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Outdoor ambient air pollution and breast cancer survival among California participants of the Multiethnic Cohort Study

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CRediT authorship contribution statement

Iona Cheng: Conceptualization, Funding acquisition, Investigation. **Juan Yang:** Formal analysis, Investigation. **Chiuchen Tseng:** Formal analysis, Investigation. **Jun Wu:** Data curation, Investigation. **Shannon M. Conroy:** Investigation. **Salma Shariff-Marco:** Investigation. **Scarlett Lin Gomez:** Investigation. **Alice S. Whittemore:** Investigation. **Daniel O. Stram:** Investigation. **Loïc Le Marchand:** Investigation. **Lynne R. Wilkens:** Investigation. **Beate Ritz:** Data curation, Investigation. **Anna H. Wu:** Conceptualization, Funding acquisition, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107088.

Abstract

Background: Within the Multiethnic Cohort (MEC), we examined the association between air pollution and mortality among African American, European American, Japanese American, and Latina American women diagnosed with breast cancer.

Methods: We used a land use regression (LUR) model and kriging interpolation to estimate nitrogen oxides (NO_x, NO_2) and particulate matter ($PM_{2.5}$, PM_{10}) exposures for 3,089 breast cancer cases in the MEC, who were diagnosed from 1993 through 2013 and resided largely in Los Angeles County, California. Cox proportional hazards models were used to examine the association of time-varying air pollutants with all-cause, breast cancer, cardiovascular disease (CVD), and non-breast cancer/non-CVD mortality, accounting for key covariates.

Results: We identified 1,125 deaths from all causes (474 breast cancer, 272 CVD, 379 non-breast cancer/non-CVD deaths) among the 3,089 breast cancer cases with 8.1 years of average follow-up. LUR and kriged NO_X (per 50 ppb) and NO_2 (per 20 ppb), $PM_{2.5}$ (per 10 μg/m^3), and PM_{10} (per 10 μg/m^3) were positively associated with risks of all-cause (Hazard Ratio (HR) range = 1.13–1.25), breast cancer (HR range = 1.19–1.45), and CVD mortality (HR range = 1.37–1.60). Associations were statistically significant for LUR NO_X and CVD mortality (HR = 1.60; 95% CI: 1.08–2.37) and kriged NO_2 and breast cancer mortality (HR = 1.45; 95% CI 1.02–2.07). Gaseous and PM pollutants were positively associated with breast cancer mortality across racial/ethnic group.

Conclusion: In this study, air pollutants have a harmful impact on breast cancer survival. Additional studies should evaluate potential confounding by socioeconomic factors. These data support maintaining clean air laws to improve survival for women with breast cancer.

1. Introduction

Breast cancer is the most commonly diagnosed non-skin cancer among U.S. women. >3.8 million breast cancer survivors were estimated in the U.S. in 2019 and this number of survivors is projected to increase to 4.9 million by 2030 (Miller et al., 2019). Prognostic factors for survival following breast cancer diagnosis include stage and other tumor characteristics, treatment factors, co-morbidities, sociodemographic factors, as well as modifiable lifestyle factors such as smoking, obesity, and physical inactivity (Hellmann et al., 2010; Lu et al., 20152015; Kwan et al., 2014). It is a public health priority to identify modifiable factors that improve outcome among this large and growing number of breast cancer survivors.

Air pollutants have been well documented to impact adversely numerous health outcomes, including mortality, particularly from cardiorespiratory diseases (Kelly and Fussell, 2015; Hoek et al., 2013). In a large US study, exposure to particulate matter (PM) <2.5 μm in diameter was estimated to be responsible for over 15,000 female deaths from 1999 through 2015, and having greatest effect of loss in life expectancy in some southern states and Los Angeles, California (Bennett et al., 2019). It has been estimated that >40% of people in the US live in counties with unhealthy air quality, placing them at risk for adverse health outcomes, particularly vulnerable groups such as those with chronic conditions (American Lung Association Association, 2019).

To date, two U.S. studies have examined the association between air pollution and survival following breast cancer diagnosis (DuPré et al., 2019; Hu et al., 2013). In a report of 255,128 breast cancer cases based on data from the Surveillance Epidemiology End Results (SEER) program, estimates of particulate matter<10 μm in diameter (PM_{10}) and $PM_{2.5}$ were significantly associated with increased breast cancer mortality with stronger associations seen for localized disease (Hu et al., 2013). In the Nurses' Health Study (NHS) with 8,936 breast cancer cases, estimates of PM_{10} and $PM_{2.5}$ based on 2-year averages were not associated with breast cancer mortality, although a statistically significant association was observed with $PM_{2.5}$ among cases with stage I disease (DuPré et al., 2019). An Italian study (Tagliabue et al., 2016) reported $PM_{2.5}$ based on a median of 3 years around diagnosis was associated with breast cancer mortality and a study in China (Huo et al., 2015) reported suggestive findings for an annual PM estimate and all-cause mortality among estrogen receptor (ER) positive breast cancers. However, these latter two studies did not consider lifestyle factors (Huo et al., 2015; Troeschel et al., 20192019). There is a need for additional studies of air pollution and breast cancer survival with adjustment for relevant individual-level covariates. In addition, investigations are warranted to evaluate whether certain racial/ethnic and/or socioeconomic groups, who often reside in areas with higher levels of air pollution (Turner et al., 2011; Wang et al., 2020), experience different mortality hazards in relation to air pollutant exposure.

Thus, we conducted a prospective study of traffic-related air pollution exposures and mortality among California female participants of the Multiethnic Cohort Study (MEC) with a breast cancer diagnosis from 1993 through 2013.

2. Methods

2.1. Study subjects

The MEC is a large population-based prospective cohort of US adults (Kolonel et al., 2000). Briefly, from 1993 through 1996, 96,810 men and 118,441 women aged 45–75 years largely from five self-reported racial/ethnic groups residing in Hawaii (HI) or CA (primarily Los Angeles County) were enrolled. Participants completed a baseline questionnaire that surveyed demographics, anthropometrics, reproductive history, and other lifestyle factors. Participants were followed for diagnosis of incident invasive breast cancer through routine linkage with the HI and CA cancer SEER registries, and for vital status through linkages to the National Death Index and state death certificate files that provide primary cause of death based on International Classification of Disease (ICD)-9 and ICD-10 codes. Clinicopathologic and treatment factors were obtained from the cancer registries. For this study, eligible female CA MEC participants with primary invasive breast cancer (ICD-O-3 C500-C509) were those who completed a baseline questionnaire with valid addresses across the study period (n = 3,113). We excluded cases with implausible or insufficient address data (n = 44), leaving 3,089 breast cancer cases for analyses. This cohort was followed from the date of diagnosis (1993–2013) to the date of death or December 31, 2013 (study end date), whichever came earlier. The institutional review boards of the University of Hawaii, University of Southern California, and University of California, San Francisco approved the study protocol.

2.2. Participant characteristics

Participant characteristics that we evaluated were age at diagnosis, race/ethnicity and baseline variables (median = 7.3, Q1 = 3.3; Q3 = 12.6 years between cohort entry and death) including marital status (married, single, divorced/widowed), body mass index (BMI) (under-weight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2)), smoking status (never, former, current smoker), alcohol intake (non-drinker (0 g alcohol/day), drinker (>0 g alcohol/day)), diabetes (yes, no), cardiovascular disease (CVD) (coronary heart disease and/or stroke, hypertension and/or hypertension medications, none), and age at first live birth (no children, ≤20, 21–30, >30 years). Clinicopathologic information included stage at diagnosis (localized, regional, distant), grade (I, II, and III & IV), histology (ductal, lobular, other, inflammatory breast cancer), ER/progesterone receptor (PR) status (ER + PR+, ER + PR-, ER-PR+, ER-PR-), and tumor size (<1cm, 1-<5cm, ≥5cm). First course of treatment included surgery (no, lumpectomy, mastectomy), chemotherapy (no, yes), hormone therapy (no, yes), and radiation (no, yes). The frequency of missing data for variables such as BMI, smoking, age at first live birth, and stage was low (≤2.9%).

2.3. Address history, geocoding, and neighborhood socioeconomic status

The MEC actively maintains a residential history of address locations on all participants based on mailings, linkages to secondary data sources, and direct communication from study participants. For the 3,089 CA MEC breast cancer cases, there were 4,305 residential addresses (74.5% non-movers, 22.4% 1–2 moves, 3.1% 3 + moves). Residential addresses were geocoded to latitude and longitude coordinates using address or street locators. Geocoded addresses were linked to 1990 (1993–1996 addresses), 2000 (1997–2005 addresses), and 2010 (2006–2013 addresses) US Census block groups. An index measure of nSES was based on principal component analysis of seven census-based indicators of SES: education, median household income, percent living 200% below the poverty level, percent blue-collar workers, percent without a job among those older than 15 years in workforce, median rent, and median house value (Yost et al., 2001; Yang et al., 2014). This nSES index was assigned to participants' address at diagnosis and at time of the event of death or censoring and was categorized into quintiles based on the nSES distribution of Los Angeles County block groups for each decennial census year.

2.4. Air pollution exposure assessment

We used established air pollution assessment approaches (Cheng et al., 2020) based on linkage of geocoded residential addresses with latitude/longitude coordinates as the geographic unit to estimate traffic-related air pollutant exposures. In brief, a land use regression (LUR) model estimated NO_x and NO_2 exposures from regional and local sources based on air monitoring data from spatially dense air monitoring campaigns (2006–2007) and incorporated spatial data on land use and traffic characteristics; for temporal adjustment, monthly scaling factors were applied based on routinely collected air monitoring data nearest to the participant's residence (Jerrett et al., 2005). Empirical Bayesian kriging interpolation was used to estimate largely regional exposures for NO_x, NO_2, PM_{10}, and $PM_{2.5}$ (Laurent et al., 2016). Measured concentrations of NO_x, NO_2, PM_{10} (1993–2013) and

$PM_{2.5}$ (2000–2013) were obtained from routinely collected air monitoring data from the US EPA. $PM_{2.5}$ concentrations for 1993–1999 were estimated from a spatiotemporal model (Li et al., 2017). A correlation matrix of pollutants is presented in Supplemental Table 1 (r = 0.59–0.98).

2.5. Statistical analysis

We used Cox regression with time-varying exposure variables to examine the hazards of four mortality endpoints: all-cause, breast cancer, CVD, and non-breast/non-CVD mortality in relation to air pollution exposure. The Cox regression model used age in months as the time variable and defined a series of risk sets based on the age of death (months) of each event (index death). Each risk set consisted of all breast cancer cases who died at the age of the index death or remained alive and uncensored at that same age. For each member of each risk set (including the index death), we used her residential history to compute an average air pollutant exposure from time of diagnosis (month/year) to time of death of the index case in each risk set.

The Cox regression model used age of breast cancer diagnosis as the strata variable, and adjusted for demographics, lifestyle factors at baseline, clinicopathologic and treatment factors at diagnosis, and nSES at diagnosis and at death/censoring. Supplemental Table 2 presents the associations of covariates and all-cause mortality among breast cancer cases in the LUR NO_x model. For Hazard ratios (HR) and 95% Confidence Intervals (CI) of cause specific deaths, we used a competing risk model where the at-risk denominator included living participants up until censoring at the time of death from other causes. HRs and 95% CI sfor common fixed size increases in air pollutants were calculated. For NO_x, we used 50 ppb, which was close to the interquartile range (IQRs) of the LUR (41.1 ppb) and kriged (42.5 ppb) estimates. For NO_2, we used 20 ppb, which was close to the IQR for LUR (13.3 ppb) and kriged (14.1 ppb) estimates. For PM_{10} and $PM_{2.5}$, we used 10 $\mu g/m^3$, which was between the IQR of kriged PM_{10} (12.5 $\mu g/m^3$) and $PM_{2.5}$ (6.4 $\mu g/m^3$). We checked the proportional hazards assumption for each pollutant and found no violation. Subgroup analyses were conducted for race/ethnicity, hormone receptor-positive (ER + or PR + denoted as ER+/PR +) and hormone receptor-negative (ER- and PR- denoted as ER-PR-) breast tumors, first course of treatment, stage, nSES at diagnosis, pre-existing CVD (CVD status at baseline), and moving status. We assessed heterogeneity in associations using a global test of interaction.

To understand differences in air pollutant-mortality associations by nSES, we plotted the linear trends in HR for mortality across NO_2 levels categorized into 20 quantiles by low (Q1–Q3) and high (Q4–Q5) nSES at diagnosis. The reference was the combination of the lowest NO_2 level (first quantile) and high nSES. HRs were adjusted for all covariates described above.

All *P* values are two-sided with a statistical significance level of 0.05. Analyses were performed using SAS 9.2 statistical software (SAS Institute, Cary, NC).

3. Results

The study population consisted of 3,089 breast cancer cases (38% African American, 19% European American, 12% Japanese American, 31% Latina American, and 0.4% Native Hawiian) with racial/ethnic differences in age at diagnosis, marital status, obesity, smoking, alcohol intake, comorbidities, and age at first birth (Table 1). Regional/distant disease was higher among African Americans (33.6%) than other racial/ethnic groups (range: 22.4%–32.5%). The proportion of ER-PR- tumors was highest in African American (19.2%) and lowest in European American (10.8%) breast cancer cases. African American (27.0%) and Latina American breast cancer cases (20.3%) were more likely to live in the lowest SES neighborhoods at diagnosis than European American (7.7%) and Japanese American (4.3%) breast cancer cases. African American and Latina American breast cancer cases had higher average NO_X exposures in comparison to Japanese American and European American breast cancer cases (Supplemental Table 3).

LUR and kriged NO_x (per 50 ppb) and NO_2 (per 20 ppb), and $PM_{2.5}$ and PM_{10} (per 10 $\mu g/m^3$) were positively associated with all-cause (HR range = 1.13–1.25; p value range = 0.05–0.25) and breast cancer mortalities (HR range = 1.19–1.45; p value range = 0.04–0.29) (Table 2). For breast cancer mortality, a statistically significant increased risk was observed for kriged NO_2 (HR = 1.45; 95% CI: 1.02–2.07). For CVD mortality, a statistically significant increased risk was observed for LUR NO_x (HR = 1.60; 95% CI: 1.08–2.37).

For all-cause mortality, similar patterns of increased risk were seen for all pollutants among African American and European American breast cancer cases; results reached formal statistical significance for LUR NO_x and PM_{10} among African American breast cancer cases and kriged NO_x and NO_2 among European American breast cancer cases (Table 3). For breast cancer mortality, consistent patterns of increased risks were seen for all pollutants across race/ethnicity with a statistically significantly increased risk for kriged NO_X and NO_2 among European American breast cancer cases. For CVD mortality, 1.6–3.6-fold increased risks of death were seen for all pollutants among African American breast cancer cases (p value range = 0.03 to < 0.0001). For non-breast cancer/non-CVD mortality, increased risk associated with air pollutants were observed among European American breast cancer cases (HR range = 1.29–2.69) with wide 95% CIs. Almost all LUR and kriged pollutants displayed relatively larger HRs among ER-PR- breast cancer in comparison to ER+/PR + disease for all-cause (HR range = 1.21–1.81 vs. HR range = 1.03–1.27, respectively) and breast cancer mortalities (HR range = 1.47–2.63 vs. HR range = 1.05–1.53, respectively) (Table 4). Yet, there was no formal statistical evidence of heterogeneity in associations by ER/PR status.

Risk of CVD mortality associated with air pollutants was higher among low than high nSES cases (Table 5; p heterogeneity > 05). However, LUR NO_2 was associated with increased risk of all-cause, breast cancer, and non-breast cancer/non-CVD mortalities among high nSES breast cancer cases, but either inversely or not associated with these outcomes among low nSES cases (p heterogeneity ≤ 05). Supplemental Figure 1 shows that at low levels of LUR NO_2, the HRs for all-cause and breast cancer mortalities were higher among low nSES cases. In contrast, at higher levels of LUR NO_2, the HRs for these outcomes were higher

for high nSES cases. That is, while starting at lower risk, the slope of increase in risk was steeper among high nSES cases with increasing LUR NO_2.

Largely similar patterns of associations were observed for localized and advanced disease (Table 6). For breast cancer cases with no pre-existing CVD, statistically significant increased risks for all-cause mortality were seen with LUR NO_X (HR = 1.38; 95% CI: 1.04–1.82), kriged NO_X (HR = 1.38; 95% CI: 1.03–1.85) and NO_2 (HR = 1.52; 95% CI: 1.06–2.18) (Supplemental Table 4). While for cases with pre-existing CVD, kriged pollutants and LUR NO_2 displayed larger HRs for CVD mortality than cases with no CVD. Analyses by breast cancer treatment showed that $PM_{2.5}$ and PM_{10} were consistently associated with increased risk of all-cause, breast cancer, and CVD mortalities among cases who did not receive either chemotherapy or radiation (Supplemental Table 5). Results by moving status showed positive associations with all-cause, breast cancer, and CVD mortalities for all pollutants among non-movers while patterns were less consistent patterns among movers (Supplemental Table 6).

4. Discussion

In this prospective study of female breast cancer cases in the MEC, NO_X, NO_2, $PM_{2.5}$, and PM_{10} were positively associated with increased risks of all-cause, breast, and CVD mortalities. Consistently positive associations were observed across race/ethnicity for breast cancer mortality. In addition, almost all kriged and LUR pollutants displayed larger HRs for breast cancer mortality among ER-PR- breast cancer than ER+/PR + disease. Heterogeneity in LUR NO_2 associations with all-cause and breast cancer mortalities by nSES were observed. Positive associations with all-cause, breast cancer and CVD mortalities were consistently observed among breast cancer cases who were non-movers. Overall, our findings provide new evidence that long-term air pollutant exposures adversely impact mortality outcomes for breast cancer survivors after adjustment for key covariates.

The positive associations observed for $PM_{2.5}$ and PM_{10} (per 10 $\mu g/m^3$; HR = 1.17 and 1.13, respectively) with all-cause mortality in the MEC support prior findings of the NHS based on time-varying spatiotemporal models (per 10 $\mu g/m^3$ $PM_{2.5}$ and PM_{10}: HR = 1.12 and 1.09, respectively) (DuPré et al., 2019). In a California SEER-based study, county-level $PM_{2.5}$ and PM_{10} were associated with increased risks of overall and breast cancer mortality for all breast cancer cases and those with localized disease (Hu et al., 2013). We also observed increased risks for breast cancer mortality with PM exposures but the 95% CIs included the null. The large SEER-based study (Hu et al., 2013) used county-level PM estimates based on a single address at diagnosis with limited individual-level covariates, while the MEC and NHS (DuPré et al., 2019) had fewer cases but used time-varying exposure estimates based on detailed residential histories and included individual-level covariate data.

The increased risks for CVD mortality associated with all air pollutants support the well-documented adverse health effects of air pollution on CVD (Brook et al., 2010). These overall CVD mortality associations were driven by associations observed among African American breast cancer cases, suggesting a particularly high risk for CVD mortality following their breast cancer diagnosis due to air pollutant exposures. Both chemotherapy

and radiation treatment for breast cancer may increase the risk of CVD. In particular, anthracycline has known cardiotoxic effects while radiotherapy may increase CVD risk through injury to the cardiac muscle or the surrounding vasculature (Doyle et al., 2005; Accordino et al., 2014). Thus, it is surprising that the HRs for $PM_{2.5}$ and PM_{10} with all-cause, breast cancer, and CVD mortalities were somewhat larger for women who did not receive chemotherapy and radiation than those who received chemotherapy and/or radiation, but the 95% CIs displayed large overlap between treatment strata.

We observed larger HRs for LUR NO_2 with all-cause and breast cancer mortalities for breast cancer cases living in high versus low SES neighborhoods. However, at low levels of LUR NO_2 larger HRs for all-cause and breast cancer mortalities were observed among low versus high nSES breast cancer cases, while at high levels of NO_2, the relationship reversed in direction. As Supplemental Figure 1 illustrates, our findings suggest that high nSES breast cancer cases start with a lower mortality risk at low air pollution levels than low nSES cases but experience a steeper risk increase with increasing pollution that surpass low nSES cases at higher levels of LUR NO_2. A similar pattern of lower baseline mortality risk and steeper increases by levels of air pollutant among the highest SES individuals was reported by a nationwide Danish study (Raaschou-Nielsen et al., 2020).

Air pollution is comprised a complex mixture of correlated gaseous pollutants and PM. We interpret the observed associations with the various air pollutants as reflecting a traffic-related air pollution mixture rather than any specific air pollutant. We did not conduct multi-pollutant modeling given the high degree of correlation between pollutants. Elevated effect estimates with LUR and kriging pollutants and all-cause mortality were consistently observed among African American and European American breast cancers with large numbers of deaths. Less consistent findings among Japanese American and Latina cases may be related to the smaller number of events overall for Japanese American cases and of non-breast cancer deaths among Latina American cases.

Air pollution includes various polycyclic aromatic hydrocarbons, metals, and benzene that are transported and metabolized throughout the body and have been linked to increased oxidative stress, inflammation, and epigenetic changes (Liu et al., 2019; Rider and Carlsten, 2019; Rao et al., 2018). Although the biological mechanisms by which air pollution may increase mortality among breast cancer cases are unclear, oxidative stress may adversely affect mortality through cell proliferation, genetic instability, and mutations (Kang and Hamasaki, 2003). Inflammation may also trigger the release of pro-inflammatory cytokines, leading to tissue and organ damage and death (Tsai et al., 2019; Li et al., 2019). Epigenetic changes, such as DNA methylation, resulting in the activation or silencing of key genes has been linked to mortality (Zhang et al., 2017).

To our knowledge, this is the first US study to evaluate associations between air pollution and mortality, overall and from different causes, among breast cancer cases across race/ethnicity, nSES, pre-existing CVD conditions, and first course of treatment. Study strengths include a diverse study population with regard to race/ethnicity and nSES. Our findings in Los Angeles County, an area that has experienced some of the highest air pollution levels in the US, provide important insights that may be particularly applicable to highly

polluted megacities in developing and rapidly industrializing countries. In addition, we captured long-term air pollution exposures using detailed residential histories, an approach that possibly reduces exposure misclassification in comparison to studies limited to a single address at diagnosis. We also accounted for a large number of individual-level covariates and nSES.

Our study has limitations. While we accounted for nSES, using a construct that captured the domains of income, poverty, employment, and housing, we were unable to account for other unmeasured individual-level SES factors (e.g. insurance status). Information on air pollution exposures at non-residential locations and indoors, and details on treatment regimens and dose are lacking. Due to the smaller sample size in subgroup analyses, we acknowledge the imprecision in some of our effect estimates and the limited statistical power to detect associations for some outcomes (e.g. CVD mortality among Japanese Americans and ER-PR- breast cancers). We also acknowledge that a large number of comparisons were made with a possibility of false positive associations.

In conclusion, this study reports adverse effects of air pollution on mortality among breast cancer cases. While it remains to be determined whether breast cancer survivors are more susceptible to the adverse effects of air pollutants than the general population of women, maintaining stringent clean air laws serves as an actionable target to reduce mortality among the many US women with breast cancer. Future large studies of multiethnic and socioeconomically diverse populations are needed to corroborate and expand our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL, Siegel RL, 2019. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 69 (5), 363–385. 10.3322/caac.21565. [PubMed: 31184787]

Hellmann SS, Thygesen LC, Tolstrup JS, Grønbæk M, 2010. Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. Eur J Cancer Prev 19 (5), 366–373. [PubMed: 20502344]

Lu Y, John EM, Sullivan-Halley J, Vigen C, Gomez SL, Kwan ML, Caan BJ, Lee VS, Roh JM, Shariff-Marco S, Keegan THM, Kurian AW, Monroe KR, Cheng I, Sposto R, Wu AH, Bernstein L, 2015. History of Recreational Physical Activity and Survival After Breast Cancer: The California Breast Cancer Survivorship Consortium. Am J Epidemiol 181 (12), 944–955. [PubMed: 25925388]

Kwan ML, John EM, Caan BJ, Lee VS, Bernstein L, Cheng I, Gomez SL, Henderson BE, Keegan THM, Kurian AW, Lu Y, Monroe KR, Roh JM, Shariff-Marco S, Sposto R, Vigen C, Wu AH,

2014. Obesity and mortality after breast cancer by race/ethnicity: The California Breast Cancer Survivorship Consortium. Am J Epidemiol 179 (1), 95–111. [PubMed: 24107615]

Kelly FJ, Fussell JC, 2015. Air pollution and public health: emerging hazards and improved understanding of risk. Environ Geochem Health 37 (4), 631–649. [PubMed: 26040976]

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD, 2013. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environ Health 12 (1). 10.1186/1476-069X-12-43.

Bennett JE, Tamura-Wicks H, Parks RM, et al. Particulate matter air pollution and national and county life expectancy loss in the USA: A spatiotemporal analysis. PLoS Med 2019;16(7):e1002856. [PubMed: 31335874]

DuPré NC, Hart JE, Holmes MD, Poole EM, James P, Kraft P, Laden F, Tamimi RM, 2019. Particulate Matter and Traffic-Related Exposures in Relation to Breast Cancer Survival. Cancer Epidemiol Biomarkers Prev 28 (4), 751–759. [PubMed: 30647065]

Hu H, Dailey AB, Kan H, Xu X, 2013. The effect of atmospheric particulate matter on survival of breast cancer among US females. Breast Cancer Res Treat 139 (1), 217–226. [PubMed: 23592372]

Tagliabue G, Borgini A, Tittarelli A, van Donkelaar A, Martin RV, Bertoldi M, Fabiano S, Maghini A, Codazzi T, Scaburri A, Favia I, Cau A, Barigelletti G, Tessandori R, Contiero P, 2016. Atmospheric fine particulate matter and breast cancer mortality: a population-based cohort study. BMJ Open 6 (11), e012580. 10.1136/bmjopen-2016-012580.

Huo Q, Cai C, Yang Q, 2015. Atmospheric particulate matter and breast cancer survival: estrogen receptor triggered? Tumour Biol 36 (5), 3191–3193. [PubMed: 25894371]

Troeschel AN, Liu Y, Collin LJ, Bradshaw PT, Ward KC, Gogineni K, McCullough LE, 2019. Race differences in cardiovascular disease and breast cancer mortality among US women diagnosed with invasive breast cancer. Int J Epidemiol 48 (6), 1897–1905. 10.1093/ije/dyz108. [PubMed: 31155644]

Turner MC, Krewski D, Pope CA, Chen Y, Gapstur SM, Thun MJ, 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med 184 (12), 1374–1381. [PubMed: 21980033]

Wang B, Eum K-D, Kazemiparkouhi F, Li C, Manjourides J, Pavlu V, Suh H, 2020. The impact of long-term PM2.5 exposure on specific causes of death: exposure-response curves and effect modification among 53 million U.S. Medicare beneficiaries. Environ Health 19 (1). 10.1186/s12940-020-00575-0.

Kolonel LN, Henderson BE, Hankin JH, Nomura AMY, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS, 2000. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 151 (4), 346–357. [PubMed: 10695593]

Yost K, Perkins C, Cohen R, et al. , 2001. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control 12 (8), 703–711. [PubMed: 11562110]

Yang J, Schupp CW, Harrati A, Ca C, Keegan THM, Gomez SL, 2014. Developing an area-based socioeconomic measure from American Community Survey data. Cancer Prevention Institute of California, Fremont, Calfornia. In.

Cheng I, Tseng C, Wu J, Yang J, Conroy SM, Shariff-Marco S, Li L, Hertz A, Gomez SL, Le Marchand L, Whittemore AS, Stram DO, Ritz B, Wu AH, 2019. Association between ambient air pollution and breast cancer risk: The multiethnic cohort study. Int J Cancer 146 (3), 699–711. 10.1002/ijc.32308. [PubMed: 30924138]

Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahsuvaroglu T, Morrison J, Giovis C, 2005. A review and evaluation of intraurban air pollution exposure models. J Expo Anal Environ Epidemiol 15 (2), 185–204. [PubMed: 15292906]

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, Escobedo L, Wu J, 2016. A Statewide Nested Case-Control Study of Preterm Birth and Air Pollution by Source and Composition: California, 2001–2008. Environ Health Perspect 124 (9), 1479–1486. [PubMed: 26895492]

Li L, Wu AH, Cheng I, Chen J-C, Wu J, 2017. Spatiotemporal estimation of historical PM2.5 concentrations using PM10, meteorological variables, and spatial effects. Atmos. Environment 166, 182–191.

American Lung Association Association, 2019. State of the Air.

Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD, 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121 (21), 2331–2378. [PubMed: 20458016]

Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL, 2005. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol 23 (34), 8597–8605. [PubMed: 16314622]

Accordino MK, Neugut AI, Hershman DL, 2014. Cardiac effects of anticancer therapy in the elderly. J Clin Oncol 32 (24), 2654–2661. [PubMed: 25071122]

Raaschou-Nielsen O, Thorsteinson E, Antonsen S, Holst GJ, Sigsgaard T, Geels C, Frohn LM, Christensen JH, Brandt J, Pedersen CB, Hvidtfeldt UA, 2020. Long-term exposure to air pollution and mortality in the Danish population a nationwide study. EClinicalMedicine 28, 100605. 10.1016/j.eclinm.2020.100605. [PubMed: 33163948]

Liu Q, Gu X, Deng F, Mu L, Baccarelli AA, Guo X, Wu S, 2019. Ambient particulate air pollution and circulating C-reactive protein level: A systematic review and meta-analysis. Int J Hyg Environ Health 222 (5), 756–764. [PubMed: 31103472]

Rider CF, Carlsten C, 2019. Air pollution and DNA methylation: effects of exposure in humans. Clin Epigenetics 11 (1), 131. [PubMed: 31481107]

Rao X, Zhong J, Brook RD, Rajagopalan S, 2018. Effect of Particulate Matter Air Pollution on Cardiovascular Oxidative Stress Pathways. Antioxid Redox Signal 28 (9), 797–818. [PubMed: 29084451]

Kang D, Hamasaki N, 2003. Mitochondrial oxidative stress and mitochondrial DNA. Clin Chem Lab Med 41 (10), 1281–1288. [PubMed: 14580153]

Tsai D-H, Riediker M, Berchet A, Paccaud F, Waeber G, Vollenweider P, Bochud M, 2019. Effects of short- and long-term exposures to particulate matter on inflammatory marker levels in the general population. Environ Sci Pollut Res Int 26 (19), 19697–19704. [PubMed: 31079306]

Li D, Zhang R, Cui L, Chu C, Zhang H, Sun H, Luo J, Zhou L, Chen L, Cui J, Chen S, Mai B, Chen S, Yu J, Cai Z, Zhang J, Jiang Y, Aschner M, Chen R, Zheng Y, Chen W, 2019. Multiple organ injury in male C57BL/6J mice exposed to ambient particulate matter in a real-ambient PM exposure system in Shijiazhuang. China. Environ Pollut 248, 874–887. [PubMed: 30856503]

Zhang Y, Wilson R, Heiss J, Breitling LP, Saum K-U, Schöttker B, Holleczek B, Waldenberger M, Peters A, Brenner H, 2017. DNA methylation signatures in peripheral blood strongly predict all-cause mortality. Nat Commun 8 (1). 10.1038/ncomms14617.

Table 1

Study characteristics of 3,089 women diagnosed with breast cancer in CA MEC (1993–2013).

		All (n = 3089)		African Americans (n = 1,177)		European Americans (n = 573)		Japanese Americans (n = 370)		Latina Americans (n = 958)	
		n	%	n	%	n	%	n	%	n	%
Race/Ethnicity[a]	African American	1177	38.1%	1177	100%	–	–	–	–	–	–
	European American	573	18.6%	–	–	573	100%	–	–	–	–
	Japanese American	370	12.0%	–	–	–	–	370	100%	–	–
	Latina American	958	31.0%	–	–	–	–	–	–	958	100%
	Native Hawaiian	11	0.4%	–	–	–	–	–	–	–	–
Age at diagnosis, years	45–49	35	1.1%	14	1.2%	5	0.9%	4	1.1%	12	1.3%
	50–54	144	4.7%	68	5.8%	20	3.5%	24	6.5%	32	3.3%
	55–59	289	9.4%	102	8.7%	57	10.0%	31	8.4%	97	10.1%
	60–64	443	14.3%	172	14.6%	64	11.2%	42	11.4%	159	16.6%
	65–69	599	19.4%	197	16.7%	123	21.5%	75	20.3%	201	21.0%
	70–74	605	19.6%	208	17.7%	113	19.7%	80	21.6%	204	21.3%
	75+	974	31.5%	416	35.3%	191	33.3%	114	30.8%	253	26.4%
Marital status[a,b]	Married	1614	52.3%	438	37.2%	352	61.4%	271	73.2%	547	57.1%
	Single	205	6.6%	63	5.4%	27	4.7%	31	8.4%	84	8.8%
	Divorced/Widowed	1229	39.8%	649	55.1%	188	32.8%	68	18.4%	319	33.3%
BMI[a,b]	Underweight	35	1.1%	9	0.8%	8	1.4%	12	3.2%	6	0.6%
	Normal	1015	32.9%	258	21.9%	255	44.5%	233	63.0%	268	28.0%
	Overweight	1094	35.4%	421	35.8%	176	30.7%	105	28.4%	385	40.2%
	Obese	913	29.6%	461	39.2%	133	23.2%	20	5.4%	296	30.9%
Smoking status[a,b]	Never smoker	1655	53.6%	524	44.5%	267	46.6%	250	67.6%	610	63.7%
	Former smoker	921	29.8%	390	33.1%	216	37.7%	98	26.5%	213	22.2%
	Current smoker	446	14.4%	236	20.1%	84	14.7%	20	5.4%	103	10.8%
Alcohol intake[a,b]	Non-drinker	1747	56.6%	696	59.1%	232	40.5%	251	67.8%	561	58.6%
	Drinker	1236	40.0%	447	38.0%	318	55.5%	105	28.4%	362	37.8%
Diabetes[a]	No	2749	89.0%	1028	87.3%	535	93.4%	344	93.0%	833	87.0%

		All (n = 3089)		African Americans (n = 1,177)		European Americans (n = 573)		Japanese Americans (n = 370)		Latina Americans (n = 958)	
		n	%	n	%	n	%	n	%	n	%
	Yes	340	11.0%	149	12.7%	38	6.6%	26	7.0%	125	13.1%
CVD[a]	Coronary heart disease, stroke	300	9.7%	148	12.6%	42	7.3%	16	4.3%	94	9.8%
	Hypertension, hypertension medications	1137	36.8%	562	47.8%	169	29.5%	126	34.1%	274	28.6%
	None	1652	53.5%	467	39.7%	362	63.2%	228	61.6%	590	61.6%
Age at first live birth[a,b]	Nulliparous	420	13.6%	156	13.3%	92	16.1%	75	20.3%	97	10.1%
	15–20y	939	30.4%	489	41.6%	124	21.6%	20	5.4%	304	31.7%
	21–30y	1421	46.0%	438	37.2%	296	51.7%	215	58.1%	463	48.3%
	>30y	221	7.2%	52	4.4%	54	9.4%	49	13.2%	66	6.9%
Stage[c]	Localized	2070	67.0%	758	64.4%	385	67.2%	285	77.0%	634	66.2%
	Regional	865	28.0%	345	29.3%	166	29.0%	77	20.8%	274	28.6%
	Distant	106	3.4%	50	4.3%	20	3.5%	6	1.6%	30	3.1%
Grade[c]	Grade I	610	19.8%	210	17.8%	136	23.7%	97	26.2%	166	17.3%
	Grade II	1183	38.3%	385	32.7%	241	42.1%	157	42.4%	394	41.1%
	Grade III & IV	984	31.9%	434	36.9%	149	26.0%	95	25.7%	302	31.5%
Histology[c]	Ductal	2191	70.9%	854	72.6%	374	65.3%	274	74.1%	678	70.8%
	Lobular	529	17.1%	181	15.4%	129	22.5%	58	15.7%	161	16.8%
	Other	336	10.9%	132	11.2%	62	10.8%	36	9.7%	106	11.1%
	Inflammatory breast cancer	33	1.1%	10	0.9%	8	1.4%	2	0.5%	13	1.4%
Estrogen/ Progesterone Receptor status[c]	ER + PR+	1714	55.5%	609	51.7%	356	62.1%	236	63.8%	504	52.6%
	ER + PR-	339	11.0%	127	10.8%	72	12.6%	39	10.5%	100	10.4%
	ER-PR+	50	1.6%	22	1.9%	8	1.4%	4	1.1%	16	1.7%
	ER-PR-	502	16.3%	226	19.2%	62	10.8%	48	13.0%	165	17.2%
Tumor size[c]	<1 cm	509	16.5%	154	13.1%	119	20.8%	85	23.0%	148	15.5%
	1-<5 cm	2136	69.2%	835	70.9%	385	67.2%	248	67.0%	660	68.9%
	≥5 cm	264	8.6%	110	9.4%	43	7.5%	27	7.3%	84	8.8%

		All (n = 3089)		African Americans (n = 1,177)		European Americans (n = 573)		Japanese Americans (n = 370)		Latina Americans (n = 958)	
		n	%	n	%	n	%	n	%	n	%
Surgery type[c]	No surgery	186	6.0%	96	8.2%	27	4.7%	14	3.8%	49	5.1%
	Lumpectomy	821	26.6%	321	27.3%	145	25.3%	92	24.9%	261	27.2%
	Mastectomy	1681	54.4%	599	50.9%	335	58.5%	217	58.7%	523	54.6%
Chemotherapy[c]	No	2329	75.4%	881	74.9%	442	77.1%	291	78.7%	708	73.9%
	Yes	760	24.6%	296	25.2%	131	22.9%	79	21.4%	250	26.1%
Hormone therapy[c]	No	2031	65.8%	777	66.0%	361	63.0%	240	64.9%	647	67.5%
	Yes	1058	34.3%	400	34.0%	212	37.0%	130	35.1%	311	32.5%
Radiation[c]	No	1888	61.1%	765	65.0%	309	53.9%	199	53.8%	610	63.7%
	Yes	1201	38.9%	412	35.0%	264	46.1%	171	46.2%	348	36.3%
Neighborhood SES[a,c]	Quintile 1-low	572	18.5%	318	27.0%	44	7.7%	16	4.3%	194	20.3%
	Quintile 2	668	21.6%	315	26.8%	73	12.7%	29	7.8%	246	25.7%
	Quintile 3	744	24.1%	277	23.5%	131	22.9%	75	20.3%	259	27.0%
	Quintile 4	613	19.8%	154	13.1%	159	27.8%	128	34.6%	169	17.6%
	Quintile 5-high	459	14.9%	98	8.3%	162	28.3%	120	32.4%	78	8.1%

[a] At baseline

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

[c] At Diagnosis

Table 2

Associations of gaseous and particulate matter air pollutants and risk of death following breast cancer diagnosis, CA MEC breast cancer cases, 1993–2013[a].

		All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality[c]			
		Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value
LUR	NO_x[b]	981	1.16	(0.96–1.40)	0.12	418	1.25	(0.93–1.66)	0.13	240	1.60	(1.08–2.37)	0.02	323	0.91	(0.64–1.30)	0.61
	NO_2[b]	1005	1.14	(0.91–1.43)	0.25	428	1.34	(0.95–1.90)	0.09	245	1.49	(0.92–2.40)	0.11	332	0.81	(0.53–1.22)	0.31
Kriging	NO_x[b]	1095	1.16	(0.96–1.39)	0.13	461	1.27	(0.96–1.68)	0.09	269	1.37	(0.93–2.02)	0.12	365	0.93	(0.67–1.29)	0.65
	NO_2[b]	1111	1.25	(1.00–1.57)	0.05	468	1.45	(1.02–2.07)	0.04	269	1.58	(0.99–2.51)	0.06	374	0.94	(0.64–1.38)	0.75
	$PM_{2.5}$[b]	1109	1.17	(0.95–1.44)	0.13	465	1.19	(0.86–1.64)	0.29	269	1.44	(0.95–2.17)	0.08	375	0.94	(0.66–1.34)	0.72
	PM_{10}[b]	1112	1.13	(1.00–1.29)	0.06	468	1.20	(0.98–1.48)	0.09	269	1.25	(0.97–1.62)	0.09	375	0.96	(0.77–1.21)	0.75

[a] Adjusted for race/ethnicity, marital status, ERPR status, stage, grade, histology, tumor size, chemotherapy, hormone treatment, radiation, surgery, nSES at diagnosis and current nSES, BMI, smoking, alcohol, diabetes, CVD risk, and age at first live birth; and stratified by age at diagnosis

[b] LUR and kriging per 50 ppb NO_X; 20 ppb Kriging and LUR NO_2; Kriging per 10ug/m^3 PM_{10} and $PM_{2.5}$

[c] Distribution of cause of deaths: other cancer site than breast cancer (42%), diabetes (9%), chronic lower respiratory disease (9%), Alzheimer's disease (8%), mental/behavioral disease (5%), pneumonia (5%), kidney disease (3%), liver disease (3%), infectious/parasitic disease (3%), other causes of deaths (5%), unknown cause (8%)

Table 3

Associations of gaseous and particulate matter air pollutants and risk of death following breast cancer diagnosis among CA MEC breast cancer cases by race/ethnicity, 1993–2013[a,b].

			All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality			
			Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value
LUR	NO_x[c]	African Americans	419	1.42	(1.04–1.94)	0.03	193	1.41	(0.88–2.25)	0.15	106	3.62	(1.91–6.86)	<0.0001	120	0.83	(0.40–1.72)	0.62
		European Americans	198	1.35	(0.80–2.30)	0.26	66	1.94	(0.63–6.02)	0.25	52	0.51	(0.09–2.72)	0.43	80	2.66	(1.0–7.07)	0.05
		Japanese Americans	80	1.91	(0.63–5.83)	0.25	–	–	–	–	–	–	–	–	–	–	–	–
		Latina Americans	282	1.05	(0.71–1.54)	0.82	126	1.46	(0.79–2.71)	0.23	61	1.14	(0.43–2.97)	0.79	95	0.51	(0.25–1.05)	0.07
		$P_{heterogenerity}$				0.46				0.82				0.02				0.02
	NO_2[c]	African Americans	437	1.33	(0.91–1.95)	0.14	199	1.73	(0.97–3.08)	0.07	110	3.34	(1.50–7.44)	0.003	128	0.53	(0.23–1.21)	0.13
		European Americans	203	1.30	(0.72–2.34)	0.39	69	2.23	(0.66–7.53)	0.20	53	0.88	(0.16–5.00)	0.89	81	1.71	(0.60–4.87)	0.32
		Japanese Americans	80	3.18	(0.90–11.20)	0.07	–	–	–	–	–	–	–	–	–	–	–	–
		Latina Americans	283	1.02	(0.63–1.65)	0.92	127	1.17	(0.56–2.44)	0.68	61	1.00	(0.30–3.30)	1.00	95	0.68	(0.28–1.64)	0.39
		$P_{heterogenerity}$				0.25				0.50				0.14				0.21
Kriging	NO_x[c]	African Americans	491	1.18	(0.90–1.56)	0.24	220	1.24	(0.82–1.88)	0.32	124	2.16	(1.21–3.84)	0.01	147	0.74	(0.42–1.29)	0.28
		European Americans	224	1.68	(1.01–2.80)	0.04	76	3.98	(1.31–12.04)	0.01	60	0.88	(0.23–3.36)	0.86	88	2.25	(0.86–5.85)	0.10
		Japanese Americans	82	0.92	(0.26–3.28)	0.89	–	–	–	–	–	–	–	–	–	–	–	–
		Latina Americans	296	1.14	(0.76–1.72)	0.52	131	1.67	(0.87–3.19)	0.12	63	0.96	(0.33–2.79)	0.93	102	0.74	(0.36–1.51)	0.41
		$P_{heterogenerity}$				0.91				0.42				0.09				0.73
	NO_2[c]	African Americans	506	1.30	(0.91–1.86)	0.15	227	1.52	(0.87–2.65)	0.14	124	3.39	(1.59–7.23)	0.002	155	0.56	(0.28–1.10)	0.09
		European Americans	224	1.87	(1.05–3.34)	0.03	76	4.90	(1.36–17.71)	0.02	60	0.85	(0.21–3.43)	0.82	88	2.69	(0.94–7.73)	0.07

		All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality			
		Deaths	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**
	Japanese Americans	83	0.88	(0.24–3.26)	0.84	–	–	–	–	–	–	–	–	–	–	–	–
	Latina Americans	296	1.19	(0.73–1.95)	0.49	131	1.61	(0.75–3.47)	0.22	63	1.05	(0.29–3.85)	0.94	102	0.85	(0.35–2.03)	0.71
	$P_{heterogenerity}$				0.59				0.25				0.12				0.05
PM2.5[c]	African Americans	504	1.35	(0.99–1.85)	0.06	225	1.33	(0.80–2.20)	0.27	124	2.10	(1.13–3.91)	0.02	155	0.92	(0.51–1.65)	0.78
	European Americans	225	1.33	(0.77–2.30)	0.30	76	2.21	(0.63–7.82)	0.22	60	0.78	(0.20–3.02)	0.72	89	1.79	(0.69–4.65)	0.23
	Japanese Americans	83	0.57	(0.15–2.20)	0.42	–	–	–	–	–	–	–	–	–	–	–	–
	Latina Americans	295	0.94	(0.60–1.47)	0.78	130	1.17	(0.59–2.33)	0.66	63	0.93	(0.29–3.02)	0.91	102	0.62	(0.28–1.36)	0.23
	$P_{heterogenerity}$				0.23				0.87				0.11				0.63
PM10[c]	African Americans	506	1.25	(1.03–1.52)	0.02	227	1.33	(0.97–1.83)	0.08	124	1.55	(1.04–2.29)	0.03	155	0.97	(0.68–1.37)	0.85
	European Americans	225	1.23	(0.83–1.81)	0.31	76	1.51	(0.63–3.64)	0.36	60	1.05	(0.38–2.93)	0.93	89	1.29	(0.67–2.46)	0.45
	Japanese Americans	83	0.85	(0.34–2.12)	0.73	–	–	–	–	–	–	–	–	–	–	–	–
	Latina Americans	296	0.98	(0.73–1.30)	0.87	131	1.11	(0.72–1.73)	0.64	63	1.24	(0.54–2.82)	0.61	102	0.79	(0.47–1.33)	0.36
	$P_{heterogenerity}$				0.21				0.52				0.34				0.66

[a] African American (n = 1117), European American (n = 573), Japanese American (n = 370), and Latina American (n = 958) breast cancer cases. Native Hawaiian (n = 11) breast cancer cases were not included.

[b] Adjusted for marital status, ERPR status, stage, grade, histology, tumor size, chemotherapy, hormone treatment, radiation, surgery, nSES at diagnosis and current nSES, BMI, smoking, alcohol, diabetes, CVD risk, and age at first live birth; age at diagnosis as a stratum variable

[c] LUR and kriging per 50 ppb NO_X; 20 ppb Kriging and LUR NO_2; Kriging per 10ug/m^3 PM_{10} and $PM_{2.5}$

Table 4

Associations of gaseous and particulate matter air pollutants and risk of death following breast cancer diagnosis among CA MEC breast cancer cases by ERPR status, 1993–2013[a].

			All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality			
			Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value
LUR	NO_x[b]	ER+/PR+	569	1.27	(0.97–1.66)	0.08	214	1.53	(0.98–2.39)	0.06	144	1.35	(0.78–2.33)	0.28	211	1.05	(0.67–1.64)	0.85
		ER-PR-	189	1.20	(0.72–1.99)	0.48	106	1.58	(0.81–3.09)	0.18	–	–	–	–	48	1.30	(0.32–5.28)	0.71
		$P_{heterogenerity}$				0.84				0.92				–				0.74
	NO2[b]	ER+/PR+	584	1.20	(0.87–1.64)	0.26	220	1.34	(0.79–2.26)	0.28	148	1.25	(0.65–2.42)	0.51	216	1.10	(0.65–1.85)	0.73
		ER-PR-	196	1.21	(0.67–2.15)	0.53	109	1.95	(0.89–4.28)	0.10	–	–	–	–	51	1.67	(0.31–9.03)	0.55
		$P_{heterogenerity}$				0.98				0.41				–				0.64
Kriging	NO_x[b]	ER+/PR+	647	1.14	(0.89–1.47)	0.31	238	1.31	(0.86–2.02)	0.21	166	1.33	(0.79–2.24)	0.29	243	0.98	(0.65–1.49)	0.93
		ER-PR-	213	1.40	(0.89–2.20)	0.15	120	1.76	(0.93–3.31)	0.08	41	2.64	(0.42–16.76)	0.30	52	0.87	(0.27–2.78)	0.81
		$P_{heterogenerity}$				0.40				0.40				0.38				0.86
	$N0_2$[b]	ER+/PR+	659	1.08	(0.80–1.45)	0.63	243	1.28	(0.76–2.14)	0.35	166	1.36	(0.73–2.55)	0.33	250	0.89	(0.55–1.44)	0.64
		ER-PR-	215	1.81	(1.04–3.15)	0.04	122	2.63	(1.19–5.83)	0.02	41	1.79	(0.21–15.2)	0.59	52	1.49	(0.33–6.83)	0.61
		$P_{heterogenerity}$				0.11				0.14				0.81				0.53
	$PM_{2.5}$[b]	ER+/PR+	657	1.03	(0.78–1.36)	0.84	241	1.05	(0.65–1.72)	0.83	166	1.12	(0.64–1.97)	0.69	250	0.98	(0.63–1.51)	0.91
		ER-PR-	215	1.41	(0.86–2.30)	0.17	121	1.76	(0.88–3.52)	0.11	41	1.30	(0.20–8.43)	0.78	53	1.22	(0.33–4.58)	0.77
		$P_{heterogenerity}$				0.20				0.18				0.72				0.72
	PM_{10}[b]	ER+/PR+	659	1.09	(0.92–1.29)	0.33	243	1.12	(0.83–1.52)	0.46	166	1.12	(0.80–1.58)	0.51	250	1.07	(0.81–1.40)	0.65
		ER-PR-	216	1.32	(0.96–1.81)	0.09	122	1.47	(0.95–2.28)	0.09	41	0.65	(0.20–2.08)	0.46	53	1.37	(0.57–3.31)	0.48
		$P_{heterogenerity}$				0.15				0.19				0.39				0.63

[a] Adjusted for race/ethnicity, marital status, stage, grade, histology, tumor size, chemotherapy, hormone treatment, radiation, surgery, nSES at diagnosis and current nSES, BMI, smoking, alcohol, diabetes, CVD risk, and age at first live birth; age at diagnosis as a stratum variable

[b] Kriging and LUR per 50 ppb NO_X; 20 ppb Kriging and LUR NO_2; Kriging per PM_{10} and $PM_{2.5}$

Table 5

Associations of gaseous and particulate matter air pollutants and risk of death following breast cancer diagnosis among CA MEC breast cancer cases by nSES at diagnosis, 1993–2013[a].

			All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality			
			Deaths	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**	**Deaths**	**HR**	**95% CI**	**p-value**
LUR	NO_x[b]	low nSES (Q1–Q3)	681	1.04	(0.82–1.31)	0.76	298	1.08	(0.75–1.55)	0.67	168	1.57	(0.99–2.50)	0.06	215	0.74	(0.47–1.16)	0.19
		high nSES (Q4–Q5)	289	1.44	(0.97–2.13)	0.07	116	1.87	(0.98–3.55)	0.06	70	0.65	(0.23–1.81)	0.41	103	1.43	(0.72–2.83)	0.31
		$P_{heterogenerity}$				0.15				0.14				0.11				0.09
	NO_2[b]	low nSES (Q1–Q3)	698	0.93	(0.69–1.24)	0.61	305	1.04	(0.66–1.63)	0.88	171	1.42	(0.78–2.59)	0.25	222	0.62	(0.36–1.08)	0.09
		high nSES (Q4–Q5)	296	1.65	(1.08–2.53)	0.02	119	2.44	(1.19–5.00)	0.02	72	0.68	(0.24–1.92)	0.46	105	1.58	(0.74–3.35)	0.23
		$P_{heterogenerity}$				0.03				0.05				0.22				0.05
Kriging	NO_x[b]	low nSES (Q1–Q3)	758	1.12	(0.90–1.40)	0.32	326	1.23	(0.88–1.71)	0.23	188	1.48	(0.92–2.38)	0.10	244	0.85	(0.57–1.27)	0.43
		high nSES (Q4–Q5)	325	1.31	(0.89–1.92)	0.17	131	1.48	(0.75–2.93)	0.26	78	0.90	(0.37–2.20)	0.82	116	1.37	(0.74–2.56)	0.32
		$P_{heterogenerity}$				0.49				0.62				0.34				0.20
	NO_2[b]	low nSES (Q1–Q3)	771	1.15	(0.87–1.53)	0.33	331	1.42	(0.91–2.21)	0.12	188	1.69	(0.93–3.07)	0.08	252	0.77	(0.47–1.26)	0.30
		high nSES (Q4–Q5)	328	1.49	(0.98–2.27)	0.07	133	1.46	(0.69–3.07)	0.32	78	0.92	(0.36–2.33)	0.86	117	1.86	(0.91–3.80)	0.09
		$P_{heterogenerity}$				0.32				0.95				0.28				0.05
	$PM_{2.5}$[b]	low nSES (Q1–Q3)	770	1.07	(0.83–1.38)	0.61	329	1.06	(0.71–1.58)	0.77	188	1.43	(0.85–2.42)	0.18	253	0.88	(0.56–1.37)	0.56
		high nSES (Q4–Q5)	327	1.38	(0.93–2.04)	0.11	132	1.32	(0.67–2.60)	0.43	78	1.40	(0.59–3.35)	0.44	117	1.33	(0.67–2.65)	0.42
		$P_{heterogenerity}$				0.29				0.59				0.97				0.32
	PM_{10}[b]	low nSES (Q1–Q3)	772	1.06	(0.90–1.25)	0.50	331	1.16	(0.89–1.50)	0.28	188	1.11	(0.79–1.55)	0.55	253	0.93	(0.70–1.25)	0.64
		high nSES (Q4–Q5)	328	1.30	(1.01–1.66)	0.04	133	1.37	(0.87–2.15)	0.18	78	1.39	(0.79–2.44)	0.25	117	1.16	(0.77–1.76)	0.48
		$P_{heterogenerity}$				0.18				0.53				0.50				0.39

[a] Adjusted for race/ethnicity, marital status, ERPR status, stage, grade, histology, tumor size, chemotherapy, hormone treatment, radiation, surgery, current nSES, BMI, smoking, alcohol, diabetes, CVD risk, and age at first live birth; age at diagnosis as a stratum variable

[b] Kriging and LUR per 50 ppb NO_X; 20 ppb Kriging and LUR NO_2; Kriging per PM_{10} and $PM_{2.5}$ PM_{10} and $PM_{2.5}$

Table 6

Associations of gaseous and particulate matter air pollutants and risk of death following breast cancer diagnosis among CA MEC breast cancer cases by stage of disease, 1993–2013[a].

			All-cause mortality				Breast cancer mortality				CVD mortality				Non-breast cancer and non-CVD mortality			
			Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value	Deaths	HR	95% CI	p-value
LUR	NOx^b	Localized	525	1.20	(0.91–1.59)	0.21	134	1.29	(0.77–2.15)	0.33	157	1.52	(0.87–2.64)	0.14	234	0.95	(0.61–1.48)	0.81
		Advanced	428	1.03	(0.77–1.39)	0.82	269	1.05	(0.72–1.54)	0.80	78	1.25	(0.55–2.84)	0.59	81	0.93	(0.42–2.09)	0.87
		$P_{heterogenerity}$				0.47				0.48				0.72				0.98
	$N0_2{}^b$	Localized	536	1.11	(0.79–1.55)	0.56	138	1.20	(0.63–2.26)	0.58	159	1.35	(0.69–2.64)	0.38	239	0.88	(0.52–1.47)	0.62
		Advanced	440	1.17	(0.82–1.68)	0.39	274	1.19	(0.74–1.90)	0.47	81	1.35	(0.53–3.41)	0.53	85	1.06	(0.41–2.75)	0.91
		$P_{heterogenerity}$				0.81				0.99				1.00				0.74
Kriging	$NO_x{}^b$	Localized	589	1.21	(0.92–1.58)	0.17	150	1.55	(0.93–2.60)	0.09	177	1.40	(0.84–2.34)	0.19	262	0.95	(0.63–1.43)	0.80
		Advanced	477	1.04	(0.78–1.39)	0.81	295	1.04	(0.72–1.51)	0.84	87	1.24	(0.54–2.84)	0.62	95	1.01	(0.52–1.98)	0.97
		$P_{heterogenerity}$				0.48				0.21				0.76				0.91
	$N0_2{}^b$	Localized	596	1.35	(0.98–1.86)	0.06	151	1.95	(1.02–3.75)	0.04	177	1.50	(0.83–2.71)	0.18	268	1.04	(0.65–1.68)	0.87
		Advanced	485	1.14	(0.79–1.65)	0.48	301	1.11	(0.69–1.78)	0.66	87	1.22	(0.42–3.55)	0.72	97	1.06	(0.45–2.47)	0.90
		$P_{heterogenerity}$				0.49				0.17				0.74				0.97
	$PM_{2.5}{}^b$	Localized	595	1.14	(0.85–1.52)	0.38	149	1.38	(0.76–2.51)	0.29	177	1.36	(0.80–2.31)	0.25	269	0.89	(0.58–1.36)	0.58
		Advanced	484	1.12	(0.80–1.56)	0.51	300	0.97	(0.63–1.49)	0.88	87	1.15	(0.47–2.83)	0.76	97	1.67	(0.78–3.61)	0.19
		$P_{heterogenerity}$				0.88				0.32				0.74				0.19
	$PM_{10}{}^b$	Localized	597	1.19	(0.99–1.43)	0.06	151	1.47	(1.01–2.13)	0.04	177	1.25	(0.90–1.73)	0.18	269	1.01	(0.77–1.33)	0.93
		Advanced	485	1.08	(0.87–1.33)	0.49	301	1.00	(0.76–1.31)	0.99	87	0.95	(0.52–1.75)	0.87	97	1.21	(0.78–1.89)	0.39
		$P_{heterogenerity}$				0.35				0.08				0.43				0.72

[a] Adjusted for race/ethnicity, marital status, ERPR status, grade, histology, tumor size, chemotherapy, hormone treatment, radiation, surgery, nSES at diagnosis and current nSES, BMI, smoking, alcohol, diabetes, CVD risk, and age at first live birth; age at diagnosis as a stratum variable

[b] LUR and kriging per 50 ppb NO_X; 20 ppb Kriging and LUR NO_2; Kriging per 10ug/m^3 $PM_{2.5}$ and PM_{10}