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Residential exposure to vehicular traffic-related air pollution during childhood and breast cancer risk

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ABSTRACT

Background: Some studies have supported an association between traffic-related air pollution exposure and breast cancer risk. However, few studies have considered exposures in early life, which may be a period of increased susceptibility.

Objectives: To examine the association of childhood residential exposure to traffic-related air pollution with breast cancer development.

Methods: The Sister Study is a prospective cohort of 50,884 initially breast cancer-free women, of whom 42,934 provided information at enrollment about roads and traffic near their primary childhood residence before age 14 as well as relevant covariates. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the association between traffic-related measures at childhood residence and adult incident breast cancer were estimated using Cox regression.

Results: During follow-up (mean = 6.3 years), 2,028 breast cancers were diagnosed. Traffic-related characteristics were not consistently associated with breast cancer risk. However, incidence was elevated among women who reported a median/barrier dividing either their primary childhood residential road (aHR = 1.2; 95% CI: 0.9–1.7) or the nearest cross-street (aHR = 1.3; 95% CI: 0.9–1.8, if the cross-street was within 100 ft.), and among women whose nearest cross-street had the highest traffic, ≥3 lanes, and/or a median/barrier (aHR = 1.4; 95% CI: 1.0–1.9).

Conclusions: Measures of potential exposure to vehicular traffic were not consistently associated with breast cancer risk. However, living during childhood on or near a road with a median or other barrier, which may be a more easily remembered road characteristic than the others assessed, was associated with increased breast cancer risk.

1. Introduction

Breast cancer has the highest incidence rate of all cancers affecting women in the US, and there has been a call for a better understanding of the role of environmental factors in breast cancer risk (Howlader et al., 2016; IOM, 2011). Air pollution levels are of substantial public health concern, particularly in urban areas and have been associated with a number of health outcomes, including lung cancer, cardiovascular disease, and childhood asthma (Brook et al., 2010; Khreis et al., 2016; Raaschou-Nielsen et al., 2013). The International Agency for Research on Cancer (IARC) has classified outdoor air pollution as a Group 1 carcinogen (Loomis et al., 2013), and traffic-related air pollution, specifically, contains many compounds with carcinogenic potential, including certain metals, carbonyls, volatile organic compounds, and polycyclic aromatic hydrocarbons (PAHs) (Chen and Bina, 2012; Crouse et al., 2010; Hamra et al., 2014; Hystad et al., 2015; Mordukhovich et al., 2016; Wei et al., 2012). PAHs, which are formed as a result of incomplete combustion of organic matter, are known to be lung carcinogens, and may be particularly relevant for breast cancer since they have the capacity to bind to DNA and form DNA adducts in breast tissue (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010). In addition, animal studies have shown that PAHs have the capacity to induce mammary tumors (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010).

Studies examining the association between adult air pollution exposure and breast cancer have not been consistent. Case-control studies of nitrogen dioxide (NO_2) (Crouse et al., 2010; Hystad et al., 2015) have reported positive associations, while prospective cohort studies

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(Andersen et al., 2016; Reding et al., 2015) have reported null or weak positive associations. For instance, a Canadian case-control study reported an odds ratio (OR) of 1.31 (95% confidence interval (CI): 1.00, 1.71) for every 5 ppb increase in NO_2 (Crouse et al., 2010), while a study examining the association between breast cancer risk and air pollution at the enrollment residence of Sister Study cohort participants did not find an overall increase in breast cancer risk, however, a modest positive association was observed between NO_2 exposure and estrogen/progesterone receptor positive breast cancer (risk ratio = 1.10, 95% CI: 1.02, 1.19 for an interquartile range difference of 5.8 parts per billion) (Reding et al., 2015). Only one study, a US-based case-control study, evaluated the association between breast cancer and long-term vehicular traffic-related PAH exposure, reporting an OR of 1.44 (95% CI: 0.78, 2.68) for the top 5% level of exposure as compared to below the median (Mordukhovich et al., 2016). In contrast, prospective cohort studies have examined the association with particulate matter (PM) exposure (Andersen et al., 2016; Hart et al., 2016; Reding et al., 2015), and all have reported null results. Distance to nearest roadway measures were found to be associated with a suggestively increased risk in a prospective cohort study (Hart et al., 2016) and to have no association in a case-control study (Hystad et al., 2015). Each of these proxy measures captures different components of traffic-related air pollution and there were differences in study design and duration of the adult exposure measures captured, which may help explain the mixed results.

Only two studies have examined the role of air pollution during early life (Bonner et al., 2005; Nie et al., 2007). Childhood and adolescence may be a time period that is particularly etiologically relevant to breast cancer development. Menarche is characterized by rapid breast cell proliferation and consequently less efficient DNA repair mechanisms, which is thought to make the breast tissue especially susceptible to carcinogenesis during the period between menarche and first childbirth (Hiatt et al., 2009; Okasha et al., 2003). This hypothesis is supported by substantial evidence of a relationship between other exposures and lifestyle factors during childhood/adolescence and later breast cancer risk (Potischman and Troisi, 1999). For instance, smoking initiation prior to menarche or after menarche but before first birth have each been associated with increased risk of breast cancer later in life (Gaudet et al., 2013) and environmental tobacco exposure during childhood has been associated with greater risk of breast cancer (White et al., 2017). Additionally, air pollution levels were likely higher during the childhood of US women who are at the highest risk of developing breast cancer today, as there has been a notable decline in emissions in the past two decades in the US (Wang et al., 2016). Therefore, it is of interest to determine whether air pollution exposure in early life is associated with future cancer risk. The objective of this study was to examine the association between potential childhood residential exposure to vehicular traffic-related air pollution and the development of adult incident breast cancer in the Sister Study cohort.

2. Materials and methods

2.1. Study population

Study participants were from the Sister Study, a prospective cohort study of 50,884 women that was designed to assess environmental and genetic risk factors for breast cancer. Participants, aged 35–74, were recruited from the US and Puerto Rico during 2003–2009, and were eligible to participate if they had at least one sister who had been diagnosed with breast cancer but had not been diagnosed with breast cancer themselves at the time of enrollment. Women were recruited for the study using a multimedia campaign and a network of volunteers and advocates. The Sister Study was approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group. All participants provided written informed consent. The data presented in this study were obtained from Sister Study Data Release 4.1 (follow-up through July 1, 2014).

2.2. Exposure assessment

At baseline, participants completed a Computer-Assisted Telephone Interview in which they reported information on characteristics of their longest lived residence before age 14, including information on nearby roads and exposure to traffic. Participants were asked about the number of lanes, presence of a median or barrier dividing the road ('yes'/'no'), and traffic volume during rush hour ('very light,' 'light,' 'moderate,' 'heavy,' 'very heavy,' which were combined as 'light,' 'moderate,' and 'heavy' for most analyses) for their residential road. They were also asked about the distance to the nearest intersection/cross-street ('within 100 feet,' 'more than 100 feet but less than a quarter mile,' 'between a quarter mile and one mile,' and 'more than one mile'). Participants who reported living within 100 feet of the nearest intersection were further asked about the number of lanes, presence of a median or barrier dividing the road ('yes'/'no'), and traffic volume during rush hour for that intersecting road ('very light,' 'light,' 'moderate,' 'heavy,' 'very heavy,' which were combined as 'light,' 'moderate,' and 'heavy' for most analyses). A combined measure suggestive of higher potential exposure to traffic-related pollutants (close proximity to nearest intersection, presence of median/barrier, multiple lanes, and heavy traffic) was also considered.

2.3. Outcome ascertainment

Incident breast cancer diagnoses were ascertained from annual health updates and biennial/triennial questionnaires that participants completed during follow-up. Women who reported a diagnosis during follow-up were asked for consent to review their medical records for confirmation and for diagnostic and treatment details. At the time of this analysis, medical records were available for 81% of cases. Due to the high concordance between self-report and medical records for first primary breast cancer diagnosis, self-reported diagnoses were included when medical record data were unavailable (A. D'Aloisio personal communication, 2017).

2.4. Statistical analysis

Early enrollees in the Sister Study (n = 2,297, "Vanguard women") were not asked about their exposure to traffic at their childhood residential residence (see Fig. S1). Of the remaining participants, we excluded 2,851 who did not live at least 5 years in their longest childhood residence. We also excluded 1,592 participants whose current or longest lived adult residence was the same as their primary childhood residence since their responses to the traffic-related questions reflected their adult traffic levels rather than traffic levels during their childhood. Both exclusions were intended to maximize the quality of recall and minimize the potential for misclassification. Participants with missing residential characteristic information (n = 616) were excluded. Thus, 43,528 women were eligible for inclusion in this analysis. We further excluded participants missing outcome, covariate, or follow-up time information (n = 594), resulting in a total analysis population of 42,934, 98.6% of those eligible. Participants diagnosed with lobular carcinoma *in situ* (LCIS) were censored at the time of diagnosis since the mechanism by which this condition is related to increased breast cancer risk is unclear (King et al., 2015), while those diagnosed with ductal carcinoma *in situ* (DCIS) were included in the outcome of total breast cancer diagnosis.

Descriptive statistics were compared for incident breast cancer cases and non-cases by case status at the end of follow-up. Participants were followed from the time of the baseline interview until a breast cancer diagnosis (either invasive or DCIS), death, or loss to follow-up. Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% CIs for the association between characteristics of the primary childhood residence and incident breast cancer. In these models, age was the time-scale and person-time was accrued from age