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# Associations between incident breast cancer and ambient concentrations of nitrogen dioxide from a national land use regression model in the Canadian National Breast Screening Study

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ABSTRACT

*Background:* Air pollution has been classified as a human carcinogen based largely on epidemiological studies of lung cancer. Recent research suggests that exposure to ambient air pollution increases the risk of female breast cancer especially in premenopausal women.

*Methods:* Our objective was to determine the association between residential exposure to ambient nitrogen dioxide ($NO_2$) and newly diagnosed cases of invasive breast cancer in a cohort of 89,247 women enrolled in the Canadian National Breast Screening Study between 1980 and 1985. Vital status and incident breast cancers through 2005 were determined through record linkage to the Canadian national mortality and cancer registries. Estimates of exposures to $NO_2$ using participants' addresses at time of entry into the study were derived from a national land use regression model. We classified women as reaching menopause according to information obtained at baseline. In addition, as we had no information from women on their menopausal status during the observation period, we conducted analyses using different cut-points for defining postmenopausal status (i.e., at 50 or at 52 years of age), and hence we had four non-independent cohorts. We computed rate ratios for the incidence of breast cancer and their 95% confidence intervals (CI) separately for premenopausal and postmenopausal women. Our Cox models used attained age as the time axis and the rate ratios were adjusted for several individual-level risk factors, including reproductive history, as well as census-based neighborhood-level characteristics.

*Results:* The median concentration of $NO_2$ was about 15 parts per billion (ppb). After adjusting for personal risk factors and contextual variables, we found no evidence of associations for the incidence of breast cancer in the postmenopausal cohorts. In premenopausal women, the rate ratio for an increase of 9.7 ppb (about the interquartile range) was 1.13 (95%CI: 0.94–1.37) for the 50 years of age cut-off for menopausal status and it was 1.17 (95%CI: 1.00–1.38) for the 52 years of age cut-off.

*Conclusions:* Our findings suggest that exposure to low concentrations of $NO_2$, a marker for traffic-related air pollution, increases the risk of premenopausal breast cancer, but not postmenopausal breast cancer.

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## 1. Introduction

Breast cancer is the most common cancer affecting women worldwide, with over 1.7 million new cases annually (International Agency for Research on Cancer). In Canada in 2015, the age-adjusted rate was 130 per 100,000 women (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015); it accounts for 25% of all cancers diagnosed in women, the lifetime probability of dying from breast cancer is 1 in 30, and 5-year survival after breast cancer is 87%. The population attributable risk percent for accepted risk factors (including alcohol consumption, hormonal therapy, age, age at menarche, age at first birth, family history of breast cancer, prior benign breast disease (Labrèche et al, 2014) has been estimated recently at 70% (Tamimi et al., 2016). Few environmental or occupational risk factors have been identified, such as ionizing radiation, and there is "limited" evidence of increased risks of female breast cancer for exposure to ethylene oxide, organic solvents, polycyclic aromatic hydrocarbons, and shift work that involves circadian disruption (Labrèche et al., 2014).

Ambient air pollution is ubiquitous, albeit varying considerably in space and time and by constitution and concentration, and is recognized by the International Agency for Research on Cancer as a human carcinogen (Loomis et al., 2013). This assessment of carcinogenicity relied mostly on studies of lung cancer. Since the mid-1990s a number of investigations have been carried out of possible associations between the risk of breast cancer and exposure to various components of air pollution, especially nitrogen dioxide ($NO_2$) and fine particulate matter ($PM_{2.5}$) (Andersen et al., 2017a, 2017b; Bonner et al., 2005; Crouse et al., 2010; Goldberg et al., 2017; Hart et al., 2016; Hystad et al., 2015; Lewis-Michl et al., 1996; Nie et al., 2007; Raaschou-Nielsen et al., 2011; Reding et al., 2015; Villeneuve et al., 2018). These studies varied in terms of design, the measurement of the components of air pollution, as well as adjusting for potential confounding factors, and some of these studies have suggested that exposure to air pollutants may be positively associated with the incidence of breast cancer (see Discussion for details).

Recently, we made use of the Canadian National Breast Screening Study (Miller et al., 1992a, 1992b, 2002, 2014) to estimate associations with fine particulates ($PM_{2.5}$) and all-cause mortality (Villeneuve et al., 2015) and the incidence of breast cancer (Villeneuve et al., 2018). The cohort comprises approximately 89,000 Canadian women who were part of randomized controlled screening trial (Miller et al., 1992a, 1992b, 2002, 2014) and whose mortality and cancer incidence experience was ascertained over a 25 year follow-up. We found associations between ambient $PM_{2.5}$ and mortality (Villeneuve et al., 2015) as well as the incidence of breast cancer (Villeneuve et al., 2018) among premenopausal women. In that study we used satellite-based estimates of $PM_{2.5}$, at a resolution of 10 square km, as a general marker of air pollution from multiple sources. As previous studies have shown associations with $NO_2$, we wished to reanalyse the cohort in order to determine whether traffic-related air pollution, using $NO_2$, a well-recognized marker of this component of ambient air pollution (Beckerman et al., 2008; HEI, 2010), estimated from a national land use regression model, was associated with the incidence of premenopausal breast cancer and postmenopausal breast cancer.

## 2. Material and methods

### 2.1. Study population

The Canadian National Breast Screening Study (Miller et al., 1992a, 1992b, 2002, 2014) included a non-random sample of 89,835 women between 40 and 59 years of age recruited mostly from urban centres in Canada between 1980 and 1985. As stated in Miller et al. 2014 (Miller et al., 2014), "Participants were recruited to the study by a general publicity campaign, by reviewing population lists and sending personal invitation letters, by group mailings, and through family doctors." The screening centres were located in teaching hospitals or in cancer centres across the country, and women were excluded if they had a breast cancer beforehand. Those women who were between 40 and 49 years of age were randomized to receive either annual mammography screening and a physical examination of the breasts, or into the control group where they were taught breast self-examination and they received a single physical examination of the breasts. Among those between the ages of 50–59, for ethical reasons it was determined some screening for breast cancer should be provided, so these women were randomized into a group that received annual mammography and breast examination, or into a control group that received annual breast examination alone. Women 50–59 years of age were also taught breast self-examination. Annual follow-up was through a postal questionnaire.

At time of entry into the screening study, the women provided informed consent, and they completed a self-administered questionnaire regarding their demographic characteristics as well as accepted risk factors (at that time). They provided information on past pregnancies, including numbers of stillbirths, miscarriages, live births, and age when their first live child was born, and whether any of their female relatives had breast cancer, and their relationship to them. They were also asked about their history of oral contraceptive and estrogen use, as well as whether they had any X-ray examinations of their breasts. They described their occupation in as much detail as possible. From these details, occupations were classified into broadly based categories (i.e., homemaker, clerical, medicine and health, teaching, management of administration, sales, service, arts, retired, social sciences, teaching, unemployed or other). We did not have information on the consumption of alcohol.

Women's height, weight and skinfold thickness were measured by a trained health professional. Residential address information was obtained at baseline, and six-character Canadian postal codes were collected for all participants. In urban areas, six-character postal codes typically represents one block face between two intersecting streets or a large complex, and in rural areas it can represent much larger areas.

In addition, participants were asked whether they still had menstrual periods, and if so, to report the date of their last period and if their periods were regular, and thus indicated whether they were postmenopausal, regardless of age. This information was not available in a time-dependent fashion throughout the follow-up period, and thus among women who were premenopausal at time of the initial study, we used attained age to determine menopausal status. Recent data published from the Canadian Longitudinal Study of Aging indicated that the median age of menopause among Canadian women was about 51 years (Costanian et al., 2017). In our previous paper on $PM_{2.5}$ (Villeneuve et al., 2018), we conducted separate analyses using ages 50, 52, and 54 years as plausible cut-offs for being menopausal, but did not find any substantial differences in the risk estimates, and thus we are presenting herein risk estimates using cut-offs of 50 and 52 years of age. We thus created two non-independent premenopausal cohorts that comprised all women who were not declared to be menopausal at the time of entry into the study until they were either 50 or 52 years of age, for which they were censored, or if before those ages they developed an incident breast cancer, died, or were lost to follow-up (end date of December 31, 2005). The two non-independent postmenopausal cohorts comprised all women who were menopausal at time of entry and included women from the premenopausal cohorts when they reached 50 or 52 years of age.

### 2.2. Ascertainment of vital status and cancer incidence

Vital status was ascertained (Statistics Canada, 2017a) using a probabilistic record linkage to the Canadian Mortality Database (Statistics Canada, 2017a) until the end of 2005. This database comprises all deaths occurring in Canada, as well as Canadian deaths that occur in approximately 20 US states. The accuracy of identifying deaths has been estimated to be approximately 98% (Goldberg et al., 1993).

Incident cases of invasive breast cancer used in the present analysis were identified through record linkage to the Canadian Cancer Registry (Statistics Canada, 2017b) between 1968 and 2005. The Registry is national and is based on Provincial cancer registries. Coverage is not available, but it should be fairly complete for all cancers that require treatment in hospital, as each province and territory is required legally to record information on cancer incidence and treatment. (See supplement for more details.) We excluded those few women who, from the record linkage, were identified with an invasive breast cancer before entry into the study. Secondary diagnoses of breast cancer were not considered in the analyses. We also did not have any information on receptor status, other molecular markers, and stage of the disease.

### 2.3. Exposure assessment for $NO_2$

We assigned estimates of exposures to ambient $NO_2$ to the residential locations of subjects at time of entry into the cohort using a national land use regression model (LUR) (Hystad et al., 2011) that was created from 2006 annual fixed-site observations of $NO_2$ from National Air Pollution Surveillance Program of Environment Canada (Environment Canada, 2018a, 2018b). Specifically, estimates were assigned to the representative point of subjects' residential six-character postal code. The LUR model comprised road length within 10 km, area of industrial land use within 2 km, mean summer rainfall, and 2005–2011 estimates of $NO_2$ from satellite-derived surface concentrations (Lamsal et al., 2008). This model explained 73% of the variation in 2006 measurements with a root mean square error of 2.9 parts per billion (ppb). Kernel density gradients (i.e., smoothed surfaces describing densities of roadways) were applied at a 10 m spatial resolution as multipliers to the LUR model, which allowed the capture of complex patterns in roadway emissions (e.g., the influence of multiple roadways, intersections, off-ramps). The LUR model therefore produced an estimate of 2006 annual mean concentrations of $NO_2$ at each postal code point location, and the spatial resolution was defined by the finest scale model predictor, namely the density gradients that were derived at a 10 m resolution.

### 2.4. Statistical methods

We used the Cox proportional hazards model, with age as the time axis, to compute associations between incident breast cancer and concentrations of $NO_2$ estimated at their residence at time of entry into the screening study. We determined the shape of the response functions for all continuous covariables using penalized splines on four degrees of freedom and determined by visual inspection whether the exposure-response function was linear. We modelled BMI as a continuous covariable and also using cut-points $< 20$, 20–24, 25–29, $\geq 30\ kg/m^2$ (approximately the categories used by the World Health Organization (World Health Organization, 2018), and missing values. Results for $NO_2$ between the smoothed and categorical estimates of BMI were similar and, because we did not want to lose subjects, we used the categorical version of BMI. We also verified the proportional hazards assumption for all variables by adding an interaction term for time (using the function "cox.zph" that is part of the "survival" package in R).

As in our previous papers on PM2.5 (Villeneuve et al., 2015, 2018), we developed a series of models that successively included covariables from previous ones. First, we fitted a model that contained only $NO_2$ using penalized splines (referred to as model I) to estimate the response pattern (essentially an age-adjusted model), and then another model that also contained individual-level factors for occupation, marital status, and attained education (model II). Model III included the covariables from the previous models as well as body mass index, and cigarette pack-years (modelled continuously). Model IV included additional covariables representing reproductive factors (i.e., ever pregnant, oral contractive use, hormone replacement therapy, age at menarche), breast self-examination, and family history of breast cancer (categorical variables). Finally, Model V included the terms in Model IV as well as penalized splines on four degrees of freedom for contextual variables adjusted for regional variations across Canada (i.e., census division means subtracted from census-tract means) obtained from the 1991 Canadian census data, namely median household income, proportion of individuals with high school education, percentage of low-income households, and unemployment rate. Census tracts correspond roughly to the size of a neighbourhood and census divisions correspond roughly to the size of a city or county.

All analyses of $NO_2$ were consistent with linearity (see results), and in each cohort we thus computed incidence rate ratios (RR) and their 95% confidence intervals (CI) for an increase of about equal to the interquartile range.

In addition, we conducted a combined analysis of previous studies of $NO_2$ and postmenopausal breast cancer, including the present study, assuming that response functions were linear and that case-control studies estimated rate ratios. As there were only two studies in premenopausal women, we only used the studies of postmenopausal women and made use of a simple random effects model, as implemented in the R package "metafor", and computed Cochran's Q to evaluate heterogeneity between the study-specific estimates.

## 3. Results

A total of 89,247 women were assigned air pollution exposures, and were included in these analyses of the Canadian National Breast Screening Study. For the cut-off of 52 years of age, residential measures of $NO_2$ were assigned in the postmenopausal cohort to 79,426 women (89.9% of the cohort) and in the premenopausal cohort to 38,210 women (90.5%). In total, over 9,400 women died during the 25-year follow-up and 646 premenopausal women (over 1.6 million person-years of observations) and 5851 postmenopausal women (over 250,000 person-years), for a total of 6503 women, who were diagnosed during the follow-up period with incident breast cancer. We did not find any substantial differences on accepted risk factors between the entire screening study cohort and those women for which $NO_2$ was missing (see Supplement Table 1).

Table 1 shows the distribution of selected sociodemographic characteristics and risk factors of the participants in each of the two cohorts using age 52 as the cut-off. The number of women in the postmenopausal cohort is close to the total number in the entire cohort, as most premenopausal women survived to age 52 years of age. (Recall we only started counting person-time in the postmenopausal cohort when women reached menopause.) We also show in this table the number of incident cases of breast cancers by each characteristic.

Referring again to the age 52-year cut-off (and results were similar for the 50 years of age cut-off, data not shown), Table 1 shows among women in the postmenopausal cohort who were initially screened between 40 and 59 years of age, with about equal numbers in each five-year age group, except for 55–60 year (18.4%). Most women were born in Canada (82.3%), most were married (79.8%), about 26% had less than a high school education and over 55% had college or higher education. About 86% of participants had a body mass index under 30, 30% had a family history of breast cancer, 69% started their periods before age 14 years, 27% took hormonal replacement therapy, 60% took oral contraceptive therapy, 88% had been pregnant, and 49% smoked cigarettes. For the premenopausal cohort, the distributions of the above variables were similar, except for age at entry, ever had hormonal therapy (5.2% versus 26.8% in the postmenopausal cohort), and oral contraceptive use (70.3% versus 59.6%).

Table 2 shows for the age 52-year cut-off the distributions of ambient $NO_2$, in ppb, assigned to the residences at time of entry into the screening study for the premenopausal and postmenopausal cohorts. The mean concentrations of $NO_2$ were just above 15 ppb and the interquartile ranges were similar (about 9.7 ppb).

We found in all analyses that the proportional hazards assumption

**Table 1**
Selected socio-demographic characteristics, and accepted or suspected risk factors of the participants of the Canadian National Breast Screening Study whose residential exposure to ambient $NO_2$ was determined, by menopausal status using the cut-off for menopausal status of 52 years of age.

| Characteristic | | Postmenopausal cohort | | | Premenopausal cohort | | |
|---|---|---|---|---|---|---|---|
| | | No. and percentage of women (88,389) | | No. of incident breast cancers (Total 5,851) | No. and percentage of women (38,210) | | No. of incident breast cancers (Total 652) |
| Age at entry (y) | 40–45 | 30,703 | 34.7 | 1558 | 24,136 | 63.2 | 463 |
| | 46–50 | 23,266 | 26.3 | 1549 | 12,549 | 32.8 | 182 |
| | 51–55 | 21,888 | 24.8 | 1696 | 1525 | 4.0 | 7 |
| | 56–60 | 12,532 | 14.2 | 1048 | | | |
| Birthplace | Canada | 72,708 | 82.3 | 4901 | 30,929 | 80.9 | 521 |
| | United Kingdom | 6775 | 7.7 | 433 | 3119 | 8.2 | 61 |
| | European (excluding UK) | 5085 | 5.8 | 301 | 2319 | 6.1 | 41 |
| | United States | 1739 | 2.0 | 110 | 733 | 1.9 | 12 |
| | Other | 2082 | 2.4 | 301 | 1110 | 2.9 | 41 |
| Marital status | Never Married | 5622 | 6.4 | 442 | 2704 | 7.1 | 45 |
| | Married | 70,506 | 79.8 | 4653 | 30,985 | 81.1 | 527 |
| | Divorced | 5729 | 6.5 | 322 | 2459 | 6.4 | 45 |
| | Separated | 2726 | 3.1 | 167 | 1219 | 3.2 | 25 |
| | Widowed | 3701 | 4.2 | 254 | 804 | 2.1 | 3 |
| | Unknown | 105 | 0.1 | 13 | 39 | 0.1 | 0 |
| Education | Less than High School | 23,133 | 26.2 | 1458 | 7750 | 20.3 | 111 |
| | Completed High School | 11,014 | 12.5 | 705 | 4908 | 12.8 | 83 |
| | Trade/Vocational School | 4963 | 5.6 | 334 | 2016 | 5.3 | 28 |
| | College/business | 30,532 | 34.5 | 2034 | 13,262 | 34.7 | 28 |
| | University | 18,676 | 21.1 | 1309 | 10,243 | 26.8 | 195 |
| | Unknown | 71 | 0.1 | 11 | | | |
| Body mass index ($kg/m^2$) | < 18.5 | 1203 | 1.5 | 72 | 639 | 1.7 | 10 |
| | 18.5–24 | 50,724 | 57.4 | 3244 | 24,022 | 62.9 | 443 |
| | 25–29 | 24,590 | 27.8 | 1701 | 9237 | 24.2 | 145 |
| | 30–34 | 7578 | 8.6 | 525 | 2639 | 6.9 | 38 |
| | ≥35 | 3184 | 3.6 | 233 | 1226 | 3.2 | 13 |
| | Unknown | 1020 | 1.2 | 76 | 447 | 1.2 | 3 |
| Breast self-examination | Yes | 44,033 | 49.8 | 3033 | 19,320 | 50.6 | 371 |
| | No | 43,894 | 49.7 | 2791 | 18,724 | 49.0 | 275 |
| | Unknown | 462 | 0.5 | 25 | 166 | 0.4 | 6 |
| Family history of breast cancer | Yes | 26,846 | 30.4 | 2135 | 11,588 | 30.3 | 248 |
| | No | 49,546 | 56.1 | 2979 | 21,890 | 57.3 | 347 |
| | Uncertain | 11,742 | 13.3 | 718 | 4637 | 12.1 | 57 |
| | Unknown | 253 | 0.3 | 19 | 95 | 0.2 | 0 |
| Age at menarche (in years) | < 12 | 14,836 | 16.8 | 987 | 6334 | 16.6 | 125 |
| | 12 | 20,483 | 23.2 | 1411 | 8923 | 23.4 | 146 |
| | 13 | 25,744 | 29.1 | 1741 | 11,464 | 29.4 | 179 |
| | ≥14 | 26,725 | 30.1 | 1674 | 11,226 | 29.4 | 197 |
| | Unknown | 601 | 0.7 | 38 | 263 | 0.7 | 5 |
| Hormonal replacement therapy | Yes | 23,679 | 26.8 | 1694 | 2003 | 5.2 | 27 |
| | No | 63,342 | 71.7 | 4066 | 347 | 0.9 | 8 |
| | Unknown | 1349 | 1.5 | 91 | 35,860 | 93.9 | 617 |
| Oral contraceptive use | Yes | 52,701 | 59.6 | 3282 | 26,867 | 70.3 | 478 |
| | No | 35,523 | 40.2 | 2555 | 11,303 | 29.6 | 173 |
| | Unknown | 160 | 0.2 | 14 | 40 | 0.1 | 1 |
| Smoking status | Never | 43,721 | 49.5 | 2801 | 19,215 | 50.3 | 335 |
| | Ever | 44,480 | 50.3 | 3038 | 18,927 | 49.5 | 315 |
| | Unknown | 188 | 0.2 | 12 | 68 | 0.2 | 2 |
| Pack-years of smoking (mean and standard deviation) | | 9.3 (12.0) | N/A | N/A | 8.1 (10.4) | N/A | N/A |
| Ever pregnant | Yes | 77,812 | 88.0 | 5001 | 33,459 | 87.6 | 542 |
| | No | 10,521 | 11.9 | 848 | 4735 | 12.4 | 110 |
| | Unknown | 56 | 0.1 | 2 | 13 | 0.0 | 0 |

N/A; not applicable.

**Table 2**
Distribution of ambient nitrogen dioxide (ppb) from the national land use regression model, Canadian National Breast Screening Study, 1982–2005, using the cut-off for menopausal status of 52 years of age.

| | Mean | Standard deviation | Minimum | 25% percentile | 50% percentile | 75% percentile | Maximum | Inter-quartile range |
|---|---|---|---|---|---|---|---|---|
| Premenopausal cohort | 15.2 | 6.3 | 0.1 | 10.5 | 14.9 | 20.1 | 48.6 | 9.6 |
| Postmenopausal cohort | 15.3 | 6.5 | 0.1 | 10.6 | 15.2 | 20.3 | 48.9 | 9.7 |

**Table 3**
Adjusted rate ratios of incident breast cancer in relation to an increase of the interquartile range (9.7 ppb) using the national land use regression model for $NO_2$*, by menopausal status**, Canadian National Breast Screening Study, 1982–2005.

| Regression model | Premenopausal | | Postmenopausal | |
|---|---|---|---|---|
| | Rate ratio | 95% CI | Rate ratio | 95% CI |
| *Age cut-off, 52 years* | | | | |
| Model I | 1.17 | 1.04–1.33 | 1.02 | 0.99–1.07 |
| Model II | 1.18 | 1.04–1.34 | 1.02 | 0.98–1.07 |
| Model III | 1.18 | 1.04–1.34 | 1.02 | 0.98–1.07 |
| Model IV | 1.19 | 1.05–1.34 | 1.03 | 0.99–1.07 |
| Model V | 1.17 | 1.00–1.38 | 1.00 | 0.95–1.06 |
| *Age cut-off, 50 years* | | | | |
| Model I | 1.13 | 0.98–1.30 | 1.04 | 1.00–1.08 |
| Model II | 1.15 | 0.99–1.33 | 1.03 | 0.99–1.07 |
| Model III | 1.15 | 0.99–1.33 | 1.03 | 0.99–1.07 |
| Model IV | 1.15 | 0.99–1.34 | 1.03 | 0.99–1.08 |
| Model V | 1.13 | 0.94–1.37 | 1.01 | 0.96–1.06 |

Model I: unadjusted model (age as time axis).
Model II: adjusted for occupation, marital status, attained education.
Model III: includes terms in Model II and further adjustment for body mass index, and cigarette pack-years.
Model IV: includes terms in Model III and further adjustment for ever pregnant, oral contractive use, hormone replacement therapy, age at menarche, breast self-examination, and family history of breast cancer.
Model V: includes terms in Model IV and further adjustment for contextual measures (median income, proportion with high school education, percentage of low-income households, and unemployment rate).

* Concentrations of $NO_2$ were assigned to women's place of residence at time of entry into the cohort.

** Premenopausal women were defined from self-reports at time of entry or were under the age of 52 years or 50 years during the follow-up period.

was not violated. For both age cut-offs, Table 3 shows adjusted rate ratios for each of the five models for the two cohorts. For the age 50 cut-off, the number of incident cases of breast cancer was 471 in the premenopausal cohort and 6032 in the postmenopausal cohort. For the age 52 cut-off, the corresponding numbers were 652 and 5851 incident cases. We considered that the response functions were consistent with linearity (see Supplement for plots of the full-adjusted penalized spline models on 4 degrees of freedom). All results are presented for an increase in concentrations of $NO_2$ of 9.7 ppb, about equal to the interquartile range in all cohorts.

For both postmenopausal cohorts, we found little evidence of an association, with rate ratios in the order of unity for an increase of 9.7 ppb. Increased rate ratios were found in both premenopausal cohorts, with higher ones found in the age 52-year cut-off. For example, model IV, that excluded the contextual variables but included all measured personal risk factors, showed in the premenopausal cohort (cut-off of 52 years) a rate ratio of 1.19 (95% CI: 1.05–1.34) compared to a rate ratio (RR) of 1.15 (95% CI: 0.99–1.34) for the cut-off of 50 years. Model V, which also included four neighborhood characteristics (median income, proportion with high school education, percentage of low-income households, and unemployment rate), showed in the age 52- and 50-year cut-offs, respectively: rate ratios of 1.17 (95%CI: 1.00–1.38) and 1.13 (95%CI: 0.94–1.37).

In a sensitivity analysis, among premenopausal women we assessed the interaction between the treatment arm and the control arm but found no important differences for both age cut-offs (Supplemental Table 2).

## 4. Discussion

In summary, we found that the rates of incident breast cancer in premenopausal women were positively associated with estimates of concentrations of $NO_2$ from a national land use regression model assigned to participants' residences when they enrolled in the cohort. As we noted in the introduction, $NO_2$ measured at street-level, is an accepted marker for traffic-related air pollution (Beckerman et al., 2008; HEI, 2010). Among postmenopausal women, we found no evidence of an association.

We analysed pre- and postmenopausal breast cancer separately as they have different age distributions, and different natural histories, with premenopausal breast cancer being much more aggressive and deadly. As well, many accepted risk factors are in common, but can vary by menopausal status (Labrèche et al., 2014; Li, 2010), especially a stronger genetic component in pre-menopausal women. Thus, these conditions represent two distinct diseases and require separate analyses, and indeed we found different patterns of response to $NO_2$ by menopausal status. In addition, there may be sub-types of breast cancer, perhaps characterized by morphology but also receptor status, in which risks may differ (e.g., by oestrogen and progesterone receptor status (Goldberg et al., 2017). We did not have any information on molecular or other markers to make such distinctions.

As in many studies of chronic diseases and ambient air pollution, assigning exposure to the place of residence at time of entry leads inevitably to errors in exposure. Some subjects could not be linked to the land use regression model, but we did not find important differences in risk factors between them and the postmenopausal cohort. Given the length of the follow-up interval, many subjects likely would have moved. Under a classical error model, this would introduce non-differential exposure measurement error that would serve to underestimate the true association, and use of estimates of $NO_2$ assigned to postal code centroids (and not civic addresses) likely caused Berkson errors. The national land use regression model (Hystad et al., 2011) relied on fixed-site monitors as well as space-based observations and had a resolution in the order of 10 × 10 m), but that does not imply that the total measurement error was minimal, and we do not have data to show whether the total measurement error was entirely independent of disease status. Approximately 19% of individuals had moved during the follow-up period (1980–2005), suggesting that residential mobility is unlikely to greatly influence the risk estimates. Indeed, in our previous paper, the rate ratios for $PM_{2.5}$ were similar among those who moved within the first 3–5 years of follow-up and those who did not (Villeneuve et al., 2018).

In addition, there may have been more measurement error for premenopausal breast cancer because it would have occurred at an earlier stage of the follow-up period than for postmenopausal breast cancer. Given the lack of air pollution monitoring in Canada before 1990, it is difficult to evaluate the extent of these potential biases, as it is not possible to describe the spatial and temporal changes in concentrations of $NO_2$ during the first 10 years of follow-up of this cohort. Thus, we have no information on critical ages of exposure that may increase risk. There are some data showing that in North America, concentrations of ground-level $NO_2$ appear to have been decreasing in time. The US Environmental protection Agency has reported since 1980 a decrease of about 50% and this varies by region (U.S. Environmental Protection Agency, 2018). In Canada, there have also been declines although it appears that these are not dependent on geographic area (Environment Canada, 2018b). Geddes and co-authors (Geddes et al., 2016) reported from satellite observations that in Canada and the United States concentrations from 1996 to 2012 have declined by 4.7%/year (95% CI: –5.3, –4.1).

We did not adjust for fine particulate mass or other ambient pollutants, such as polycyclic aromatic hydrocarbons, that have not been measured on a national scale. Others may hold the view that adjustments for other pollutants are necessary, but our position is derived from concerns that adjusting for other markers of pollution that derive from vehicular exhaust as well as other sources may cause over-adjustments (Goldberg, 2007). Briefly, the argument is that when one has a complex mixture and one is measuring its different components, especially those that derive from similar source(s), regardless of the

empirical correlations between measured pollutants, that adjustments may be biased. This argument is analogous to, for example, adjusting for carbon monoxide when measuring nicotine in cigarette smoke or adjusting for factors in a common pathway, which is known to lead to biased results. In our case, $NO_2$ is an excellent measure of traffic-related pollution but particulate matter derives from a number of sources as well as traffic, especially when measurements are made near roadways. We contend that spatial exposures need to be considered differently from personal exposures, such as smoking and alcohol consumption.

We found in both cohorts that estimates did not vary across the models that accounted for the accepted and suspected risk factors that we had in hand, which implies that there were no important associations between ambient $NO_2$ and these variables. It is possible that estimates may have changed had we adjusted for other risk factors (e.g., alcohol consumption, X- or gamma-radiation, dieldrin, digoxin, ethylene oxide, polychlorinated biphenyls or shift work) (International Agency for Research on Cancer, 2007; Labrèche et al., 2014). Of interest, was that rate ratios were attenuated somewhat when we included the four contextual variables, and this may have been due to spatial confounding but also could have been due to over-adjustment on exposure, as the census tract areas used were rather small (they typically have populations ranging from 2500 to 8000 people). In any event, it is likely that the results of models II-V provide a plausible range of estimates of effect.

The strengths of the study include 1) a relatively large cohort with a large number of cases of incident breast cancer, thereby providing sufficient statistical power to estimate response patterns, 2) assignment of exposure to virtually all participants regardless of whether they lived in rural or urban areas, 3) availability of individual-level risk factors that allowed us to adjust for smoking behaviours and body mass, and 4) adjustment for contextual variables from the Census.

A limitation of the study is that because we did not have contact with subjects during the follow-up, we could not determine menopausal status using other information, such as the WHO criteria for menopausal status that accounts for hormone replacement therapy, hysterectomy, and bilateral oophorectomy) (WHO, 1996; World Health Organization, 1981). In our previous paper on incidence of breast cancer and $PM_{2.5}$ (Villeneuve et al., 2018), we showed that estimates were similar for three different age cut-offs to classify women as postmenopausal (namely, 50, 52, and 54 years of age), and we found here that the results did not vary dramatically between the two definitions. Other limitations of the study include missing covariables that were not measured as a risk factors when the trial was conducted (e.g., alcohol consumption, ethnicity) and possible residual confounding using crude categories for covariables (e.g., ever pregnant or not).

### 4.1. Summary of the literature

#### 4.1.1. Studies of $NO_2$

A number of papers on postmenopausal breast cancer have now been published on the possible association between ambient air pollution and the incidence of breast cancer. Table 4 shows these results for ambient $NO_2$ standardized to an increase of 5 ppb. In our hospital-based case-control study in Montreal using a dense LUR model assigned at time of interview we found for each increase of 5 ppb an adjusted OR of 1.35 (95% CI: 0.94, 1.94) (Crouse et al., 2010, 2009). In the same study, we observed associations with a number of occupational risk factors for postmenopausal breast cancer, including combustion-related exposures, especially amongst women exposed before the age of 35 years and those with ER+/PR + receptor status (Labreche et al., 2010). In a latter population-based case-control study using the same LUR (Goldberg et al., 2017), we found an odds ratio of 1.07 (95%CI: 0.85–1.35) for an increase of 5 ppb. In a case-control study conducted in eight Canadian provinces (Hystad et al., 2015), we observed for an increase of 10 ppb in scaled satellite observations of $NO_2$ an OR of 1.32 (95%CI: 1.05, 1.67) for premenopausal women and an OR of 1.10 (95%CI: 0.94, 1.28)

**Table 4**
Summary of adjusted effects of breast cancer studies in relation to a 5 ppb increase of $NO_2$.

| Study | No. of cases | Exposure methodology | Rate ratio per increase of 5 ppb (about 9.44 μg/m$^3$) | 95% Confidence interval |
|---|---|---|---|---|
| *Postmenopausal women* | | | | |
| Montreal hospital-based c-c study) (Crouse et al., 2010) | 383 | Dense LUR assigned at time of interview | 1.35 | 0.94–1.94 |
| Montreal population-based c-c study (Goldberg et al., 2017) | 679 | Dense LUR assigned at time of interview | 1.07 | 0.85–1.35 |
| 8-province c-c study (Hystad et al., 2015) | 1140 | National LUR assigned at time of interview | 1.03 | 0.93–1.15 |
| Sister cohort (USA) (Reding et al., 2015); | 1749 | Spatial model using fixed-site monitors | 1.02 | 0.97–1.06 |
| Danish Nurses Cohort (Andersen et al., 2017a); | 1145 | Emissions/dispersion model | 1.03 | 0.95–1.10 |
| ESCAPE cohort (Europe, 15 cities) (Andersen et al., 2017b) | 3612 | LUR back extrapolated at time of entry | 1.02 | 0.97–1.07 |
| Present study (age cut-off of 52 years) | 5851 | National LUR assigned at time of entry | 1.00 | 0.98–1.02 |
| *Premenopausal women* | | | | |
| 8-province Canadian c-c study (Hystad et al., 2015) | 619 | National LUR assigned at time of interview | 1.13 | 0.96–1.34 |
| Present study (age cut-off of 52 years) | 646 | National LUR assigned at time of entry | 1.09 | 1.07–1.11 |

c-c, case-control; LUR, land use regression model; ppb, parts per billion.

for postmenopausal women. In the Sister Cohort (Reding et al., 2015), for an increase of 5.8 ppb, Reding and co-workers presented a rate ratio of 1.02 (95%CI: 0.97, 1.02), and increased risks were found for cases with positive oestrogen receptor and positive progesterone receptor status (1.10; 95%CI: 1.02, 1.19). In the Danish Nurse's Cohort study (Andersen et al., 2017a), an atmospheric chemistry transport model was used (THOR, AirGIS), and a rate ratio of 0.99 per 7.4 μg/m$^3$ (95%CI:0.93, 1.05) was reported. In the ESCAPE cohorts, Andersen and colleagues (Andersen et al., 2017b) made use of separate LUR models for $NO_2$, $PM_{10}$ and $PM_{2.5}$, and back-extrapolated values were assigned to the residential addresses of participants, and the pooled estimate for $NO_2$ was 1.07 (95%CI: 0.98, 1.07) for an increase of 10 μg/m$^3$.

There are a sufficient number of studies in postmenopausal women to attempt a pooled analysis. Assuming comparability of the studies (Buteau and Goldberg, 2015) and assuming that odds ratios in the case-control studies represent hazard ratios, we computed a combined estimate using standard random effects meta-analysis regression methods. We found for a 5 ppb increase a summary rate ratio of 1.01 (95%: 0.99–1.03; heterogeneity between studies: Cochran's Q = 5.9 (df = 6), p = 0.5).

Two studies of postmenopausal women reported estimates for $NO_x$ that were not included in Table 4. Raaschou-Nielsen and collaborators made use of the Danish Diet Cancer and Health Cohort (Raaschou-Nielsen et al., 2011) and found an adjusted rate ratio for mostly postmenopausal incident breast cancer, for an increase of 100 μg/m$^3$ of $NO_x$ was 1.16 (95%CI: 0.89, 1.51), according to computed concentrations from the Danish AirGIS system. In the ESCAPE cohort (Andersen et al., 2017b), the pooled estimates for $NO_x$ was 1.04 (95%CI: 1.00, 1.08).

In addition, only two studies have been published on premenopausal breast cancer, and these include the present study and our 8-province case-control study (Hystad et al., 2011), both finding much higher estimates than the postmenopausal studies (1.09 and 1.13 per 5 ppb increase, respectively).

#### 4.1.2. Studies of fine particulate matter and postmenopausal breast cancer

With regards particulate matter, the association with this pollutant was first reported in a case-control study of postmenopausal women in New York State, with associations found with increased volumes of vehicular traffic (Lewis-Michl et al., 1996). In a subsequent paper from this study, a dispersion model for exposures to benzo[a]pyrene (Bonner et al., 2005; Nie et al., 2007) was used as a proxy for emissions to traffic-related pollution, and associations were found among premenopausal women using their address at time of menarche. In the Nurses' Health Study II (Hart et al., 2016), no associations were found for incident breast cancer and $PM_{2.5}$ but increased rates were found among premenopausal and postmenopausal women living within 50 m of major roads. In the Sister Cohort, (Reding et al., 2015) adjusted rate ratios for incident breast cancer for an increase in the interquartile range of $PM_{2.5}$ (3.6 μg/m$^3$), from a smoothed national surface from fixed-site monitors, was 1.03 (95% CI: 0.96–1.11). In the Danish Nurse's Cohort study (Andersen et al., 2017a), no associations were reported for $PM_{2.5}$ (RR = 0.99 per increase of 3.3 μg/m$^3$; 95%CI: 0.94, 1.10) or $PM_{10}$ (1.02 per 2.9 μg/m$^3$; 95%CI: 0.94, 1.10). The pooled estimates were for the ESCAPE cohort were: for $PM_{2.5}$, the RR was 1.05 (95%CI: 0.77, 1.51) for an increase of 5 μg/m$^3$, and for $PM_{10}$ the RR was 1.00 (95%CI: 0.80, 1.25) for an increase of 10 μg/m$^3$.

#### 4.1.3. Studies of ultrafine particulate matter and postmenopausal breast cancer

Ultrafine particles are secondary particles that form through other processes, and while related to combustion sources, notably mobile diesel sources, appear to have in Montreal a spatial distribution that is different from $NO_2$. Two analyses of ultrafine particles and postmenopausal breast cancer based on our two case-control studies in Montreal (Goldberg et al., 2017, 2018). In the former study, we found an 8% increase in risk for an increase in the interquartile range (95%CI: 0.96, 1.21) and among cases with positive estrogen and negative progesterone receptor the odds ratio (OR) was 1.23 (95%CI: 1.04, 1.45) and for women with negative estrogen and negative progesterone receptor the OR was 1.23 (95%CI: 0.99, 1.54). In the latter study, we did not find evidence of an association (OR about unity) and amongst cases with positive oestrogen and progesterone receptor status the OR was 1.05 (95%CI: 0.96, 1.14).

## 5. Conclusions

Our findings suggest that ambient exposure to $NO_2$ increases the risk of developing premenopausal breast cancer with no associations found for postmenopausal breast cancer. Considering the entire literature for exposures to $NO_2$, it is premature to make causal statements regarding premenopausal breast cancer as results have been reported from only two other studies. Despite the null association in the present study in postmenopausal women, the results across studies suggest a possible positive association for specific markers of traffic-related pollution (NOx and $NO_2$).

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Due to ethics requirements, individual-level data from this study cannot be distributed.

## Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105182.

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