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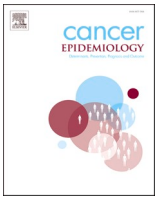

Residential exposure to ambient fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) and incident breast cancer among young women in Ontario, Canada

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ABSTRACT

Background: Air pollution has been classified as a human carcinogen based largely on findings for respiratory cancers. Emerging, but limited, evidence suggests that it increases the risk of breast cancer, particularly among younger women. We characterized associations between residential exposure to ambient fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) and breast cancer. Analyses were performed using data collected in the Ontario Environmental Health Study (OEHS).

Methods: The OEHS, a population-based case-control study, identified incident cases of breast cancer in Ontario, Canada among women aged 18–45 between 2013 and 2015. A total of 465 pathologically confirmed primary breast cancer cases were identified from the Ontario Cancer Registry, while 242 population-based controls were recruited using random-digit dialing. Self-reported questionnaires were used to collect risk factor data and residential histories. Land-use regression and remote-sensing estimates of NO_2 and $PM_{2.5}$, respectively, were assigned to the residential addresses at interview, five years earlier, and at menarche. Logistic regression was used to estimate odds ratios (OR) and their 95 % confidence intervals (CI) in relation to an interquartile range (IQR) increase in air pollution, adjusting for possible confounders.

Results: $PM_{2.5}$ and NO_2 were positively correlated with each other (r = 0.57). An IQR increase of $PM_{2.5}$ (1.9 μg/m^3) and NO_2 (6.6 ppb) at interview residence were associated with higher odds of breast cancer and the adjusted ORs and 95 % CIs were 1.37 (95 % CI = 0.98–1.91) and 2.33 (95 % CI = 1.53–3.53), respectively. An increased odds of breast cancer was observed with an IQR increase in NO_2 at residence five years earlier (OR = 2.16, 95 % CI: 1.41–3.31), while no association was observed with $PM_{2.5}$ (OR = 0.96, 95 % CI 0.64–1.42).

Conclusions: Our findings support the hypothesis that exposure to ambient air pollution, especially those from traffic sources (i.e., NO_2), increases the risk of breast cancer in young women.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide [1] and its incidence is increasing [2,3], particularly among younger women [4,5]. Breast cancers detected before menopause are often associated with more aggressive tumor subtypes and less favorable outcomes [6,7]. While some risk factors are shared for both pre- and postmenopausal breast cancer, the etiologies are recognized to be different [8]. Shared established risk factors across all ages include reproductive history, age at menarche, cigarette smoking, alcohol and diet, while obesity is recognized to increase the risk of postmenopausal, but not premenopausal, breast cancer [8].

Environmental exposures play a prominent role in the etiology of breast cancer with increased risks reported for organophosphate insecticides [9], polycyclic aromatic hydrocarbons [10,11], artificial light at night [12], dioxin [13–15], and ionizing radiation [16]. These exposures are more strongly associated with premenopausal breast cancer [17] and, from a timing perspective, exposures that occur around the time of birth or puberty are particularly relevant [17–19].

The possibility that air pollution increases the risk of breast cancer warrants further scrutiny given the ubiquity of this exposure, and because it is the most diagnosed cancer in woman. Fine particulate matter ($PM_{2.5}$) has been classified as a human carcinogen based on experimental evidence, and epidemiological studies of respiratory cancers [20]. $PM_{2.5}$, consisting of particles with an aerodynamic median diameter of less than 2.5 microns, can penetrate deep into lung passageways and enter the bloodstream [21]. Laboratory animal and toxicological data suggest a link between several carcinogens present in ambient air pollution and breast cancer [22]. While the exact mechanisms remain uncertain, components of air pollution may interact with estrogen receptors, impacting hormonal balance, and induce oxidative stress and inflammation [23].

In addition to the experimental evidence, findings from a series of case-control and cohort studies suggest that air pollution increases the risk of breast cancer [24]. Moreover, results suggest that the effects are strongest among younger women [25–28]. Some studies reported a positive association between NO_2, a marker of traffic pollution [29], and premenopausal breast cancer [24,30–40]. With respect to exposure to ambient $PM_{2.5}$, both null [33,35,37,39,41] and positive [27,28] associations have been reported. Two studies in the United States [33,34] and one in Spain [39] found no association between breast cancer and air pollution (i.e., B[*a*]P proxy for traffic emissions exposures, Particulate matter (PM_{10}, $PM_{2.5-10}$, and $PM_{2.5}$) and measures of distance to roadway and NO_2) in premenopausal women. However, Canadian [28] and Danish [35] studies reported that a 10 $\mu g/m^3$ rise in $PM_{2.5}$ resulted in a hazard ratio of 1.37 (95 % CI = 1.09–1.73) while a 3.21 $\mu g/m^3$ increase was linked to an odds ratio of 1.09 (95 % CI = 1.03–1.16) for premenopausal breast cancer, respectively. Another Canadian cohort study reported no association between air pollution and breast cancer risk [42]. The discrepancies in these findings may be explained by several factors including: differences in the methods to characterize exposure, exposures measured at different periods relative to disease onset, differences in study design, and differences in the ability to control for confounders.

In this context, our objective was to evaluate the relationship between ambient residential concentrations of $PM_{2.5}$ and NO_2 and the risk of breast cancer among young women(ages 18−45). Our study addresses important gaps in the literature by focusing on a younger population where the impact of air pollution on breast cancer risk is not well understood. This study also explored differences in risk related to the timing of the exposure. By doing so, we sought to provide valuable insights on the relevance of the timing of exposure for early onset breast cancer.

2. Methods

We analyzed data from the Ontario Environmental Health Study (OEHS), a case-control study focusing on environmental, dietary, and occupational risk factors for breast cancer among Ontario women aged 18–45. Eligible cases consisted of women diagnosed with primary cancer between 2013 and 2015 who were identified through the Ontario Cancer Registry ePATH system. This registry captures all newly diagnosed cancer cases in the province of Ontario [41]. Women with breast cancer were recruited within 6 months of diagnosis. Controls were identified by York University's Institute of Social Research (ISR) using random-digit dialing (RDD). These recruitment methods incorporated frequency-matching of the control to the case series by 5-year age-groups. Invitations to participate were sent by mail and email, and participants completed online consent and questionnaire forms in English. The estimated response rates for the case and control series were 70 % and 47 %, respectively.

2.1. Data collection

A web-based Environmental Health Questionnaire (EHQ) was used to collect data at interview on sociodemographic, lifestyle, anthropometric, reproductive factors and occupational histories. Residential histories, including street address, six-character postal code and duration of residency, were collected for participant's current residence, previous residence, residence of the longest duration between the ages of 10–17, and place of residence at birth. In Canada, six-character postal codes in urban areas correspond to one side of a street between intersecting streets or a single apartment building, while in rural areas, they tend to cover larger areas such as entire towns [43].

2.2. $PM_{2.5}$ and NO_2 exposures

Participants 'residential annual average exposure to $PM_{2.5}$ ($\mu g/m^3$) was estimated using satellite instrument measurements of aerosol optical depth, and the Goddard Earth Observing System chemical transport model (GEOS-Chem) for atmospheric dispersion simulation [44,45]. The calibration of satellite data to ground-based observations was performed using Geographically Weighted Regression to refine estimates based on local conditions. These estimates were derived annually at a spatial resolution of $0.01^\circ \times 0.01^\circ$ (~1 km) for each year between 2000 and 2018. Missing data before 2000 were imputed using the average annual concentration values from 2000 at the postal code level. Spatiotemporal estimates for NO_2 (annual average) were obtained through a national surface Land Use Regression (LUR) model [46] that integrated fixed-site monitoring data, satellite-derived NO_2 estimates, and geographical factors, including road length, and industrial land use. This method was used to generate estimates for 1984–2015 across Canada at 30-meter resolution and this dataset was made available by the Canadian Urban Environmental Health Research Consortium (CANUE) [46–48]. The gridded estimates of NO_2 and $PM_{2.5}$, created by Hystad and collaborators for NO_2 and by Van Donkelaar and collaborators for $PM_{2.5}$, were assigned to the geographical centroids of all Canadian postal codes by CANUE [49]. We provided CANUE with a list of the postal codes from the OEHS participants, including the years of residency, and they, in turn, provided us with the corresponding exposure data. The annual air pollution estimates correspond to the participants' residential postal code at the time of interview, five years prior, and at the time of menarche.

2.3. Other risk factors

The OEHS gathered data for a comprehensive set of breast cancer risk factors. We accounted for a large number of established or potential risk factors for premenopausal breast cancer, which encompassed age, ethnicity, education level, household income, body mass index (BMI),

smoking status, alcohol consumption, age at menarche, family history, parity, age at first pregnancy, personal history of benign breast disease, and oral contraceptive use. Potential confounders were determined based on prior knowledge and through guidance provided by Directed Acyclic Graphs (DAGs) (Supplementary Figure 1).

2.4. Statistical analysis

Descriptive analyses were undertaken to provide an overview of sociodemographic characteristics, key covariates and the estimated exposures at residence during the different time points captured. We also calculated Pearson correlation coefficients between the pollutants as well as the Canadian Index of Marginalization (CAN-Marg) and the Normalized Difference Vegetation Index (NDVI). We presented Pearson rather than Spearman correlations as these independent variables were linearly related to each other. The NDVI and CAN-Marg were measured at a neighborhood level. The CAN-Marg [50,51], derived at the census dissemination area (~400–700 residents), provides measures of four dimensions of marginalization: residential instability, material deprivation, ethnic concentration, and dependency. We calculated a summary measure of marginalization by consolidating the quintile rank scores for these four dimensions into a summary measure (1 – least marginalized to 5 – most marginalized) according to a methodology described elsewhere [52]. The 2006 version of the CAN-Marg Index was utilized. The NDVI is a commonly used, remote-sensing based measure of greenness that ranges between 0 (no vegetation) to 1 (full vegetation) [53]. This is an objectively-defined measure of greenness that is less prone to bias arising from self-reported measures of proximal greenness. Similar to air pollution, the CAN-Marg and NDVI measures at participant's residential postal codes were supplied to us by CANUE [49].

Unconditional logistic regression was used to estimate the odds ratios (ORs) of breast cancer in relation to an interquartile range (IQR) increase in air pollution concentrations. These odds ratios were estimated for exposures at three time points (interview, 5 years before interview, and at menarche). We chose to model the exposures using an IQR to facilitate comparisons of the odds ratios between the two pollutants (measured on difference scales), and at different time periods. The use of the IQR in this manner assumes of linearity between exposure and the logit of the probability of breast cancer. This assumption was formally tested, and satisfied, using second-order fractional polynomials. We also verified linearity by evaluating the shape of the exposure-response curve for both pollutants at each exposure period by fitting restricted cubic splines with 4 knots (at the 5th, 35th, 65th, and 95th percentiles) (Supplementary Figure 2). We selected the knots at these percentiles based on previously described methodology [54].

To comprehensively evaluate the impact of confounding variables, we fitted and presented the results for three separate regression models. The initial model (M1) was only adjusted for age at interview. The second model (M2) integrated additional confounding factors identified through the DAG, i.e., ethnicity (White, Asian or other), educational level (bachelor's and above, trade or certificate, high school and below), household income (in $CDN) ($50,000, $50,000 to $99,999, $100,000 to $149,999 or $150,000 or more), BMI two years prior interview (in kg/m^2), and smoking status two years prior interview (categorized as never, former or current smoker). The third model (M3) further extended the second model to incorporate various lifestyle risk factors related to breast cancer. These factors were: alcohol consumption two years prior interview (never drinker, non-heavy drinker, heavy drinker), age at menarche (< 12, 12–14, ≥ 14 years) for descriptive analyses and modelled in years), family history of breast cancer (yes or no), parity (no, 1–2, or ≥ 3 pregnancies) for descriptive analyses and modelled as number of children), age at first pregnancy (< 30 or ≥ 30 years for descriptive analyses and modelled in years), history of benign breast disease (yes or no), and ever oral contraceptive use (yes or no).

We undertook a sensitivity analysis to assess the influence of residential mobility on the measures of association between air pollution and breast cancer. This was motivated by the knowledge that there is likely less exposure measurement error when assigning air pollution exposures to women who were more residentially stable. These analyses were done by fitting separate models for those who had lived in their residence at the time of interview for >7 and ≤ 7 years. This cut-point was chosen based on the median length of residency observed in the control series.

All analyses were conducted using R software version 4.2.0 [55].

3. Results

Selected characteristics of the 465 breast cancer cases and 242 controls are summarized in Table 1. Relative to controls, cases were less likely to be Caucasian and to be obese, were more likely to have smoked, while also having lower parity, younger age at first childbirth, and no longer be menstruating (i.e., menopausal). A similar proportion of cases (86 %) and controls (83 %) resided in urban areas at the time of interview.

Fig. 1 displays the frequency distribution in ambient $PM_{2.5}$ and NO_2 concentrations between cases and controls at three-time intervals (time of interview, 5 years before interview, and at menarche). $PM_{2.5}$ concentrations averaged around 7.7 $\mu g/m^3$ across the different periods. For NO_2, the mean exposure was of 8.1 ppb at interview; 10.5 ppb five years prior interview and 23.1 ppb at menarche. Concentrations of $PM_{2.5}$ and NO_2 at the time of interview were positively correlated with each other ($r = 0.57$) (Table 2). In contrast, both measures of pollution were inversely correlated with residential proximity to greenness. Specifically, the correlations between the NDVI and $PM_{2.5}$ and between the NDVI and NO_2, were -0.36 and -0.54, respectively. The Can-Marg index was positively correlated with pollution suggesting that concentrations of air pollution were higher in areas that were more marginalized ($r = 0.21$ for $PM_{2.5}$ and $r = 0.26$ for NO_2 at interview).

An increased odds of breast cancer was observed for $PM_{2.5}$ and NO_2 at the time of interview (Table 3). Specifically, in a fully adjusted model (Model 3), an IQR increase in NO_2 was found to more than double the risk of breast cancer (OR = 2.33, 95 % CI: 1.53–3.53). The corresponding estimate for $PM_{2.5}$ was 1.37 (95 % CI: 0.98–1.91). Using estimates of exposures at the residence five years before interview, an increased odds ratio was found for NO_2 but not for $PM_{2.5}$,. No clear association was found for exposure at the age at menarche for either NO_2 or $PM_{2.5}$ (p-value = 0.14 for $PM_{2.5}$ and 0.99 for NO_2). These analyses are based on a substantially smaller number of participants due to missing data on the place of residence for a larger proportion of subjects ($n = 206$ cases and 120 controls for $PM_{2.5}$ and $n = 191$ cases and 112 controls for NO_2). Our sensitivity analyses, based on the duration of residency, revealed a stronger association for those who lived in their homes for less than seven years compared to those who lived longer at the same residence (Supplementary Table 1).

4. Discussion

In this case-control study of Ontario women, we found evidence that supports the hypothesis that ambient NO_2 and $PM_{2.5}$ increase the risk of breast cancer in pre-menopausal women. The positive associations with NO_2, a marker of traffic-related pollution, were more compelling given we found stronger associations relative to $PM_{2.5}$, and these were consistently observed across different exposure periods except for at time of menarche. Our findings align with recent findings from other case-control studies [25–28], and suggest that air pollution, even at the relatively low levels of concentrations that are observed in Canada, represents an important etiological risk factor.

We observed that a 6.6 ppb increase in annual concentration of NO_2 more than doubled the risk of breast cancer. Several studies conducted in the US, Canada, Denmark, and France have observed stronger associations between ambient air pollution, particularly NO_2, and breast cancer in younger women compared to older women [25–28,31,32–36].

Table 1
Descriptive characteristics for selected risk factors of early-onset breast cancer for cases and controls in the Ontario Environmental Health Study.

Characteristics	Cases N = 465	Controls N = 242	aOR (95 % CI) *	p-value**
Socio-demographics factors				
Age at interview (years), *median [Q1-Q3]*	40 [37–43]	38 [34–41]	1.5(1.3,1.8)	*< 0.001*
Ethnicity, *n (%)*				*0.032*
Caucasian	362 (77.9)	207 (85.5)	1.0	
Asian	56(12.0)	24(9.9)	1.36 (0.81,2.29)	
Other[a]	47(10.1)	11(4.5)	4.45 (1.26,15.74)	
Educational level, *n (%)*				*0.040*
Bachelor's and above	58(12.5)	25 (10.33)	1.0	
Trade/certificate	144 (31.0)	86(35.5)	0.81 (0.57,1.14)	
High school and below	263 (56.6)	131 (54.1)	1.19 (0.70,2.02)	
Household income (CAD), *n (%)*				*0.842*
< $50,000	57(12.3)	28(11.6)	1.0	
$50,000 to $99,999	121 (26.0)	69(28.5)	0.74 (0.42,1.30)	
$100,000 to $149,999	103 (22.2)	48(19.8)	0.84 (0.46,1.53)	
$150,000 or more	103 (22.2)	54(22.3)	0.73 (0.41,1.32)	
Missing	81(17.4)	43(17.8)	-	
Behavior-related factors				
BMI[b] (kg/m2), *n (%)*				*< 0.001*
<25	290 (62.4)	111 (45.9)	1.0	
[25–30[	107 (23.0)	59(24.4)	0.70 (0.47,1.04)	
≥30	64(13.8)	63(26.0)	0.39 (0.24,0.66)	
Missing	4(0.9)	9(3.7)	-	
Smoking status, *n (%)*				*0.002*
Never	292 (62.8)	167 (69.0)	1.0	
Former	138 (29.7)	43(17.8)	1.74 (1.17,2.58)	
Current	25(5.4)	20(8.3)	0.68 (0.36,1.28)	
Missing	10(2.2)	12(5.0)	-	
Alcohol consumption, *n (%)*	129 (53.3)	1.0		*0.081*
Never[c]	229 (49.2)	129 (53.3)	1.0	
Non-heavy drinker[d]	175 (37.6)	87(36.0)	1.17 (0.83,1.65)	
Heavy drinker[e]	53(11.4)	15 (6.2)	1.85 (1.00,3.45)	
Missing	8(1.7)	11(4.5)	-	
Reproductive history and other hormonal factors				
Age at menarche (years), *n (%)*				*0.057*
< 12	80(17.2)	58(24.0)	0.68 (0.45,1.02)	
[12–14[	292 (62.8)	131 (54.1)	1.0	
≥ 14	88(18.9)	43(17.8)	0.88 (0.58,1.35)	
Missing	5(1.1)	10(4.1)	-	
Hormonal contraception use, *n (%)*				*0.435*
Yes	372 (80.0)	199 (82.2)	1.0	
No	92(19.8)	199 (82.2)	0.82 (0.54,1.25)	
Missing	1(0.2)	2(0.8)	-	
Parity[f], *n (%)*				*0.003*
No pregnancy	135 (29.0)	46(19.0)	1.0	
1 or 2 pregnancies	245 (52.7)	132 (54.5)	0.41 (0.26,0.65)	
≥ 3 pregnancies	76(16.3)	59(24.4)	0.27 (0.16,0.46)	
Missing	9(1.9)	5(2.1)	-	
Age at first pregnancy (years), *n (%)*				*0.083*
< 30	115 (24.7)	41(19.4)	1.0	
≥ 30	231 (49.7)	140 (57.9)	1.12 (0.76,1.66)	
Nulliparous	114 (24.5)	55(22.7)	2.26(1.45,3.5)	
Missing	5(1.1)	6(2.5)	-	
Menstrual status, *n (%)*				*< 0.001*
Still having menstrual period	345 (74.2)	222 (91.7)	1.0	
Menstrual period stopped[i]	118 (25.4)	18(7.4)	3.74 (2.20,6.36)	
Missing	2(0.4)	2(0.8)	-	
Medical History				
Family history of breast cancer[j], *n (%)*				*< 0.001*
Yes	186 (40.0)	58(24.0)	2.07 (1.45,2.97)	
No	272 (58.5)	175 (72.3)	1.0	
Missing	7(1.5)	9(3.7)	-	
History of benign breast disease, *n (%)*				*< 0.001*
Yes	41(8.8)	4(1.7)	5.26 (1.85,14.97)	
No	407 (87.5)	233 (96.3)	1.0	
Missing	17(3.7)	5(2.1)	-	
Mammography, *n (%)*				*< 0.001*
Yes	449 (96.6)	172 (71.1)	-	
No	14(3.0)	65(26.9)	-	
Missing	2(0.4)	5(2.1)	-	

Notes - CI, confidence interval; *aOR age adjusted odds ratio from unconditional logistic regression; **P-values were calculated using the following tests: Student's t-test for continuous variables (Age at interview), Chi-square test for categorical variables; min, minimum; max, maximum; sd, standard error; AFP, Age at First Pregnancy; Q1, Fist Quartile; Q3, Third Quartile.
a Other include Black, Latin, Jewish, Indigenous, etc.
b Body Mass Index two years before interview.
c someone who did not regularly consume at least one alcoholic beverage per week.
d (<10 drinks per week).
e (>10 drinks per week).
f Parity is determined by the total number of pregnancies completed (after 20 weeks) in a woman's lifetime, whether single or multiple.
i Women were asked if they still have their menstrual period or not and the reason why menstrual period stopped could be natural, following radiation/chemotherapy or surgery (hysterectomy or ovaries removed).
j Breast cancer occurring in parents, brothers, sisters or grandparents.

For instance, Goldberg et al. [26], in a cohort study of approximately 80,000 Canadians, reported a 17 % increase in premenopausal breast cancer in relation to a 9.7 ppb increase in NO_2, but found no association among postmenopausal women. In another Canadian case-control study, Hystad et al. [25], reported between 19 % and 32 % increased odds in relation to a 10 ppb increase in NO_2 for premenopausal, while a 7 % and 20 % increased odds among postmenopausal women. Although our estimates are higher than those observed in these two other Canadian studies, they are more similar to those reported in other case-control studies [25,28,32,34]. The mentioned cohort study was reliant on a single measure of exposure that was assigned to a woman's place of residence at baseline at the beginning of a twenty-year follow-up period [26]. This potential non-differential exposure measurement error may have attenuated their estimates. Our findings suggest that capturing exposures at recent places of residence are important to understanding environmental breast cancer risks in young women. It is also important

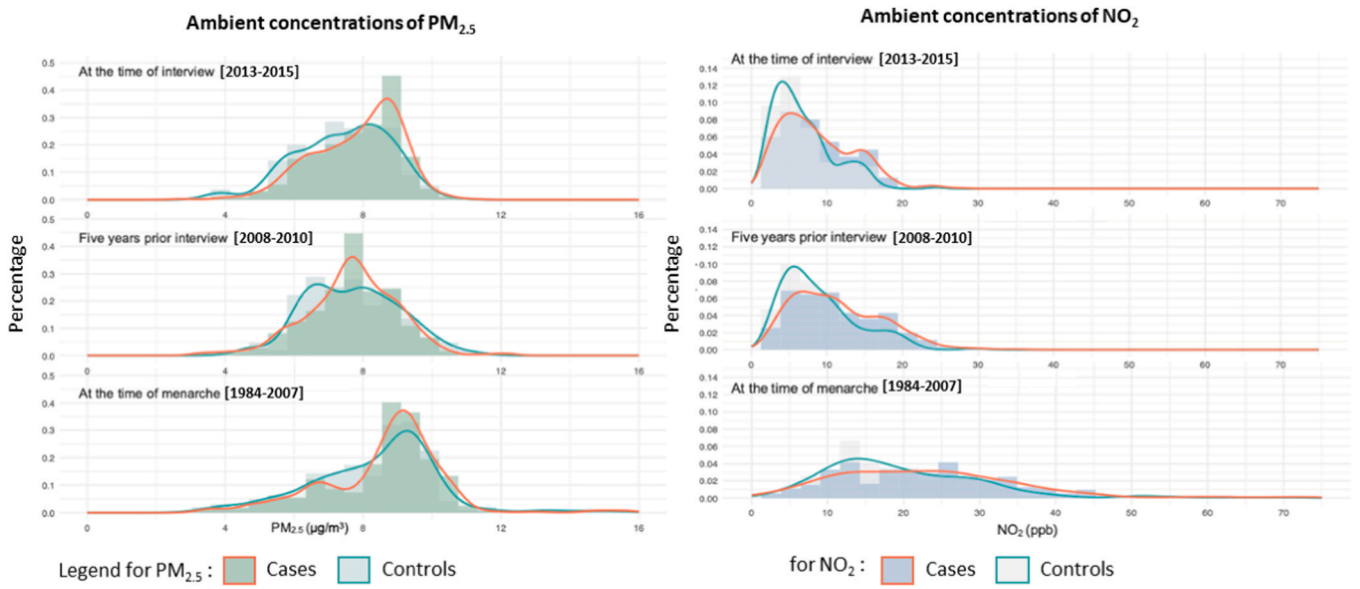

Fig. 1. Frequency distribution of $PM_{2.5}$ (µg/m^3) and NO_2 exposure (ppb) at the time of the interview, 5 years before the interview, and for cases and controls in the Ontario Environmental Health Study. Notes: PM = Particulate Matter, NO_2 = Nitrogen Dioxide.

Table 2
Pearson correlations between $PM_{2.5}$, NO_2 and NDVI and Canadian Marginalization Index at interview, five years before the interview and at menarche among participants of the Ontario Environmental Health Study.

	At interview				Five years before interview				At menarche			
	$PM_{2.5}$	**NO_2**	**NDVI**	**Can Marg Index**	**$PM_{2.5}$**	**NO_2**	**NDVI**	**Can Marg Index**	**$PM_{2.5}$**	**NO_2**	**NDVI**	**Can Marg Index**
At interview												
$PM_{2.5}$	1.00	0.57 (n = 703)	-0.36 (n = 706)	0.21 (n = 703)	0.78 (n = 519)	0.59 (n = 519)	-0.41 (n = 519)	0.01 (n = 519)	0.52 (n = 473)	0.07 (n = 449)	-0.21 (n = 449)	0.07 (n = 456)
NO_2		1.00	-0.54 (n = 703)	0.26 (n = 700)	0.39 (n = 518)	0.93 (n = 518)	-0.59 (n = 518)	0.06 (n = 516)	0.33 (n = 472)	0.19 (n = 448)	-0.36 (n = 448)	0.12 (n = 455)
NDVI			1.00	-0.31 (n = 703)	-0.19 (n = 519)	-0.57 (n = 519)	0.84 (n = 519)	-0.04 (n = 519)	-0.25 (n = 473)	-0.24 (n = 449)	0.30 (n = 449)	-0.10 (n = 456)
Can-Marg*				1.00	0.21 (n = 516)	0.28 (n = 516)	-0.28 (n = 516)	-0.00 (n = 519)	0.02 (n = 472)	-0.01 (n = 449)	-0.16 (n = 449)	0.20 (n = 456)
Five years before interview												
$PM_{2.5}$					1.00	0.46 (n = 520)	-0.21 (n = 520)	0.06 (n = 516)	0.47 (n = 356)	-0.03 (n = 338)	-0.11 (n = 338)	0.09 (n = 343)
NO_2						1.00	-0.61 (n = 520)	0.07 (n = 516)	0.35 (n = 356)	0.21 (n = 38)	-0.35 (n = 338)	0.14 (n = 343)
NDVI							1.00	-0.02 (n = 516)	-0.29 (n = 356)	-0.19 (n = 338)	0.35 (n = 338)	-0.08 (n = 343)
Can-Marg								1.00	0.02 (n = 355)	0.04 (n = 338)	-0.06 (n = 338)	0.07 (n = 343)
At menarche												
$PM_{2.5}$									1.00	0.39 (n = 448)	-0.41 (n = 448)	0.15 (n = 455)
NO_2										1.00	-0.23 (n = 449)	0.14 (n = 444)
NDVI											1.00	-0.29 (n = 444)
Can-Marg												1.00

Notes: Can-Marg = Canadian Marginalization Index; PM = Particulate Matter; NDVI = Normalized Difference Vegetation Index; NO_2 = Nitrogen Dioxide.

Table 3
Adjusted odds ratios and 95 % Cis in relation to an interquartile range increase in ambient concentrations of NO_2 and $PM_{2.5}$ at interview, five years prior interview, at menarche and the risk of early-onset breast cancer among participants of the Ontario Environmental Health Study.

Variables	Median [Q1-Q3]	Case-Controls	Model 1[a]aOR (95 % CI)	Case-Controls	Model 2[b]aOR (95 % CI)	Case-Controls	Model 3[c]aOR (95 % CI)
Exposure estimates at interview for an increase equal to the IQR[d]							
$PM_{2.5}$ (μg/m^3)	7.9 [6.8–8.7]	464–242	1.56 [1.24, 1.97]	381–196	1.64 [1.24–2.16]	272–151	1.37 [0.98–1.91]
NO_2 (ppb)	7.0 [4.3–10.9]	462–241	1.93 [1.49, 2.49]	379–195	2.25 [1.61–3.14]	270–150	2.33 [1.53–3.53]
Exposure estimates 5 years prior interview for an increase equal to the IQR at interview							
$PM_{2.5}$(μg/m^3)	7.7[6.8–8.6]	332–188	1.09[0.84-1.41]	272–147	1.07[0.78–1.49]	196–109	0.96[0.64–1.42]
NO_2 (ppb)	9.5[5.8–14.5]	332–188	1.81[1.42, 2.31]	272–147	2.10[1.51–2.91]	205-110205–110	2.16[1.41–3.31]
Exposure estimates at menarche for an increase equal to the IQR at interview							
$PM_{2.5}$ (μg/m^3)	8.5[7.5–9.5]	297–176	1.15[0.94-1.41]	271–157	1.11[0.88–1.38]	206–120	1.18[0.90–1.54]
NO_2 (ppb)	23.1 [13.5–28.9]	282–167	1.09[0.99-2.12]	256–150	1.01[0.91–1.12]	191–112	1.02[0.89–1.16]

CI, confidence interval; aOR adjusted odds ratio from unconditional logistic regression; ppb = particles per billion
[a] adjusted for age at interview (in years modelled for an increase of 5 years).
[b] further adjusted for ethnicity (Caucasian, Asian or other), educational level (High school or below, Trade or certificate, Bachelor's degree or above), household income ([< $50,000], [$50,000 to $99,999], [$100,000 to $149,999], [$150,000 or more]), BMI at two years prior interview (in kg/m^2) and tobacco consumption (never, former or current smoker).
[c] adjusted for Model 2 + alcohol consumption (never drinker, non-heavy drinker, heavy drinker), age at menarche (in years), family history of breast cancer (yes or no), parity (in number of children), age at first pregnancy (in years), personal history of BBD (yes or no) and oral contraceptive use (yes or no).
[d] IQR at interview for $PM_{2.5}$ = 1.9 μg/m^3 and NO_2 = 6.615 ppb.

to note that differences to those of other studies may be influences by regional differences in the air pollution mix. Past research has shown there is substantial variability in the oxidative potential of $PM_{2.5}$ across Canada [56]. Moreover, it is worth noting that our study population was largely based in Southern Ontario, and therefore, these women would be more highly exposed to air pollution than those living in other parts of Canada.

The elevated risk for NO_2 might indicate that exposure to specific pollutants in vehicle exhaust, including PAHs, increase the risk of breast cancer, notably during critical periods like puberty and pregnancy [17, 32]. Although this study was able to examine ambient air pollution exposure at menarche and found only slight suggestive positive associations, the results should be interpreted carefully due to the limited number of participants with residential information at time of menarche. Understanding the effect of air pollution exposures during susceptibility windows is crucial for comprehending the possible etiological role of air pollution on breast cancer. However, characterizing past environmental exposures in epidemiological studies is challenging. Most studies are unable to characterize lifetime patterns of exposure due to practical limitations such as the difficulty for participants to recall their residential history accurately. Moreover, for air pollution, there is a lack of historical spatiotemporal air pollution data from prior decades. Consequently, statistical analyses often focus on average exposure intensity or cumulative exposure dose over a more restrictive time window. To better understand how exposures during windows of susceptibility could affect the risk of developing breast cancer, future studies should work on estimating the association between exposure to air pollutants and breast cancer risk using a life course approach.

The air pollution and breast cancer odds ratios were higher for women who lived less than seven years at the interview address when compared to those who lived there longer. However, caution should be taken when interpreting these estimate differences due to the low number of observations and because it may be an artifact of potential participation bias (i.e., those who live at interview residence for a shorter period of time are less likely to be participating controls).

An important limitation of our study was the relatively small study size due to the original study objective to assess associations between Polybrominated Diphenyl Ethers (PBDEs) and breast cancer, and the requirement for urine and blood biomonitoring data from participants. Moreover, the number of study subjects was determined to have sufficient power to evaluate the relationship between PBDEs and breast cancer in young women. This small sample size limited the types of analyses we could pursue. For example, other studies have shown that tumour receptor status may modify the air pollution and breast cancer relationship [37–41,43,44,45,57,46–54,58,55,56,59]. In both Lemarchand et al. [37] and Reding et al. study [59], there was a stronger association between NO_2 exposure and hormone-receptor positive breast tumor subtypes (ER+/PR+) than there was for hormone-receptor negative tumors (ER-/PR-). We were unable to carry out similar analyses in our study due to small sample sizes and the lack of receptor subtype status for most of cases.

NO_2 was strongly related to breast cancer in our study. NO_2 is not a recognized carcinogen, but is often modelled in epidemiological studies to represent a complex mixture of traffic related pollution. While we also observed a positive association for $PM_{2.5}$, we chose not to model both exposures simultaneously in two pollutant models. Goldberg et al. has argued against modelling multiple pollutants in the same model because of the challenges involved in identifying the causal components of air pollution, or complex mixtures in general [60]. Others hold the view that multivariate regression models should incorporate mutual adjustments for other pollutants (i.e., multi-pollutant modelling) [61]. However, we reason that this may cause over adjustment because NO_2 and $PM_{2.5}$, while being different markers of air pollution, are both impacted by vehicular exhaust [60]. In general, NO_2 is more specific to vehicle emissions, particularly diesel exhaust and diesel particles which are known carcinogens (IARC) [20].

Our study had relatively low participation rates among both case and control series (70 and 47 % respectively). In the case series, the lower participation rates were in part due to changes in the recruitment of cases in the province that required individuals to be contacted initially by the Ontario Cancer Registry to first provide consent to be subsequently contacted by the OEHS Study PI. Potential controls were identified by the York University's ISR via RDD and indicated that they were interested in participation, but only 47 % consented andcompleted

questionnaire information. These rates of participation may have introduced a form of selection bias. However, it is worth noting that for widely recognized risk factors such as parity, obesity, alcohol consumption and family history of breast cancer, we observed patterns of risk in the OEHS study population that are consistent with the published literature [62]. This suggests that this form of selection bias in the control series did not unduly bias the risk estimates.

5. Conclusion

Our findings suggest that ambient exposure to air pollution may represent an important risk factor among young women. While our study provides valuable insights, it is important to consider the limitations inherent in our sample size and methodology. Future research, involving larger and more diverse samples, should further investigate the specific periods of susceptibility over a woman's life course and look into the components of $PM_{2.5}$, as well as associations with specific types of breast cancer. This will enhance our understanding of the temporal dynamics and cumulative impacts of air pollution, enabling more effective and targeted public health interventions.

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CRediT authorship contribution statement

Shelley A. Harris: Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Rose Dugandzic:** Writing – review & editing. **Eric Lavigne:** Writing – review & editing, Funding acquisition. **Jeffrey R. Brook:** Writing – review & editing, Funding acquisition, Data curation. **Claudia M. Waddingham:** Writing – review & editing, Investigation, Data curation. **Paul J. Villeneuve:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Marie-Élise Parent:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Blandine Le Provost:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul J. Villeneuve reports financial support was provided by The Canadian Institutes of Health Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2024.102606.

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