recent results from the ESCAPE Project, which exclusively used LUR models to assess air pollution exposure, and reported an increased risk of breast cancer associated with LUR NO_x[1]. For LUR NO_x and breast cancer, meta-analysis of MEC results with those from ESCAPE[1] demonstrated a significant association with no evidence of heterogeneity (Supplemental Figure 4) and a statistically non-significant increased risk in association with LUR NO_2. These collective findings suggest that the LUR approach with high temporal and high spatial resolution may be a valuable approach for capturing both regional and local long-term air pollutant exposures.

It is of note that CALINE4 (dispersion modelling) estimate of NO_x, local traffic exposures was not significantly associated with breast cancer risk in our study. Several limitations may have contributed to uncertainties in CALINE4 model estimates in this study. In CALINE4 simulations, traffic counts in 2002 were scaled to other years using total vehicle miles traveled for the region in each year, assuming traffic counts decreased or increased at the same scale on all roads. This likely introduced uncertainties in traffic counts on individual roads and subsequently affected CALINE4 simulations. We also used meteorological data from the closest meteorological monitoring stations with more than 75% of complete data in a given year. Depending on the missingness in data, these stations were up to 80 km of each residential location. The heterogeneously distributed meteorological stations and frequent missing data in some years likely further affected the quality of the CALINE4 estimates. Future studies using higher quality meteorological data with higher resolution and uniform spatial coverage may help to refine our CALINE4 assessment and reduce exposure misclassification.

Weaker associations for $PM_{2.5}$, PM_{10}, NO_2, and NO_x have been reported in prospective cohort studies that used single air pollution approaches in the U.S. (spatial-temporal modelling[5] and kriging[6]), Denmark (dispersion modelling),[7,8] and Canada (satellite-based modelling)[34]. A recent review of air pollution and breast cancer was reported by White et al. [35] summarizing these published studies. Multiple reasons may contribute to these not all consistent findings. Accurate assessment of long-term ambient air pollution exposure is notoriously difficult[36,37] with incomplete residential history as a common limitation. Most prior studies have relied on a single residential location at either baseline or at the most recent residence to estimate air pollution exposure with much less dense monitoring of exposures prior to 1990. The latter concern also affects case-control studies[2,3] and cohort studies[6,34] that typically estimated air pollution exposure based on residential address at diagnosis of cancer or study enrollment. Some case-control studies with lifetime residential history[38,39] determined historical air pollution monitoring data by imputation of past exposures. Information on residential history prior to cohort entry was not available in the MEC, but it was complete for up to 18 years after cohort entry – a time of intense air pollution monitoring in Los Angeles during which we captured secular changes and spatial patterns (Supplemental Figure 2).

Previous studies have been largely limited to whites while the MEC includes a large, diverse, multiethnic population. Reasons for the stronger associations observed among African Americans and Japanese Americans in comparison to Latinos and whites in the MEC are not apparent and may be related to geographic differences in residence and associated exposures. African American and Japanese American communities in the MEC are more clustered in Los Angeles County than whites or Latinos (Supplemental Figure 5). These communities are situated along the two sides of the 405 freeway in Los Angeles County with exposures not only from vehicle emissions but also refineries, ports,[40] and from the Los Angeles International Airport[41]. The proximity of African American and Japanese American communities to major sources of pollutant exposures may have contributed to the distinct risk patterns we observed. In addition, we controlled for the established risk factors for breast cancer, but found that racial/ethnic differences in the prevalence of established risk factors (e.g., BMI, parity, age at menopause) are unlikely to account for the observed associations.

It is intriguing that findings were suggestive for ER−PR− breast cancer risk and krigged PM_{10} exposure in all MEC women except for whites. Previous studies by hormone receptor status are not consistent. NO_2 exposure was associated with ER+PR+ breast cancer in the Sister Study[6] and a recent case-control study in Montreal[4]. However, high levels of benzene and exposure to traffic-related benzo(a)pyrene exposure was implicated for ER−PR− breast cancer respectively in the California Teachers Cohort[42] and Long Island Breast Cancer study[43]. Given the incomplete understanding of the etiology of ER−PR− breast cancers, the potential role of air pollution warrants further investigation.

The specific mechanism by which gaseous and particulate matter air pollutants may influence breast cancer development is not known. Exposure to NO_x and NO_2 is believed to be a proxy of exposure to traffic-related air pollutants, which is a complex mixture containing numerous polycyclic aromatic hydrocarbons (PAHs), benzo(a)pyrene (BaP), benzene, metals, and other chemicals. PAHs have well-documented mutagenic and carcinogenic effects and have been shown to cause mammary cancers in rodent models[44]. Traffic-related PAH exposures may increase risk by increasing the formation of PAH-DNA adducts in breast tissues[45]. The Long Island Breast Cancer Study found a higher risk of breast cancer in relation to PAH-adducts in blood lymphocytes although traffic pollutants was only one of the sources of PAHs[46]. Methylation may be another potential biologic mechanism as PAH sources have been associated with hypo- and hypermethylation at multiple promoter regions in breast tumors and in blood of control women[35]. Two of the ESCAPE cohorts conducted a genome-wide DNA methylation study in relation to exposure to gaseous and particulate matter pollutants and found association between global hypomethylation with exposure to NO_x (P=0.089) and NO_2 (P=0.014) but not to exposures of particulate matter[47]. High epigenome-wide DNA methylation in pre-diagnostic blood samples has been associated with lower risk of breast cancer[48] . Thus, it is a reasonable hypothesis that hypomethylation, often a hallmark of genetic instability, in relation with exposure to traffic-related air pollutants may lead to high risk of breast cancer.

Despite notable strengths in this study, there are also some limitations. Although exposure to NO_x was assessed by all three methods (kriging, LUR, and CALINE4), NO_2 (kriging and

LUR) and $PM_{2.5}$ (kriging and CALINE4) were assessed by two methods while PM_{10} was assessed by kriging only. Information on LUR PM_{10} and $PM_{2.5}$ was not available because we used previously published LUR models for Los Angeles[19], Orange[49] and San Diego[50] counties, which used Ogawa passive air samplers to conduct dense sampling of ambient of NO_x and NO_2 but not the particulate matter pollutants. Our CALINE4 approach modeled local traffic emissions and characterized Gaussian dispersion but did not consider other physical and chemical mechanisms such as photochemistry and hence we did not have reliable estimates of NO_2 exposure[51, 52]. While we have estimates of CALINE4 $PM_{2.5}$, they were highly correlated ($R^2=0.99$) with NO_x. We do not have specific emission source information but the krigged estimates were based on regional measured pollutant concentrations. Our LUR models of NO_x and NO_2 reflected mainly local and regional traffic emission as five out of the nine predictor variables were traffic-related but other sources (e.g., industrial, commercial, others) were also predictors of the LUR model[19]. We recognize that the use of distance to major road at baseline address may introduce misclassification, yet we observed similar positive associations as seen in Table 3 when restricting our analysis to non-movers. Future studies that also collect emission sources will likely advance our understanding of the relationship between ambient air pollution and breast cancer risk.

Information on residential history prior to cohort entry was not available; thus, the influence of exposures in earlier time windows was not investigated. Our assessment is only based on location of residence. Most adults may spend part of the day away from their residences while commuting and working. It is estimated that California adults spent about 87% of their time indoors;[53] however, we have no assessment of time spent outdoors for each individual. Thus, while we have captured a key component of the exposure of interest, random misclassification may exist in our assessment of air pollution exposure but this misclassification should be non-differential and would diminish our power to identify any true associations[54, 55]. In addition, it is difficult to separate effects from a mixture of air pollutants into its components. Although consistent patterns of associations were observed for certain subgroups (e.g., smoking status, nSES; data not shown), we cannot rule out the possibility of chance and false positive associations given the number of comparisons made. Lastly, we are not aware of and thus unable to control for residual confounding due to any breast cancer risk factors that are also associated with proximity to major roads or other air pollution exposures.

In conclusion, this prospective study of air pollution and breast cancer captured long-term spatial and temporal variation in air pollution exposures, using kriging, LUR, and CALINE4 modelling approaches, among Southern California female participants in the MEC. The collective findings suggest NO_x assessed by LUR and air pollutants near major roadways are associated with breast cancer risk. Additional well-designed studies in multiethnic populations comparing air pollution measures based on different assessment approaches are warranted to understand the role of ambient air pollution on breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations:

MEC	Multiethnic Cohort
CA	California
LUR	Land use regression
CALINE4	California line source dispersion Model, version 4

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Novelty and Impact:

Prior studies of air pollution and breast cancer have focused on a single exposure assessment among primarily white women. In this study, we used three exposure assessment methods to investigate the association between long-term air pollutant exposure and risk of breast cancer in a Multiethnic Cohort of 57,589 women from Southern California. Breast cancer risk was significantly increased in association with air pollution exposure among women residing near major roads. These findings warrant further confirmation in multiethnic populations.

Table 1.

Distributions of breast cancer risk factors and neighborhood factors by race/ethnicity among CA MEC women at baseline, 1993-1996[a]

	All Women (n=57,589)[b]		African Americans (n=20,695)		Japanese Americans (n=6,016)		Latinos (n=22,037)		Whites (n=8,766)	
	N	%	N	%	N	%	N	%	N	%
Age at cohort entry										
45-49	7644	13.30%	3120	15.10%	753	12.50%	2747	12.50%	1007	11.50%
50-54	8093	14.10%	2988	14.40%	736	12.20%	3285	14.90%	1070	12.20%
55-59	10837	18.80%	3064	14.80%	912	15.20%	5162	23.40%	1680	19.20%
60-64	10750	18.70%	2852	13.80%	1064	17.70%	5064	23.00%	1752	20.00%
65-69	10090	17.50%	4114	19.90%	1102	18.30%	3263	14.80%	1607	18.30%
70-74	8684	15.10%	3843	18.60%	1186	19.70%	2225	10.10%	1429	16.30%
75+	1491	2.60%	714	3.50%	263	4.40%	291	1.30%	221	2.50%
BMI										
Underweight	1039	1.80%	225	1.10%	414	6.90%	200	0.90%	197	2.20%
Normal	19271	33.50%	4760	23.00%	4078	67.80%	6530	29.60%	3882	44.30%
Overweight	19963	34.70%	7277	35.20%	1232	20.50%	8697	39.50%	2726	31.10%
Obese	16080	27.90%	7580	36.60%	275	4.60%	6278	28.50%	1927	22.00%
Family history of breast cancer in mother or sisters										
No family history	47172	81.90%	16762	81.00%	5136	85.40%	18069	82.00%	7141	81.50%
At least one of mother of sisters had breast cancer	5781	10.00%	2215	10.70%	583	9.70%	1856	8.40%	1121	12.80%
Age at first birth										
No children	6852	11.90%	2732	13.20%	1032	17.20%	1781	8.10%	1303	14.90%
< 20 Years	20976	36.40%	9304	45.00%	424	7.00%	8741	39.70%	2487	28.40%
21-30 Years	24661	42.80%	6959	33.60%	3795	63.10%	9679	43.90%	4183	47.70%
>30 Years	3261	5.70%	867	4.20%	636	10.60%	1141	5.20%	615	7.00%
Age at menarche										
<12 Years	27218	47.30%	9972	48.20%	2734	45.40%	10118	45.90%	4353	49.70%
13-14 Years	21719	37.70%	7552	36.50%	2376	39.50%	8390	38.10%	3376	38.50%
>14 Years	7488	13.00%	2654	12.80%	816	13.60%	3080	14.00%	931	10.60%
Parity										

	All Women (n=57,589)[b]		African Americans (n=20,695)		Japanese Americans (n=6,016)		Latinos (n=22,037)		Whites (n=8,766)	
	N	%	N	%	N	%	N	%	N	%
0 children (nulliparous)	6695	11.60%	2684	13.00%	1023	17.00%	1700	7.70%	1284	14.60%
1 child	6652	11.60%	3284	15.90%	718	11.90%	1545	7.00%	1094	12.50%
2-3 children	21828	37.90%	7319	35.40%	3307	55.00%	7020	31.90%	4153	47.40%
>4 children	21404	37.20%	7021	33.90%	924	15.40%	11297	51.30%	2132	24.30%
Menopause Status										
Pre-menopause	6140	10.70%	2284	11.00%	805	13.40%	2241	10.20%	798	9.10%
Natural menopause	27606	47.90%	8120	39.20%	3399	56.50%	11470	52.00%	4575	52.20%
Oopherectomy	7937	13.80%	3374	16.30%	721	12.00%	2449	11.10%	1388	15.80%
Hysterectomy	9848	17.10%	4445	21.50%	557	9.30%	3479	15.80%	1358	15.50%
Hormone Therapy Usage										
Never estrogen use, with or without past or current progesterone use	30958	53.80%	11873	57.40%	3253	54.10%	11966	54.30%	3829	43.70%
Past estrogen use, with or without past progesterone use	10042	17.40%	3987	19.30%	757	12.60%	3699	16.80%	1582	18.00%
Current estrogen use alone	6617	11.50%	2201	10.60%	782	13.00%	2262	10.30%	1361	15.50%
Current estrogen use, with past or current progesterone use	6307	11.00%	1311	6.30%	1034	17.20%	2267	10.30%	1688	19.30%
Physical Activity, hours/day										
0	4641	8.10%	1210	5.80%	149	2.50%	2927	13.30%	352	4.00%
Quartile 1, <0.4	9669	16.80%	3631	17.50%	868	14.40%	4176	18.90%	983	11.20%
Quartile 2, 0.4-<0.7	14047	24.40%	5936	28.70%	1565	26.00%	4643	21.10%	1886	21.50%
Quartile 3, 0.7-<1.2	12657	22.00%	4643	22.40%	1483	24.70%	4346	19.70%	2167	24.70%
Quartile 4, 1.2-<13.3	14308	24.80%	4354	21.00%	1862	31.00%	4847	22.00%	3219	36.70%
Energy Intake, kcal/day										
Quintile 1, 417.4-<1,158.5	10994	19.10%	4789	23.10%	1084	18.00%	3504	15.90%	1608	18.30%
Quintile 2, 1,158.5-<1,539.8	10995	19.10%	3972	19.20%	1451	24.10%	3565	16.20%	1993	22.70%
Quintile 3, 1,539.8-<1,961.1	10995	19.10%	3716	18.00%	1465	24.40%	3879	17.60%	1920	21.90%
Quintile 4, 1,961.1-<2,633.8	10995	19.10%	3646	17.60%	1185	19.70%	4402	20.00%	1746	19.90%
Quintile 5, 2,633.8-<7211.3	10995	19.10%	3601	17.40%	596	9.90%	5733	26.00%	1046	11.90%
Drinker										
Non-drinker	34396	59.70%	12455	60.20%	4224	70.20%	13758	62.40%	3910	44.60%

	All Women (n=57,589)[b]		African Americans (n=20,695)		Japanese Americans (n=6,016)		Latinos (n=22,037)		Whites (n=8,766)	
	N	%	N	%	N	%	N	%	N	%
Drinker	20578	35.70%	7269	35.10%	1557	25.90%	7325	33.20%	4403	50.20%
Smoking status										
Never smoker	30985	53.80%	9203	44.50%	4000	66.50%	13719	62.30%	4020	45.90%
Former smoker	16696	29.00%	7013	33.90%	1417	23.60%	5127	23.30%	3122	35.60%
Current smoker	8346	14.50%	4139	20.00%	541	9.00%	2150	9.80%	1502	17.10%
Education										
<=High school graduate	30329	52.70%	8581	41.50%	2140	35.60%	16046	72.80%	3532	40.30%
Some college	16353	28.40%	7407	35.80%	2167	36.00%	3904	17.70%	2844	32.40%
College graduate	5184	9.00%	2274	11.00%	1028	17.10%	776	3.50%	1098	12.50%
Graduate and professional school	4787	8.30%	2108	10.20%	624	10.40%	856	3.90%	1195	13.60%
Baseline neighborhood SES										
Quintile 1 - Low	14597	25.30%	7671	37.10%	293	4.90%	5970	27.10%	652	7.40%
Quintile 2	15080	26.20%	6006	29.00%	754	12.50%	6886	31.20%	1423	16.20%
Quintile 3	11286	19.60%	3156	15.30%	1475	24.50%	4667	21.20%	1966	22.40%
Quintile 4	9740	16.90%	2711	13.10%	1826	30.40%	2832	12.90%	2352	26.80%
Quintile 5 - High	6255	10.90%	806	3.90%	1646	27.40%	1475	6.70%	2318	26.40%
Number of residential moves over follow-up										
0	33367	57.90%	11840	57.20%	4266	70.90%	12208	55.40%	5010	57.20%
1-2	19592	34.00%	7030	34.00%	1596	26.50%	7748	35.20%	3191	36.40%
3-5	4402	7.60%	1729	8.40%	148	2.50%	1976	9.00%	544	6.20%
6+	228	0.40%	96	0.50%	6	0.10%	105	0.50%	21	0.20%
Distance of baseline address to the nearest major road[c], meters										
<500	17075	29.60%	4738	22.90%	1939	32.20%	7628	34.60%	2770	31.60%
500	40514	70.40%	15957	77.10%	4077	67.80%	14409	65.40%	5996	68.40%

[a] Numbers may not total to 100% due to missing

[b] Includes Native Hawaiians (9 cases/75 cohort); numbers not shown separately

[c] Major roads classified according to U.S. Census: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), and A3 (smaller, secondary roads, usually with more than two lanes)

Table 2.

Associations of gaseous and particulate matter air pollutants and risk of breast cancer by race/ethnicity among CA MEC women, 1993–2010[a,b,c]

Exposure Assessment	Air Pollutant[d]	All Women*			African Americans			Japanese Americans			Latinos			Whites		
		Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI
Kriging	NOx	2693	1.12	(0.96-1.31)	1024	1.19	(0.93-1.51)	315	1.28	(0.72-2.27)	834	1.26	(0.92-1.74)	512	0.98	(0.68-1.40)
	NO2	2727	1.09	(0.91-1.31)	1058	1.15	(0.86-1.53)	315	1.42	(0.79-2.55)	834	1.10	(0.75-1.62)	512	1.00	(0.69-1.47)
	PM10	2729	1.05	(0.95-1.16)	1059	1.02	(0.88-1.17)	315	1.26	(0.86-1.83)	834	1.14	(0.9-1.44)	513	1.09	(0.85-1.39)
	PM2.5	2726	1.10	(0.85-1.42)	1057	1.04	(0.72-1.50)	315	1.54	(0.61-3.89)	833	1.50	(0.83-2.71)	513	1.09	(0.60-1.97)
LUR	NOx	2557	1.08	(0.96-1.22)	934	**1.26**	**(1.01-1.58)**	312	**1.42**	**(1.05-1.91)**	810	0.99	(0.80-1.24)	493	0.92	(0.71-1.20)
	NO2	2590	1.04	(0.90-1.20)	961	1.14	(0.87-1.49)	312	1.34	(0.93-1.92)	811	0.88	(0.67-1.15)	498	0.99	(0.75-1.32)
CALINE4	NOx	2352	0.97	(0.73-1.26)	882	1.11	(0.67-1.86)	273	1.97	(0.99-3.92)	742	0.62	(0.39-0.99)	447	1.10	(0.59-2.05)
	PM2.5	2352	1.00	(0.92-1.09)	882	1.06	(0.90-1.26)	273	1.25	(1.01-1.54)	742	0.87	(0.75-1.01)	447	1.03	(0.84-1.26)

NOTE: Values in bold represent $P < 0.05$.

[a] HR=Hazard Ratio; CI=Confidence Intervals. HR represent the increase in breast cancer per 50 ppb NOx, 20 ppb NO2, $10 ug/m^3$ PM10, PM2.5 (Kriging); per 50 ppb NOx, 20 ppb NO2 (LUR), per 50 ppb NOx. 1 ug/m3 PM2.5 (CALINE4). Models adjusted for age at entry (as a strata variable, 5-year categories), race/ethnicity for all women, BMI, family history of breast cancer, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity, energy intake, alcohol use, smoking, education, neighborhood SES.

[b] Phet by race/ethnicity 0.05 for all pollutants

[c] Among all women HR and 95% CI representing increase in interquartile range (IQR) of kriging NOx (50.2 ppb) HR=1.12 (0.96-1.13), NO2 (16.5 ppb) HR=1.08 (0.93-1.25),

[d] Interquartile range: Kriging NOx (50.2 ppb), NO2 (16.5 ppb), PM10 (8.9 ug/m³), PM2.5 (3.8 ug/m3), LUR NOx (45.6 ppb), NO2 (18.6 ppb), CALINE4 NOx (8.7 ppb), PM 2.5

Table 3.

Associations of gaseous and particulate matter air pollutants and risk of breast cancer by distance to major roads among CA MEC women, 1993-2010[a,b]

Exposure Assessment	Air pollutant	Distance to major roads[c] <500m			Distance to major roads[c] 500m		
		Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI
Kriging	NO_X	781	**1.35**	**(1.02-1.79)**	1912	1.05	(0.87-1.27)
	p value			**0.04**			0.61
	NO_2	791	**1.44**	**(1.04-1.99)**	1936	0.98	(0.78-1.21)
	p value			**0.03**			0.82
	PM_{10}	792	**1.29**	**(1.07-1.55)**	1937	0.95	(0.85-1.08)
	p value			**0.01**			0.45
	$PM_{2.5}$	791	**1.85**	**(1.15-2.99)**	1935	0.89	(0.65-1.21)
	p value			**0.01**			0.45
LUR	NO_X	738	**1.21**	**(1.01-1.45)**	1819	1.02	(0.86-1.22)
	p value			**0.04**			0.80
	NO_2	748	**1.26**	**(1.00-1.59)**	1842	0.93	(0.77-1.12)
	p value			**0.05**			0.43
CALINE4	NO_X	671	0.99	(0.68-1.44)	1681	1.07	(0.59-1.94)
	p value			0.95			0.83
	$PM_{2.5}$	671	1.01	(0.90-1.14)	1681	1.04	(0.85-1.26)
	p value			0.85			0.73

NOTE: Values in bold represent P 0.05.

[a]HR=Hazard Ratio; CI=Confidence Intervals. HR represent the increase in breast cancer per 50 ppb NO_X, 20 ppb NO_2, 10ug/m^3 PM_{10}, $PM_{2.5}$ (Kriging); per 50 ppb NO_X, 20 ppb NO_2 (LUR), per 50 ppb NOX, 1 ug/m^3 $PM_{2.5}$ (CALINE4). Models adjusted for age at entry (as a strata variable, 5-year categories), race/ethnicity for all women, BMI, 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, education, neighborhood SES.

[b]Phet by distance to major road >0.05 for all pollutants.

[c]Major roads classified according to U.S. Census: A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), and A3 (smaller, secondary roads, usually with more than two lanes)

Table 4.

Associations of gaseous and particulate matter air pollutants and risk of breast cancer by hormone receptor status and race/ethnicity among CA MEC women, 1993-2010[a,b]

Exposure Assessment	Air pollutant[c]	All Women			African Americans			Japanese Americans			Latinos			Whites		
		Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI	Case (n)	HR[a]	95% CI
ER+/PR+ Breast Cancer																
Kriging	NOx	1762	1.13	(0.93-1.37)	631	1.19	(0.89-1.61)	233	1.16	(0.59-2.25)	517	1.19	(0.79-1.80)	374	1.11	(0.72-1.71)
	NO2	1789	1.06	(0.85-1.32)	658	1.02	(0.72-1.44)	233	1.09	(0.55-2.16)	517	1.24	(0.76-2.04)	374	1.16	(0.74-1.82)
	PM10	1791	0.97	(0.86-1.09)	659	0.90	(0.76-1.07)	233	0.99	(0.64-1.55)	517	1.12	(0.84-1.50)	375	1.19	(0.89-1.60)
	PM2.5	1791	0.96	(0.71-1.31)	659	0.91	(0.59-1.40)	233	1.12	(0.39-3.25)	517	1.39	(0.67-2.88)	375	1.18	(0.59-2.35)
LUR	NOx	1672	1.07	(0.92-1.25)	570	1.26	(0.94-1.69)	231	1.29	(0.91-1.83)	503	1.00	(0.75-1.32)	361	0.95	(0.69-1.30)
	NO2	1692	0.98	(0.63-1.51)	587	1.07	(0.45-2.52)	231	1.11	(0.38-3.27)	504	0.85	(0.36-1.99)	363	1.03	(0.45-2.38)
CALINE4	NOx	1560	0.91	(0.64-1.29)	553	1.12	(0.58-2.17)	201	1.16	(0.92-4.65)	466	**0.51**	**(0.27-0.95)**	333	1.01	(0.48-1.10)
	PM2.5	1560	0.98	(0.88-1.10)	553	1.07	(0.86-1.33)	201	1.25	(0.97-1.60)	466	0.82	(0.67-1.00)	333	1.01	(0.80-1.28)
ER-/PR- Breast Cancer																
Kriging	NOx	430	0.87	(0.59-1.27)	189	0.83	(0.48-1.46)	39	1.00	(0.20-5.00)	140	1.19	(0.54-2.62)	61	0.63	(0.23-1.72)
	NO2	435	0.95	(0.60-1.51)	194	1.04	(0.51-2.10)	39	4.28	(0.78-23.40)	140	0.74	(0.29-1.91)	61	0.57	(0.20-1.61)
	PM20	435	1.25	(0.96-1.63)	194	1.26	(0.88-1.82)	39	**3.90**	**(1.34-11.39)**	140	1.40	(0.78-2.50)	61	0.70	(0.35-1.39)
	PM2.5	433	1.25	(0.65-2.44)	193	1.07	(0.44-2.63)	39	5.19	(0.35-76.84)	139	1.63	(0.36-7.34)	61	0.8	(0.14-4.39)
LUR	NOx	401	1.22	(0.90-1.64)	169	1.33	(0.79-2.23)	39	2.02	(0.89-4.58)	135	1.02	(0.60-1.73)	57	1.16	(0.54-2.50)
	NO2	411	1.2	(0.83-1.72)	176	1.26	(0.67-2.34)	39	**3.81**	**(1.47-9.88)**	135	0.77	(0.39-1.53)	60	0.96	(0.42-2.20)
CALINE4	NOx	376	0.96	(0.48-1.94)	159	0.70	(0.19-2.61)	35	2.67	(0.45-15.83)	124	0.63	(0.19-2.08)	57	2.15	(0.46-10.14)
	PM2.5	376	1.00	(0.80-1.25)	159	0.88	(0.57-1.37)	35	1.40	(0.83-2.36)	124	0.88	(0.61-1.28)	57	1.25	(0.75-2.08)

NOTE: Values in bold represent $P< 0.05$.

[a] HR=Hazard Ratio; CI=Confidence Intervals. HR represent the increase in breast cancer per 50 ppb NOX, 20 ppb NO2, 10ug/m3 PM10, PM2.5 (Kriging); per 50 ppb NOX, 20 ppb NO2 (LUR), per 50 ppb NOX, 1 ug/m3 PM2.5 (CALINE4). Models adjusted for age at entry (as a strata variable, 5-year categories), race/ethnicity for all women, BMI, family history of breast cancer, age at menarche, number of children, menopausal status, hormone replacement therapy, physical activity, energy intake, alcohol use, smoking, education, neighborhood SES.

[b] Phet by race/ethnicity 0.05 for all pollutants except CALINE4 NOX p het=0.04

[c] Kriging per 50 ppb NOX, 20 ppb NO2, 10ug/m3 PM10, PM2.5; LUR per 50 ppb NOX, 20 ppb NO2; CALINE4 per 50ppb NOX, 1 ug/m, PM2.5