Current Epidemiology Reports (2018) 5:92–100
https://doi.org/10.1007/s40471-018-0143-2

ENVIRONMENTAL EPIDEMIOLOGY (F LADEN AND J HART, SECTION EDITORS)

Air Pollution and Breast Cancer: a Review

Alexandra J. White[1] · Patrick T. Bradshaw[2] · Ghassan B. Hamra[3]

Published online: 27 March 2018

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 17 studies evaluating the risk of breast cancer associated with air pollution. A higher risk of breast cancer has been associated with nitrogen dioxide (NO_2) and nitrogen oxide (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 PM_{10}. 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 NO_2 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.

Keywords Air pollution · Breast cancer · Particulate matter · Vehicular traffic · Polycyclic aromatic hydrocarbons

Introduction

Breast cancer is the most common cancer diagnosed among women in the United States (USA) [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 [7, 9]. 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 USA has been associated with an increase in breast cancer risk [18, 19].

This article is part of the Topical Collection on *Environmental Epidemiology*

✉ Alexandra J. White
alexandra.white@nih.gov

[1] Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC 27709-2233, USA

[2] Division of Epidemiology and Biostatistics, School of Public Health, University of California Berkeley, Berkeley, CA, USA

[3] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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 (NO_2) and nitrogen oxides (NOx), traffic-related air pollution), proximity to roadways and traffic density, and other air pollution assessments (indoor air pollution, hazardous air toxics).

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 Tables 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 [37]. 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).

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 or 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.

Directly Measured Air Pollution

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 PM_{10}, which are inhalable particles with diameters ≤ 10 μm; $PM_{2.5}$ which is defined as fine inhalable particles with diameters ≤ 2 μm; and $PM_{10–2.5}$ which is also referred to as PM_{coarse}. Ultrafine particles (UFPs) are defined as being < 0.1 μm in diameter and are generated by internal combustion engines and through secondary processes [38]. Prior to the use of $PM_{2.5}$ and PM_{10}, total suspended particle (TSP) was a more crude measure of air pollution that relied on high volume samplers to capture particles $\leq 50–100$ μm 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 TSP was estimated to be associated with a twofold higher odds of postmenopausal breast cancer for TSP exposure at birth [26]. 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 [30, 31•, 32•]. No association was observed in the USA-based Sister Study, a cohort of women with a family history of breast cancer (1749 invasive cases, 4.9 years of follow-up) [32•]. Neither $PM_{2.5}$ nor PM_{10} levels assessed at the baseline residence were associated with overall invasive breast cancer or when considering ER/PR status of the tumor [32•]. In the Nurses' Health Study II (3416 cases), residential PM exposure ($PM_{2.5}$, PM_{coarse}, PM_{10}) 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 10 $\mu g/m^3$) [31•]. No association was observed between 3-year running mean $PM_{2.5}$ and PM_{10} levels in the Danish nurse cohort ($N = 1145$ cases), with

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 [20]	Canada	681 postmenopausal cases and 596 controls	NO_2 and UFP	Land-use regression models	NO_2: For an IQR increase (3.75 ppb): 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 [21]	USA	1508 cases and 1556 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 [22••]	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	NO_2: For 10 ppb increase, OR = 1.13 (95% CI: 0.99–1.27) Premenopausal OR = 1.32 (95% CI: 1.05–1.67) Postmenopausal OR = 1.10 (95% CI: 0.94–1.28)
White 2014 [23]	USA	1508 cases and 1556 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 [24]	Canada	383 cases, 416 controls	NO_2	Land-use regression model	NO_2: For 5 ppb increase, OR = 1.31 (95% CI: 1.00–1.71)
Nie 2007 [25]	USA	1166 cases, 2105 controls	B[a]P proxy for traffic	Land-use regression model	Traffic emissions at the time of menarche: 4th quartile vs 1st quartile, premenopausal OR = 2.07 (95% CI: 0.91–4.72) Traffic emissions at the time of a woman's first birth: 4th quartile vs 1st quartile, premenopausal OR = 1.22 (95% CI: 0.44–3.36) Postmenopausal, OR = 2.58 (95% CI: 1.15–5.83) 20 years prior: 4th quartile vs 1st quartile, premenopausal OR = 1.29 (95% CI: 0.59–2.82) Postmenopausal OR = 0.82, (95% CI: 0.58–1.18) 10 years prior: 4th quartile vs 1st quartile, premenopausal OR = 1.49, 95% CI: 0.65–3.43); Postmenopausal OR = 0.80, 95% CI: 0.55–1.17)
Bonner 2005 [26]	USA	1166 cases, 2105 controls	Total suspended particles (TSPs)	Land-use regression model	TSP at birth: for > 140 μg/m^3 compared to < 84 μg/ m^3, premenopausal 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 Premenopausal OR = 0.66 (95% CI: 0.38–1.16); Postmenopausal OR = 1.45 (95% CI: 0.74–2.87)
Lewis-Michl 1996 [27]	USA	793 cases, 966 controls	Traffic density	Traffic counts in Nassau and Suffolk counties	High traffic density: postmenopausal, Nassau OR = 1.29 (95% CI: 0.77–2.15) Suffolk, OR = 0.89 (95% CI: 0.40–1.99)

IQR interquartile range

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 [28••]	Europe	ESCAPE	74,750 postmenopausal women, $N = 3612$ 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 1 ng/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 2 ng/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 [29]	USA	Sister Study	50,884 women, $N = 2208$ 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 [30]	Denmark	Danish Nurse Cohort	22,877 women, $N = 1145$ 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 [31•]	USA	Nurses' Health Study II	115,921 women $N = 3416$ cases	$PM_{2.5}$, PM_{10}, PM_{coarse} Distance to roadway	Land-use regression models Geocoded residential data	$PM_{2.5}$: per 10 μg/m^3, HR = 0.90 95% CI: 0.79–1.03) PM_{10}: per 10 μg/m^3, HR = 1.00 95% CI: 0.93–1.07) PM_{coarse}: per 10 μg/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. < 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.
Reding 2015 [32•]	USA	Sister Study	50,884 women, $N = 1749$ cases	$PM_{2.5}$, PM_{10}, NO_2	Land-use regression models	$PM_{2.5}$: per IQR increase of 3.6 μg/m^3, HR = 1.03 (95% CI: 0.96–1.11) PM_{10}: per IQR increase of 5.8 μg/m^3, HR = 0.99 (0.98–1.00) NO_2: 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 [33]	USA	California Teachers Study	112,378, $N = 5361$ cases	Air toxics—11 endocrine disruptor compounds selected a priori	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 [34]	USA	California Teachers Study	112,378, $N = 5676$ cases	Air toxics—24 mammary gland carcinogens selected a priori	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, ethylidene dichloride, and vinyl chloride: associated with ER + PR+ breast cancer Benzene: associated with ER−PR− breast cancer
White 2017 [35•]	USA	Sister Study	50,884 women, $N = 2416$ 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-Nielson 2011 [36]	Demark	Danish Diet Cancer and Health Study	27,735 women, $N = 987$ cases	NO_x	Land-use regression	NO_x: for 100 μg/m^3, IRR = 1.16 (95% CI: 0.89–1.51)

IQR interquartile range

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 3.3 μg/m^3) but not postmenopausal breast cancer (HR = 0.93, 95% CI: 0.85–1.05, p for interaction = 0.07) [30]. 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 = 3612 cases) were observed for $PM_{2.5}$ (HR = 1.08, 95% CI: 0.77–1.51, per 5 μg/m^3), PM_{10} (HR = 1.07, 95% CI: 0.89–1.30, per 10 μg/m^3), PM_{coarse} (HR = 1.20, 95%CI 0.96–1.49, per 5 μg/m^3) but the authors noted considerable heterogeneity between individual cohort estimates [28••]. The ESCAPE project also considered elemental components of $PM_{2.5}$ and PM_{10}, 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 PM_{10} nickel (HR = 1.30, 95% CI: 1.09–1.55, per 2 ng/m^3) and vanadium (HR = 1.30, 95% CI: 0.95–1.77, per 3 ng/m^3) with respect to postmenopausal breast cancer [28••]. 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 [20]. This is the only study to consider UFPs as a measure of air pollution exposure.

Nitrogen Dioxide (NO_2) and Nitrogen Oxides (NOx)

Nitrogen oxide (NO_x) represents the total concentration of NO and NO_2 produced from combustion processes. NO_2 levels are considered to be a marker for traffic-related pollution [39], and thus may be a proxy for other components of traffic-related air pollution such as PAHs. NO_2 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 NO_2 levels in relation to postmenopausal breast cancer [24]. Elevated ORs were observed in association with NO_2 across a number of different exposure time periods; for example, for NO_2 levels estimated near the time of breast cancer diagnosis in 1996, a 5 ppb increase in NO_2 exposure was associated with an OR of 1.31 (95% CI: 1.00–1.71) [24]. Results were similar to those later reported for a larger population-based case-control study conducted in 8 Canadian provinces (1569 cases, 1872 controls) [22••]. In Hystad et al. [22••], NO_2 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 NO_2 and a national land-use regression model [22••]. All three NO_2 measurements were associated with both premenopausal and postmenopausal breast cancer cases, with estimates more pronounced for premenopausal breast cancer [22••].

Between 2008 and 2011, another population-based case-control study of postmenopausal breast cancer in Montreal assessed exposure to NO_2 for 2005–2006 using a land-use regression model (681 cases and 596 controls) [20]. For an interquartile range (IQR) increase in NO_2 (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) [20].

Elevated associations with NO_2 have also been observed in cohort studies. In the Sister Study cohort, NO_2 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 5.8 bbp) but not ER−PR− breast cancer (223 ER−PR− cases, RR = 0.92, 95% CI: 0.77–1.09, p for interaction = 0.04) [32•]. In the ESCAPE project, both NO_2 and NO_x were both associated with postmenopausal breast cancer (NO_2, HR = 1.02, 95% CI: 0.98–1.07 per 10 μg/m^3; NO_x, HR = 1.04, 95% CI: 1.00–1.08 per 20 μg/m^3) [28••]. The ESCAPE project included data from the Danish Diet Cancer and Health Study (n = 987 breast cancer cases), which separately reported that a 100 μg/m^3 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) [36]. In contrast, no increase in risk was observed with NO_2 levels in the Danish Nurse Cohort (N = 1145 cases) using a 3-year running mean average level [30].

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 (1508 cases and 1556 controls) [21], 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 [21].

In the WEB study, they reported a twofold higher odds of premenopausal breast cancer for traffic exposure at age at menarche and a twofold higher odds for postmenopausal breast cancer in relation to traffic exposure at age at first birth

[25]. 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 [25].

Proximity to Roadways and Traffic Volume

No association was observed with proximity to nearest roads or vehicular traffic volume metrics in Hystad et al. [22••], in the Danish Diet and Cancer Study [36] or in the ESCAPE project [28••]. 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 [31•]. 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) [27].

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 [29].

Other Measures

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 [40]. 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 [23]. 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 [35•].

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 [33, 41]. 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-choloraniline), propylene oxide, and vinyl chloride with overall breast cancer, noting that associations were largely not monotonic [41]. 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 [41]. When focusing on 11 a priori selected endocrine disrupting hazardous air pollutants, the authors found little evidence for an association with these compounds except 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 [33].

Conclusions

In this review, we have summarized the results for eight case-control studies and nine 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 NO_2 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 [28••], 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 NO_2, 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 NO_2 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 NO_2, 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 [42] and prevalence estimates suggest that frequency of use is high in the USA as well [35•]. 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 [23, 35•]. 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 [33, 34]. 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 [29]. 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 was associated with premenopausal and postmenopausal breast cancer, respectively [25]. 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 NO_2 to be limited to ER+/PR+ breast cancer [32•]. Similarly, in Goldberg et al., an IQR increase in NO_2 was most strongly related to ER+/PR+ breast cancer, as was UFPs [20]. The Nurses' Health Study II found PM_{coarse} to be related to ER+/PR+ breast cancer [31•]. In contrast, the LIBCSP study found results using the B[a]P traffic model to be strongest for ER−/PR− breast cancer [21]. 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 [33, 34]. 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 [20, 24, 28••] 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 [22••, 30, 31•] and some with postmenopausal breast cancer [25–27]. 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, a higher risk of mortality after a breast cancer diagnosis has been observed in relation to $PM_{2.5}$ [47–49] and PM_{10} 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 NO_2 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.

Acknowledgements This research was supported by the Intramural Research Program of the NIH.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. IOM. Washington, DC: Institute of Medicine, the National Academies. Breast cancer and the environment: a life course approach. 2011. Available: https://www.nap.edu/catalog/13263/breast-cancer-and-the-environment-a-life-course-approach. Accessed 22 March 2018.
3. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. Environ Health Perspect. 2015;123(11):1107–12.
4. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013;14(13):1262–3.
5. Hill P, Wynder EL. Nicotine and cotinine in breast fluid. Cancer Lett. 1979;6(4–5):251–4.
6. White AJ, Bradshaw PT, Herring AH, Teitelbaum SL, Beyea J, Stellman SD, et al. Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. Environ Int. 2016;90:185–92.
7. International Agency for Research on Cancer. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 2010;92:35–818.
8. Sievers CK, Shanle EK, Bradfield CA, Xu W. Differential action of monohydroxylated polycyclic aromatic hydrocarbons with estrogen receptors alpha and beta. Toxicol Sci. 2013;132(2):359–67.
9. Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. Metals and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(1):63–73.
10. Wang T, Feng W, Kuang D, Deng Q, Zhang W, Wang S, et al. The effects of heavy metals and their interactions with polycyclic aromatic hydrocarbons on the oxidative stress among coke-oven workers. Environ Res. 2015;140:405–13.
11. Adams K, Greenbaum DS, Shaikh R, van Erp AM, Russell AG. Particulate matter components, sources, and health: systematic approaches to testing effects. J Air Waste Manage Assoc. 2015;65(5):544–58.
12. Chen ST, Lin CC, Liu YS, Lin C, Hung PT, Jao CW, et al. Airborne particulate collected from Central Taiwan induces DNA strand breaks, poly(ADP-ribose) polymerase-1 activation, and estrogen-disrupting activity in human breast carcinoma cell lines. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2013;48(2):173–81.
13. Huff JE, Haseman JK, DeMarini DM, Eustis S, Maronpot RR, Peters AC, et al. Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. Environ Health Perspect. 1989;82:125–63.
14. White AJ, Chen J, Teitelbaum SL, McCullough LE, Xu X, Hee Cho Y, et al. Sources of polycyclic aromatic hydrocarbons are associated with gene-specific promoter methylation in women with breast cancer. Environ Res. 2016;145:93–100.
15. Binachon B, Dossus L, Danjou AM, Clavel-Chapelon F, Fervers B. Life in urban areas and breast cancer risk in the French E3N cohort. Eur J Epidemiol. 2014;29(10):743–51.
16. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, Deapen D, et al. Regional variations in breast cancer among California teachers. Epidemiology. 2004;15(6):746–54.
17. Parikh PV, Wei Y. PAHs and PM2.5 emissions and female breast cancer incidence in metro Atlanta and rural Georgia. Int J Environ Health Res. 2016;26(4):458–66.
18. Chen F, Bina WF. Correlation of white female breast cancer incidence trends with nitrogen dioxide emission levels and motor vehicle density patterns. Breast Cancer Res Treat. 2012;132(1):327–33.
19. Wei Y, Davis J, Bina WF. Ambient air pollution is associated with the increased incidence of breast cancer in US. Int J Environ Health Res. 2012;22(1):12–21.
20. Goldberg MS, Labreche F, Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, et al. The association between the incidence of postmenopausal breast cancer and concentrations at street-level of nitrogen dioxide and ultrafine particles. Environ Res. 2017;158:7–15.
21. Mordukhovich I, Beyea J, Herring AH, Hatch M, Stellman SD, Teitelbaum SL, et al. Vehicular traffic-related polycyclic aromatic hydrocarbon exposure and breast cancer incidence: the Long Island breast cancer study project (LIBCSP). Environ Health Perspect. 2016;124(1):30–8.
22. •• Hystad P, Villeneuve PJ, Goldberg MS, Crouse DL, Johnson K. Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: a case-control study. Environ Int. 2015;74:240–8. **Used three different modeling approaches for ambient NO2 concentrations and found consistent associations across all three assessments.**
23. White AJ, Teitelbaum SL, Stellman SD, Beyea J, Steck SE, Mordukhovich I, et al. Indoor air pollution exposure from use of indoor stoves and fireplaces in association with breast cancer: a case-control study. Environ Health. 2014;13(108):13–108.
24. Crouse DL, Goldberg MS, Ross NA, Chen H, Labreche F. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. Environ Health Perspect. 2010;118(11):1578–83.
25. Nie J, Beyea J, Bonner MR, Han D, Vena JE, Rogerson P, et al. Exposure to traffic emissions throughout life and risk of breast cancer: the western New York exposures and breast cancer (WEB) study. Cancer Causes Control. 2007;18(9):947–55.
26. Bonner MR, Han D, Nie J, Rogerson P, Vena JE, Muti P, et al. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiol Biomark Prev. 2005;14(1):53–60.
27. Lewis-Michl EL, Melius JM, Kallenbach LR, Ju CL, Talbot TO, Orr MF. Breast cancer risk and residence near industry or traffic in Nassau and Suffolk counties, Long Island, New York. Arch Environ Health: Int J. 1996;51(4):255–65.
28. •• Andersen ZJ, Stafoggia M, Weinmayr G, Key T. Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. 2017. **Pooled analysis of European cohort studies with extensive exposure information including novel consideration of PM elemental composition.**
29. Shmuel S, White AJ, Sandler DP. Residential exposure to vehicular traffic-related air pollution during childhood and breast cancer risk. Environ Res. 2017;159:257–63.
30. Andersen ZJ, Ravnskjær L, Andersen KK, Loft S, Brandt J, Becker T et al. Long-term exposure to fine particulate matter and breast cancer incidence in the Danish nurse cohort study. Cancer epidemiology and prevention biomarkers. 2016:cebp 0578.2016
31. • Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, Tamimi RM, et al. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the Nurses' health study II prospective cohort. Cancer Epidemiol Biomarkers Prev. 2016;25(8):1274–6. **Large US cohort study with menopausal status and hormone receptor subtype information and multiple air pollution measurements.**

32.• Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, Weinberg C, et al. Breast Cancer risk in relation to ambient air pollution exposure at residences in the sister study cohort. Cancer Epidemiol Biomarkers Prev. 2015;24(12):1907–9. **Large US cohort study with menopausal status and hormone receptor subtype information and multiple air pollution measurements.**

33. Liu R, Nelson DO, Hurley S, Hertz A, Reynolds P. Residential exposure to estrogen disrupting hazardous air pollutants and breast cancer risk: the California teachers study. Epidemiology. 2015;26(3):365–73.

34. Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health. 2015;14(14):14.

35.• White AJ, Sandler DP. Indoor wood-burning stove and fireplace use and breast Cancer in a prospective cohort study. Environmental health perspectives. 2017;125(7):077011. **First prospective study on indoor air pollution and breast cancer risk.**

36. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M, et al. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ Health. 2011;10(1):67.

37. Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahsuvaroglu T, et al. A review and evaluation of intraurban air pollution exposure models. J Expo Sci Environ Epidemiol. 2005;15(2):185–204.

38. Ahlm L, Liu S, Day DA, Russell LM, Weber R, Gentner DR, et al. Formation and growth of ultrafine particles from secondary sources in Bakersfield, California. J Geophys Res: Atmos. 2012;117(D21)

39. Beckerman B, Jerrett M, Brook JR, Verma DK, Arain MA, Finkelstein MM. Correlation of nitrogen dioxide with other traffic pollutants near a major expressway. Atmos Environ. 2008;42(2):275–90.

40. Gullett BK, Touati A, Hays MD. PCDD/F, PCB, HxCBz, PAH, and PM emission factors for fireplace and woodstove combustion in the San Francisco Bay region. Environ Sci Technol. 2003;37(9):1758–65.

41. Garcia E, Hurley S, Nelson DO, Gunier RB, Hertz A, Reynolds P. Evaluation of the agreement between modeled and monitored ambient hazardous air pollutants in California. Int J Environ Health Res. 2014;24(4):363–77.

42. Bonjour S, Adair-Rohani H, Wolf J, Bruce NG, Mehta S, Pruss-Ustun A, et al. Solid fuel use for household cooking: country and regional estimates for 1980-2010. Environ Health Perspect. 2013;121(7):784–90. https://doi.org/10.1289/ehp.1205987.

43. Environmental Protection Agency Research Triangle Park, NC: office of air quality, planning, and standards. An overview of methods for EPA's national-scale air toxics assessment. 2011. Available: https://www.epa.gov/sites/production/files/2015-10/documents/2005-nata-tmd.pdf. Accessed 22 March 2018.

44. Hiatt RA, Haslam SZ, Osuch J. The breast cancer and the environment research centers: transdisciplinary research on the role of the environment in breast cancer etiology. Environ Health Perspect. 2009;117(12):1814–22.

45. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst. 2004;96(3):218–28.

46. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7(12):7.

47. Hu H, Dailey AB, Kan H, Xu X. The effect of atmospheric particulate matter on survival of breast cancer among US females. Breast Cancer Res Treat. 2013;139(1):217–26.

48. Tagliabue G, Borgini A, Tittarelli A, van Donkelaar A, Martin RV, Bertoldi M, et al. Atmospheric fine particulate matter and breast cancer mortality: a population-based cohort study. BMJ Open. 2016;6(11):e012580. https://doi.org/10.1136/bmjopen-2016-012580.

49. Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, et al. Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomark Prev. 2016;25(5):839–45.

50. Huo Q, Cai C, Yang Q. Atmospheric particulate matter and breast cancer survival: estrogen receptor triggered? Tumour Biol: J Int Soc Oncodevelop Biol Med. 2015;36(5):3191–3. https://doi.org/10.1007/s13277-015-3291-8.