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Air pollution and Breast Cancer: A Review

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Abstract

Purpose of Review—Breast cancer is the most common cancer diagnosed among US women. Air pollution is a pervasive mixture of chemicals containing carcinogenic compounds and chemicals with endocrine disrupting properties. In the present review, we examine the epidemiologic evidence regarding the association between air pollution measures and breast cancer risk.

Recent Findings—We identified seventeen studies evaluating the risk of breast cancer associated with air pollution. A higher risk of breast cancer has been associated with nitrogen dioxide (NO₂) and nitrogen oxides (NO_x) levels, both of which are proxies for traffic exposure. However, there is little evidence supporting a relationship for measures of traffic count or distance to nearest road, or for measures of particulate matter (PM), except potentially for nickel and vanadium, which are components of PM₁₀. Hazardous air toxic levels and sources of indoor air pollution may also contribute to breast cancer risk. There is little existing evidence to support that the relationship between air pollution and breast cancer risk varies by either menopausal status at diagnosis or combined tumor hormone receptor subtype defined by the estrogen receptor (ER) and progesterone receptor (PR).

Summary—Epidemiologic evidence to date suggests an association between breast cancer risk and NO₂ and NO_x, markers for traffic-related air pollution; although there was little evidence supporting associations for proxy measures of traffic exposure or for PM. More research is needed to understand the role of specific PM components and whether associations vary by tumor receptor subtype and menopausal status at diagnosis.

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Compliance with Ethical Standards

Conflict of Interest

Alexandra J. White, Patrick T. Bradshaw, and Ghassan B. Hamra declare no conflicts of interest.

Human and Animal Rights and Informed Consent

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Keywords

air pollution; breast cancer; particulate matter; vehicular traffic; polycyclic aromatic hydrocarbons

1. Introduction

Breast cancer is the most common cancer diagnosed among women in the United States (US) [1] and there is an interest in better understanding the role of environmental factors on breast cancer risk [2]. Air pollution is an established environmental risk factor for lung cancer [3] and outdoor air pollution has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen [4].

Air pollution contains a mixture of many compounds, including polycyclic aromatic hydrocarbons (PAHs), metals, and benzene; these may act as carcinogens or as endocrine disruptors and, thus, be relevant for breast carcinogenesis. Inhaled toxicants have been measured in breast fluid, showing that airborne pollutants can reach the breast tissue [5]. The most well-studied compounds are PAHs [6], a combustion by-product, which has the capacity to bind to DNA and form adducts in the breast tissue [7]. Both PAHs and metals have estrogenic properties [8, 9], produce oxidative stress [10] and induce mammary tumors in animal models [9, 7]. Particulate matter, a complex mixture of small airborne particles including metals and hydrocarbons [11], has been shown to exhibit estrogenic properties and DNA-damaging activity *in vitro* [12] and benzene induces mammary tumors in rodents [13]. Both indoor and outdoor air pollution have been associated with breast tumor methylation of candidate genes selected *a priori* based on their relationship with breast cancer [14].

Breast cancer risk has been shown to be elevated in urban areas where air pollution is higher [15–17] and ecologic studies suggest that increasing traffic emissions in the US has been associated with an increase in breast cancer risk [18, 19]. However, the epidemiologic evidence to date has been inconsistent and sparse. In this review, we will summarize the existing literature on air pollution and breast cancer risk and highlight recent studies that have advanced our understanding of the relationship between air pollution and breast cancer. We will summarize the research to date on directly measured air pollution (including particulate matter, nitrogen dioxide (NO₂) and nitrogen oxides (NO_x), traffic-related air pollution); proximity to roadways and traffic density; and, other air pollution assessments (indoor air pollution, hazardous air toxics).

2. Exposure and Outcome Considerations

The exposure of interest for this review was either indoor or outdoor air pollution exposure and study characteristics and findings are summarized in Table 1 and 2. Measurement of air pollution varies widely and includes: direct measurement at fixed sites, estimation of residential exposure using modeling methods, or proxies of exposure such as density of traffic or proximity to roadways. Generally, studies utilizing modeling techniques such as air dispersion or land-use regression are believed to better capture the air pollution exposures by at least partially overcoming exposure misclassification[20]. Given the considerable heterogeneity of exposure assessment reviewed here (continuous monitored data, categorical

exposure categories based off of modeled estimates, questionnaire responses), it is challenging to directly compare many of the estimates. As such, we include the comparisons used for each measure of effect when describing the study findings.

The outcome of interest for this review was incident breast cancer. We considered whether studies considered variation in the association by menopausal status at diagnosis (premenopausal vs. postmenopausal) and by tumor hormone receptor subtype defined by the estrogen receptor (ER) and the progesterone receptor (PR).

3. Article Search Strategy

To identify articles related to air pollution exposure and breast cancer risk we did a search of PubMed using the following search criteria: (diesel[Title/Abstract] OR pm2.5[Title/Abstract] OR pm10[Title/Abstract] OR air pollution[Title/Abstract] OR particulate matter[Title/Abstract] OR traffic[Title/Abstract] OR Nitrogen dioxide[Title/Abstract] OR NO2[Title/Abstract] OR NOx[Title/Abstract] OR Nitrogen oxide[Title/Abstract]) AND (breast cancer[Title/Abstract]). We restricted our search to articles that were in English and that addressed either indoor and outdoor air pollution exposure in relation to breast cancer incidence. We first narrowed down the articles identified by the PubMed search criteria based on the article title. We next reviewed the abstracts for relevance to the review. We incorporated three additional studies related to the topic that did not arise from the PubMed search but were cited in the articles identified by the search.

4. Directly Measured Air Pollution

4.1 Particulate Matter

Particulate matter (PM) is a complex mixture of extremely small particles and liquid droplets that disperse into the air. PM is classified based on its diameter; the most commonly measured groups are PM₁₀, which are inhalable particles with diameters $\leq 10 \mu\text{m}$, PM_{2.5} which is defined as fine inhalable particles with diameters $\leq 2.5 \mu\text{m}$, and PM_{10-2.5} which is also referred to as PM_{coarse}. Ultrafine particles (UFPs) are defined as being $<0.1 \mu\text{m}$ in diameter and are generated by internal combustion engines and through secondary processes [21]. Prior to the use of PM_{2.5} and PM₁₀, total suspended particles (TSP) was a more crude measure of air pollution that relied on high volume samplers to capture particles $\leq 50\text{--}100 \mu\text{m}$ in diameter.

In an early study of air pollution and breast cancer, Bonner and colleagues published findings from the Western New York Exposures and Breast Cancer (WEB) case-control study, where exposure to total suspended particles (TSP) was estimated to be associated with a 2-fold higher odds of postmenopausal breast cancer for TSP exposure at birth [22]. Notably, TSP levels at other time periods were not positively associated with either premenopausal or postmenopausal breast cancer and in some instances TSP was inversely associated with breast cancer risk. Nonetheless, this study suggested a possible role for particulate matter in relation to breast cancer risk.

Most subsequent cohort studies evaluating the relationship between more precise PM measurements and breast cancer risk have not observed a positive association [23–25]. No association was observed in the US-based Sister Study, a cohort of women with a family history of breast cancer (1,749 invasive cases, 4.9 years of follow-up) [23]. Neither PM_{2.5} nor PM₁₀ levels assessed at the baseline residence were associated with overall invasive breast cancer or when considering ER/PR status of the tumor [23]. In the Nurses' Health Study II (3,416 cases), residential PM exposure (PM_{2.5}, PM_{coarse}, PM₁₀) was assessed for a 48-month time period. As in the Sister Study, no associations were observed for any PM metric with breast cancer risk with consideration of menopausal status at diagnosis and ER/PR status of the tumor, with the exception for PM_{coarse} and ER+/PR+ breast cancer (HR=1.13, 95% CI: 0.99–1.29, per 10µg/m³) [24]. No association was observed between 3 year running mean levels PM_{2.5} and PM₁₀ levels in the Danish Nurse Cohort (N=1,145 cases), with possible differences by menopausal status as PM_{2.5} was observed to be associated with premenopausal (HR=1.06, 95% CI: 0.94–1.18, per 3.3µg/m³) but not postmenopausal breast cancer (HR=0.93, 95% CI 0.85–1.05, p for interaction=0.07)[25]. These three cohort studies assessed PM levels using land-use regression models.

In the ESCAPE project, which pooled nine European prospective cohorts, elevated associations with postmenopausal breast cancer (N=3,612 cases) were observed for PM_{2.5} (HR=1.08, 95% CI 0.77–1.51, per 5 µg/m³), PM₁₀ (HR=1.07, 95% CI 0.89–1.30, per 10 µg/m³), PM_{coarse} (HR=1.20, 95%CI 0.96–1.49, per 5 µg/m³) but the authors noted considerable heterogeneity between individual cohort estimates [26]. The ESCAPE project also considered elemental components of PM_{2.5} and PM₁₀, which were assayed using X-ray fluorescence of PM filters. Specific PM components were selected based on their expected relationship to health effects and representativeness as well as data quality. The authors observed an association for PM₁₀ nickel (HR=1.30, 95% CI 1.09–1.55, per 2ng/m³) and vanadium (HR=1.30, 95% CI 0.95–1.77, per 3ng/m³) with respect to postmenopausal breast cancer [26]. Nickel and vanadium have estrogenic properties that may make those PM components particularly relevant to breast cancer [9] and were specifically included as PM components based on their hypothesized representation of mixed oil-burning and industry exposure sources.

In a Canadian case-control study (681 cases and 596 controls), Goldberg et al., estimated UFPs applying 2011–2012 monitoring data in a land-use regression model but found little to no association with postmenopausal breast cancer [27]. This is the only study to consider UFPs as a measure of air pollution exposure.

4.2 Nitrogen Dioxide (NO₂) and Nitrogen Oxides (NO_x)

Nitrogen oxide (NO_x) represents the total concentration of NO and NO₂ produced from combustion processes. NO₂ levels are considered to be a marker for traffic-related pollution [28], and thus may be a proxy for other components of traffic-related air pollution such as PAHs. NO₂ levels have been shown to be correlated with breast cancer incidence in ecological studies [18, 19].

In a mid-1990s case-control study in Quebec (383 invasive cases, 416 controls), a land-use regression model was used to assess NO₂ levels in relation to postmenopausal breast cancer

[29]. Elevated ORs were observed in association with NO₂ across a number of different exposure time periods; for example, for NO₂ levels estimated near the time of breast cancer diagnosis in 1996, a 5 ppb increase in NO₂ exposure was associated with an OR of 1.31 (95% CI: 1.00–1.71) [29]. Results were similar to those later reported for a larger population-based case-control study conducted in 8 Canadian provinces (1,569 cases, 1,872 controls) [30]. In Hystad et al., [30] NO₂ levels for the 20 years prior to diagnosis were estimated using three different methods: satellite-derived observations, satellite-derived observations scaled with historical fixed-site measurements of NO₂ and a national land-use regression model [30]. All three NO₂ measurements were associated with both premenopausal and postmenopausal breast cancer cases, with estimates more pronounced for premenopausal breast cancer [30].

Between 2008–2011, another population-based case-control study of postmenopausal breast cancer in Montreal assessed exposure to NO₂ for 2005–2006 using a land use regression model (681 cases and 596 controls) [27]. For an inter-quartile range (IQR) increase in NO₂ (3.75 ppb), the OR for postmenopausal breast cancer was 1.08 (95% CI 0.92–1.27); the estimated OR was higher in women who lived in their homes for 10 years before the study and for women with ER+PR+ breast cancer (OR=1.13, 95% CI 0.94–1.35) [27].

Elevated associations with NO₂ have also been observed in cohort studies. In the Sister Study cohort, NO₂ assessed using a land-use regression model at the baseline residence was associated with risk of ER+PR+ breast cancer (947 ER+PR+ cases; RR=1.10, 95% CI: 1.02–1.19 per IQR of 5.8bbp) but not ER–PR– breast cancer (223 ER–PR– cases, RR=0.92, 95% CI: 0.77–1.09, p for interaction=0.04) [23]. In the ESCAPE project, both NO₂ and NO_x were both associated with postmenopausal breast cancer (NO₂, HR=1.02, 95% CI: 0.98–1.07 per 10 µg/m³; NO_x, HR=1.04, 95% CI 1.00–1.08 per 20 µg/m³) [26]. The ESCAPE project included data from the Danish Diet Cancer and Health Study (n=987 breast cancer cases), which separately reported that a 100µg/m³ increase in modeled NO_x estimated over a 5-year period, was associated with breast cancer risk (IRR=1.16, 95% CI: 0.89–1.51) [31]. In contrast, no increase in risk was observed with NO₂ levels in the Danish Nurse Cohort (N=1,145 cases) using a 3-year running mean average level [25].

4.3 Traffic-related pollution models

The Long Island Breast Cancer Study Project (LIBCSP) and the WEB study both employed similar validated traffic-related pollution models that estimated residential exposure to benzo[a]pyrene. In the population-based LIBCSP (1,508 cases and 1,556 controls) [32], women in the top 5% of exposure when compared to those below the median had an elevated but imprecise OR for overall breast cancer (OR=1.47, 95% CI: 0.70–3.08) when considering longer-term exposure (1960–1990); the OR was slightly more elevated for ER–PR– breast cancer (OR=1.67, 95% CI: 0.91–3.05) also for longer-term traffic-related exposure [32].

In the WEB study, they reported a 2-fold higher odds of premenopausal breast cancer for traffic exposure at age at menarche and a 2-fold higher odds for postmenopausal breast cancer in relation to traffic exposure at age at first birth [33]. However, associations were not

evident for traffic exposure at age at first birth, or for exposure at 10 or 20 years prior to diagnosis when considering both premenopausal and postmenopausal breast cancer [33].

5. Proximity to Roadways and Traffic Volume

5.1 Proximity to Roadways and Traffic Volume

No association was observed with proximity to nearest roads or vehicular traffic volume metrics in Hystad et al., 2014 [30], in the Danish Diet and Cancer Study [31] or in the ESCAPE project [26]. In the Nurses' Health Study II, living within 50 m of a major road was suggestively associated with breast cancer, although confidence intervals were wide [24]. High traffic density measures were not significantly elevated in relation to breast cancer risk in another case-control study conducted on Long Island, New York (793 cases, 966 controls) [34].

Using self-reported childhood residential characteristics of main road and nearest intersecting road as proxies for traffic exposure (i.e., number of lanes, presence of a median or barrier, traffic), Shmuel et al., reported an elevated risk of breast cancer for living on a road with a median or barrier (HR=1.2, 95% CI 0.9–1.7) and for living near an intersecting road with high proxy measures of traffic (HR=1.4, 95% CI 1.0–1.9) in the Sister Study [35].

6. Other measures

6.1 Indoor air pollution

Burning wood or gas in the home for indoor heating and cooking purposes can release compounds similar to that observed in outdoor air, including particulate matter, PAHs and benzene [36]. Two studies have evaluated the relationship between air pollution from using indoor stove/fireplaces in the home and breast cancer risk. The first study was conducted in the LIBCSP and reported a OR=1.42 (95% CI: 1.11–1.84) of breast cancer for burning synthetic or artificial firelogs in the home relative to no indoor stove/fireplace use [37]. In the prospective Sister Study cohort, using an indoor stove/fireplace at the longest adult residence was also associated with breast cancer; risk was higher with increasing frequency of use (at least once per week relative to no stove/fireplace use, HR=1.17, 95% CI: 1.02–1.34) and was most evident for burning wood or gas [38].

6.2 Hazardous air toxics

The California Teacher's Study used the 2002 Environmental Protection Agency's (EPA) National Air Toxics Assessment (NATA) database to evaluate the association between quintiles of hazardous air toxic pollutants estimated at the census-track level and breast cancer risk [39, 40]. In a study of 24 air toxics selected based on toxicological data for the ability to induce mammary gland tumors, they reported an association for acrylamide, carbon tetrachloride, chloroprene, 4,4'-methylene bis(2-chloroaniline), propylene oxide and vinyl chloride with overall breast cancer, noting that associations were largely not monotonic [39]. Interestingly, the authors found variability in the associations by hormone receptor subtype; ER+ or PR+ tumors were associated with higher levels of acrylamide, benzidine, carbon tetrachloride, ethylidene dichloride and vinyl chloride whereas ER-/PR- tumors

were associated with higher levels of benzene [39]. When focusing on 11 *a priori* selected endocrine disrupting hazardous air pollutants, the authors found little evidence for an association with these compounds expect for an elevated risk in a select subgroup of never-smoking non-movers for ER-/PR- breast cancer in relation to higher exposure to cadmium compounds and inorganic arsenic [40].

7. Conclusions

In this review, we have summarized the results for 8 case-control studies and 9 cohort studies that have used a range of metrics to analyze the relationship between breast cancer and exposure to indoor and outdoor air pollution. The association with breast cancer tended to vary based on the air pollutant assessed, with more consistent findings reported for elevated NO₂ or NO_x levels and traffic-related air pollution models.

Together the studies to date suggest little evidence to support a relationship between particulate matter and breast cancer risk. However, it is possible that individual components of PM, such as vanadium and nickel as demonstrated in the ESCAPE project [26], may be relevant for breast cancer. Additional research is needed to better understand PM components and their potential for a relationship with breast cancer risk.

The results from studies that considered NO_x and NO₂, indicators of vehicular traffic exposure, are more suggestive of a role for air pollution in breast carcinogenesis than those for particulate matter. Most studies reported positive estimates in relation to higher NO₂ and NO_x levels, with the possibility that risk may vary by ER/PR subtype as observed in the Sister Study cohort. Consistent with the results for NO_x and NO₂, the vehicular traffic B[a]P models applied in the LIBCSP and in the WEB study also suggest an elevated risk of breast cancer in relation to PAH exposure from vehicular traffic.

There is little to no association observed across studies that used distance to nearest road or traffic volume as a proxy for air pollution exposure in relation to breast cancer risk. However, some suggestion of an association was observed for childhood exposure to high residential traffic.

Indoor burning of biomass is of concern worldwide [41] and prevalence estimates suggest that frequency of use is high in the US as well [38]. Two studies, the LIBCSP and Sister Study cohort, observed associations with indoor stove/fireplace use in relation to breast cancer risk although associations were not consistent in terms of type of material burned [38, 37]. More research is needed to better understand the importance of indoor air pollution components in relation to breast cancer risk.

Exposure to hazardous air toxics, as demonstrated in the California Teacher's Study, may be relevant for breast cancer [40, 42]. The EPA NATA relies on modeled data from reported industry emissions and other sources in conjunction with air pollution modeling techniques to assess air toxics on the census-track level [43]. Because hazardous air pollutants are rarely monitored, better assessment of exposure to these air toxics is needed.

Most of the literature on air pollution and breast cancer risk has focused on adult-level air pollution exposure, predominately measuring and estimating air pollution in the years immediately preceding diagnosis. However, early life may represent a potentially susceptible time period for breast tissue [44]. In the Sister Study cohort, self-reported childhood residential characteristics as proxy measures for traffic exposure were associated with an elevated association with breast cancer risk [35]. Similarly, in the WEB study, TSP exposure levels at birth were associated with later postmenopausal breast cancer risk and when using a geographic traffic BaP exposure model, exposure at age of menarche and at age at first childbirth were associated with premenopausal and postmenopausal breast cancer, respectively [33]. Early life exposure to air pollution is challenging to measure accurately as studies usually have women at a range of ages (thus having a range of calendar years relevant for early life exposure) and air pollution monitoring data often does not go back far enough in time to capture the relevant period. Advanced modeling that can reliability extrapolate back would be useful in quantifying early life air pollution exposure.

Few studies have been able to incorporate information regarding ER/PR tumor subtype. The impact of breast cancer risk factors have been shown to vary by ER/PR status suggesting etiologic heterogeneity [45]. The Sister Study found the association with NO₂ to be limited to ER+/PR+ breast cancer [23]. Similarly, in Goldberg et al., an IQR increase in NO₂ was most strongly related to ER+/PR+ breast cancer, as was UFPs [27]. The Nurses' Health Study II found PM_{coarse} to be related to ER+/PR+ breast cancer [24]. In contrast, the LIBCSP study found results using the B[a]P traffic model to be strongest for ER-/PR- breast cancer [32]. Hazardous air toxics and breast cancer associations also appeared to vary by ER/PR status of the tumor, with associations reported for both ER+/PR+ breast cancer and ER-/PR- breast cancer depending on the air toxic [40, 42]. Different air pollutant constituents may have differing carcinogenic properties and thus may be relevant for hormone-receptor positive or negative disease. More research is needed, especially in large studies with good power to describe differences in hormone receptor status.

A few studies in this review were limited to only postmenopausal women [26, 29, 27] although most studies included both pre- and postmenopausal women. Other risk factors for breast cancer have been shown to vary by menopausal status at diagnosis, such as obesity [46]. It is unclear whether associations vary by menopausal status at diagnosis; with some studies reporting stronger associations of air pollution exposures with premenopausal breast cancer [25, 24, 30] and some with postmenopausal breast cancer [22, 33, 34]. As with tumor receptor subtype, more research is needed in well-powered studies to quantify differences in exposure by menopausal status at diagnosis.

The purpose of this review was to evaluate the relationship between metrics of air pollution and breast cancer incidence. However, there is a recent and growing body of research that is worth noting on the relationship between air pollution and mortality after a breast cancer diagnosis. Specifically, an higher risk of mortality after a breast cancer diagnosis has been observed in relation to PM_{2.5} [47–49] and PM₁₀ levels [50]. More research is needed to understand the contribution of air pollution to survival after breast cancer.

In conclusion, epidemiologic research on the association between indoor and outdoor air pollution and breast cancer risk suggests a relationship between air pollution when using NO₂ as a marker for traffic related air pollution. Improved exposure assessment in order to better capture and characterize exposure is needed. Future research needs to consider early life time periods of exposure, stratification by tumor subtype and menopausal status, indoor air pollution metrics and hazardous air toxics as potential contributors to breast cancer risk.

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Table 1
The relationship between air pollution and breast cancer risk by recency of publication: case-control studies.

First author, year, reference	Location	Sample size	Air Pollution Metric	Air Pollution Assessment	Important Findings
Goldberg, 2017 [27]	Canada	681 postmenopausal cases and 596 controls	NO ₂ and UFP	Land-use regression models	NO₂ : For an IQR increase (3.75ppb); OR= 1.08 (95% CI: 0.92–1.27); ER+PR+ OR=1.13 (95% CI: 0.94– 1.35) UFPs : For an IQR increase (~3500cm ⁻³), OR=1.02 (95% CI: 0.94–1.11); ER+PR+ OR=1.05 (95% CI: 0.96– 1.14)
Mordukhovich, 2016 [32]	US	1,508 cases and 1,556 controls	B[a]P proxy for traffic	Land-use regression model	long-term 1960–1990 : For top 5% vs below the median, OR=1.44 (95%CI: 0.78–2.68); ER+/PR+ OR=0.86 (95%CI: 0.52– 1.41); ER-/PR- OR=1.67 (95% CI: 1.08– 4.06)
Hystad, 2015 [30]	Canada	1569 cases, 1872 controls	NO ₂	(1) satellite-derived estimates (2) satellite-derived estimates with historical fixed-site NO ₂ (reported here) (3) land-use regression model	NO₂ : For 10ppb increase, OR=1.13 (95% CI 0.99–1.27); Pre-menopausal OR=1.32 (95% CI: 1.05–1.67); Postmenopausal OR= 1.10 (95% CI: 0.94–1.28)
White, 2014 [37]	US	1,508 cases and 1,556 controls	Indoor stove/fireplace use	Self-reported questionnaire	Synthetic logs : ever burning vs. no stove/fireplace use, OR = 1.42 (95% CI 1.11, 1.84) Wood : ever burning, vs no stove/fireplace use OR=0.93, 95% CI 0.77–1.12) Gas : ever burning vs. no stove/fireplace use, OR=0.86, 95% CI: 0.42–1.73) Coal : ever burning vs. no stove/fireplace use, OR=1.28 (95% CI:0.88–1.86)
Crouse, 2010 [29]	Canada	383 cases, 416 controls	NO ₂	Land-use regression model	NO₂ : For 5ppb increase, OR=1.31 (95% CI: 1.00–1.71)
Nie, 2007 [33]	US	1,166 cases, 2,105 controls	B[a]P proxy for traffic	Land-use regression model	Traffic emissions at the time of menarche : 4 th quartile vs 1 st quartile, Pre-menopausal OR=2.07 (95% CI 0.91–4.72) Traffic emissions at the time of a woman's first birth : 4 th quartile vs 1 st quartile, Pre-menopausal OR=1.22 (95% CI 0.44–3.36); Postmenopausal, OR= 2.58 (95% CI 1.15–5.83) 20 years prior :4 th quartile vs 1 st quartile, Pre-menopausal OR=1.29 (95% CI: 0.59–2.82); Postmenopausal OR=0.82, (95% CI: 0.58–1.18); 10 years prior : 4 th quartile vs 1 st quartile, Pre-menopausal OR=1.49, 95% CI: 0.65–3.43); Postmenopausal OR=0.80, 95% CI: 0.55–1.17)
Bonner, 2005 [22]	US	1,166 cases, 2,105 controls	Total Suspended Particles (TSP)	Land-use regression model	TSP at birth : for >140 µg/m ³ compared to <84 µg/ m ³ , Pre-menopausal OR=1.78 (95% CI: 0.62–5.10); Postmenopausal OR= 2.42 (95% CI: 0.97–6.09) TSP at menarche : for >140 µg/m ³ compared to <84 µg/ m ³ Pre-menopausal OR=0.66 (95% CI: 0.38–1.16);

First author, year, reference	Location	Sample size	Air Pollution Metric	Air Pollution Assessment	Important Findings
Lewis-Michi, 1996 [34]	US	793 cases, 966 controls	Traffic density	Traffic counts in Nassau and Suffolk counties	Postmenopausal OR= 1.45 (95% CI: 0.74-2.87) High traffic density: Postmenopausal, Nassau OR=1.29 (95% CI: 0.77-2.15); Suffolk, OR=0.89 (95% CI 0.40- 1.99)

/ Abbreviations: interquartile range (IQR)

Table 2
The relationship between air pollution and breast cancer risk by recency of publication: cohort studies.

First author, year, reference	Location	Study Name	Sample size	Air Pollution Metric	Air Pollution Assessment Tool	Important Findings
Andersen, 2017 [26]	Europe	ESCAPE	74,750 postmenopausal women, N=3,612 cases	PM _{2.5} , PM ₁₀ , PM _{coarse} , PM _{2.5} absorbance, NO ₂ and NO _x PM elemental composition	Land-use regression X-ray fluorescence	PM _{2.5} : per 5 µg/m ³ , HR=1.08 (95% CI: 0.77–1.51) PM ₁₀ : per 10 µg/m ³ , HR=1.07 (95% CI: 0.89–1.30) PM _{coarse} : per 5 µg/m ³ , HR=1.20 (95% CI: 0.96, 1.49) NO ₂ : per 10 µg/m ³ , HR=1.02 (95% CI: 0.98, 1.07) NO _x : per 20 µg/m ³ , HR=1.04 (95% CI: 1.00, 1.08) PM _{2.5} nickel: per 1ng/m ³ , HR=1.13 (95% CI 0.89–1.44) PM _{2.5} vanadium: per 2 ng/m ³ , HR=1.29 (95% CI 0.93–1.78) PM ₁₀ nickel: per 2ng/m ³ , HR=1.30 (95% CI 1.09–1.55) PM ₁₀ vanadium: per 3 ng/m ³ HR=1.30 (95% CI 0.95–1.77)
Shmuel, 2017 [35]	US	Sister Study	50,884 women, N=2,208 cases	Childhood residential traffic exposure characteristics	Self-reported questionnaire	median/barrier dividing primary road: HR =1.2 (95% CI: 0.9–1.7) nearest cross-street had the highest traffic, 3 lanes, and/or a median/barrier: HR = 1.4 (95% CI: 1.0–1.9)
Andersen, 2016 [25]	Denmark	Danish Nurse Cohort	22,877 women, N=1,145 cases	PM _{2.5} , PM ₁₀ , NO ₂	Land-use regression	PM _{2.5} : per 3.3 µg/m ³ , HR=0.99 (95% CI: 0.94 – 1.10); Premenopausal HR=1.06 (95% CI: 0.94–1.18) Postmenopausal HR=0.93 (95% CI: 0.82–1.05) PM ₁₀ : per 2.9 µg/m ³ , HR 1.02 (95% CI: 0.94, 1.10) NO ₂ : per 7.4 µg/m ³ , HR 0.99 (95% CI: 0.93, 1.05)
Hart, 2016 [24]	USA	Nurses' Health Study II	115,921 women, N=3,416 cases	PM _{2.5} , PM ₁₀ , PM _{coarse} , Distance to roadway	Land-use regression models Geocoded residential data	PM _{2.5} : per 10µg/m ³ , HR=0.90 95% CI: 0.79–1.03 PM ₁₀ : per 10µg/m ³ , HR=1.00 95% CI: 0.93–1.07 PM _{coarse} : per 10µg/m ³ , HR=1.06, 95% CI 0.96–1.17 <50 m of the largest (A1) road: HR = 1.60 (95% CI: 0.80–3.21) compared with women living farther (200 m) away.

First author, year, reference	Location	Study Name	Sample size	Air Pollution Metric	Air Pollution Assessment Tool	Important Findings
Reding, 2015 [23]	USA	Sister Study	50,884 women, N=1,749 cases	PM _{2.5} , PM ₁₀ , NO ₂	Land-use regression models	<50 m of the two largest road types (A1-A2): HR=1.14 (95% CI: 0.84–1.54) compared with women living farther (200 m) away. PM_{2.5}: per IQR increase of 3.6 µg/m ³ , HR=1.03 (95% CI: 0.96–1.11) PM₁₀: per IQR increase of 5.8 µg/m ³ , HR=0.99 (0.98–1.00) NO₂: per IQR increase of 5.8 ppb, HR=1.02 (95% CI 0.97–1.07); ER+PR+ RR=1.10 (95% CI: 1.02–1.19); ER-PR- RR=0.92 (95% CI: 0.77–1.09)
Liu, 2015 [40]	USA	California Teachers Study	112,378, N=5,361 cases	Air toxics – 11 endocrine disruptor compounds selected <i>a priori</i>	EPA 2002 National Air Toxics Assessment (NATA)	No associations with overall breast cancer risk or with subtypes except in select subgroups. In residentially stable non-smokers: Arsenic: Quintile 5 vs 1, ER-PR- HR=1.65; (95% CI:1.08–2.53) Cadmium: Quintile 5 vs 1, ER-PR- HR=1.64 (95% CI=1.08–2.49)
Garcia, 2015 [42]	USA	California Teachers Study	112,378, N=5,676 cases	Air toxics – 24 mammary gland carcinogens selected <i>a priori</i>	EPA 2002 National Air Toxics Assessment (NATA)	Propylene oxide: Quintile 2 vs 1, HR=1.11 (1.02, 1.20) Vinyl chloride: Quintile 2 vs 1, HR=1.12 (1.03, 1.21) for Acrylamide, benzidine, carbon tetrachloride, ethyldene dichloride, and vinyl chloride: associated with ER+PR+ breast cancer Benzene: associated with ER-PR- breast cancer
White, 2017 [38]	USA	Sister Study	50,884 women, N=2,416 cases	Indoor stove/fireplace use	Self-reported questionnaire	Any indoor stove/fireplace: HR=1.11 (95% CI: 1.01–1.22) relative to no stove/fireplace Frequency of use once/week: HR=1.17 (95% CI: 1.02, 1.34)] (p for trend=0.01) relative to no stove/fireplace use Burning wood: HR=1.09 (95% CI: 0.98–1.21) relative to no stove/fireplace use Natural gas/propane: HR=1.15 (95% CI: 1.00, 1.32) relative to no stove/fireplace use
Raaschou-Nielsen, 2011 [31]	Denmark	Danish Diet Cancer and Health Study	27,735 women, N=987 cases	NO _x	Land-use regression	NO_x: for 100ug/m ³ , IRR=1.16 (95%CI 0.89–1.51)

/ Abbreviations: interquartile range (IQR)