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Breast cancer risk in relation to ambient concentrations of nitrogen dioxide and particulate matter: results of a population-based case-control study corrected for potential selection bias (the CECILE study)

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ABSTRACT

Background: There is only scant evidence that air pollution increases the risk of breast cancer.
Objectives: We investigated this relationship for three air pollutants: nitrogen dioxide (NO_2) and particulate matter with an aerodynamical diameter below 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$).
Methods: We conducted a population-based case-control study on breast cancer in two French *départements*, including 1,229 women diagnosed with breast cancer in 2005–2007 and 1,316 control women frequency-matched on age. Concentrations of NO_2, PM_{10} and $PM_{2.5}$ at participants' addresses occupied during the last 10 years were assessed using a chemistry transport model. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using multivariable logistic regression models where each woman was assigned a weight depending on her probability of selection into the study.
Results: The OR for breast cancer per 10-μg/m^3 increase in NO_2 was 1.11 (95% CI, 0.98, 1.26), and 1.41 (95% CI 1.07, 1.86) in the highest exposure quintile (Q5), compared to the first. The ORs per 10-μg/m^3 NO_2 did not markedly differ between pre- (OR 1.09, 95% CI 0.89, 1.35)) and post-menopausal women (OR 1.14, 95% CI 0.97, 1.33)), but the OR was substantially higher for hormone-receptor positive (ER+/PR+) breast tumor subtypes (OR 1.15, 95% CI 1.00, 1.31) than for ER–/PR– tumors (OR 0.95, 95% CI 0.72, 1.26). Breast cancer risk was not associated with either PM_{10} (OR per 1 μg/m^3 1.01, 95% CI, 0.96, 1.06) or $PM_{2.5}$ (OR per 1 μg/m^3 1.02, 95% CI 0.95, 1.08), regardless of the menopausal status or of the breast tumor subtype.
Discussion: Our study provides evidence that NO_2 exposure, a marker of traffic-related air pollutants, may be associated with an increased risk of breast cancer, particularly ER+/PR+ tumors.

1. Introduction

Breast cancer is the most common cancer affecting women worldwide, with more than 2 million new cases annually (Ferlay et al. 2019). Unlike hormonal, reproductive or lifestyle–related risk factors, the role of environmental exposures such as air pollution in relation to breast cancer risk has remained inconclusive.

Air pollution was classified by the International Agency for Research on Cancer as a human carcinogen (Loomis et al. 2013), based mostly on studies showing an association with lung cancer (Hamra et al., 2014). However, air pollution contains a mixture of many compounds such as polycyclic aromatic hydrocarbons (PAHs), metals, and benzene, that may act as carcinogens or endocrine disruptors relevant for breast carcinogenesis (Rodgers et al. 2018). Since the mid-1990s, several cohort or case-control studies on breast cancer and exposure to various components of air pollution, especially nitrogen dioxide (NO_2) and particulate matter ($PM_{2.5}$ or PM_{10}), have been conducted in Europe, North America, and South-Korea (Lewis-Michl et al. 1996; Bonner et al. 2005; Nie et al. 2007; Crouse et al. 2010; Raaschou-Nielsen et al. 2011; Hystad et al. 2015; Reding et al. 2015; Hart et al. 2016; Andersen et al. 2017b; a; Goldberg et al. 2017, 2019; Villeneuve et al. 2018; Datzmann et al. 2018; White et al. 2019; Hwang et al. 2020; Cheng et al. 2020; Bai

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et al., 2020). Although positive associations between exposure to air pollutants and breast cancer were inconsistently reported, most studies have focused on air pollution measured over a relatively short period of time before diagnosis (White et al. 2018), others were based on relatively small numbers (Crouse et al. 2010; Goldberg et al. 2017), had very limited adjustment for potential confounders (Datzmann et al. 2018), or used confounders measured at ecological level (Hwang et al. 2020). Because of these limitations, there remains great uncertainty about the existence of a causal link between air pollution and breast cancer.

Breast cancer is a molecularly diverse disease, that includes distinct molecular subtypes characterized by the expression of the estrogen (ER) or progesterone (PR) hormone receptors, and expression of proliferative markers such as Human Epidermal growth factor Receptor 2 (HER2). The subtypes defined by the combinations of tumor receptors vary in prognosis and response to treatment, but they may also reflect distinct etiologic pathways that appear to be fixed at the time of tumor initiation (Lacroix et al. 2004). The association of air pollution with specific breast cancer subtypes may be indicative of specific etiological pathways, but only a few studies on breast cancer in relation to air pollution have examined etiological heterogeneity by breast cancer subtype, and results have been conflicting (Reding et al. 2015; Hart et al. 2016; Goldberg et al. 2017; Cheng et al. 2020). Further data examining these associations are thus needed.

Studies have also suggested that the increase in risk of breast cancer was stronger in pre-menopausal than in post-menopausal women (Hystad et al. 2015; Hart et al. 2016; Andersen et al. 2017a; Villeneuve et al. 2018; Goldberg et al. 2019), but whether or not air pollution affects breast cancer risk differently according to menopausal status is debated and requires clarification.

In this article, we investigated the association between air pollution and breast cancer risk and examined whether the risk differed by menopausal status and tumor subtype. Using data from a population-based case-control study in France, we estimated the level of air pollution in the 10 years preceding diagnosis, and paid particular attention to possible selection biases inherent in this type of study.

2. Material and methods

2.1. Study population

We conducted a population-based case-control study in *Ille-et-Vilaine* and *Côte d'Or,* two French *départements* (administrative areas) located in the Western and Eastern part of France, respectively.

Cases were women residing in these areas, aged 25–75 years, and diagnosed with a histologically confirmed *in situ* or invasive breast cancer between 2005 and 2007. In *Ille-et-Vilaine,* incident cases of breast cancer were recruited in the main local cancer hospital (*Centre Eugène Marquis*) as well as in local public and private hospitals treating breast cancer patients, with the aim to recruit in the study all breast cancer cases diagnosed during the study period among women in the *département*. This is in contrast with *Côte d'Or* where cases were exclusively recruited in the main local cancer hospital (*Centre Georges-François Leclerc*) that recruit most, but not all, breast cancer patients in this area. Information on ER, PR and HER2 status was obtained from the pathology reports. Of the 1,553 eligible cases identified during the study period, 163 refused to participate, 151 could not be contacted, and seven died before the interview. Finally, 1,232 (79%) incident breast cancer cases were included in the study.

To form the control group, we contacted by phone a random sample of private homes in the study areas and invited resident women with no history of breast cancer to participate. Women who agreed to participate were frequency-matched to the cases by 10-year age group and were re-contacted by a research nurse at their home address for an in-person interview. To account for possible differential participation rate of the controls across categories of socio-economic status (SES), we used quotas by SES to obtain a distribution by SES similar to that of the general female population in each study area. Among the 1,731 controls identified by phone fulfilling eligibility criteria for age and SES, 260 declined participation and 154 could not be re-contacted for the in-person interview, leaving 1,317 controls available for the study (participation 76%).

2.2. Data collection and data coding

A structured questionnaire was completed by a trained interviewer during an in-person interview with the cases and the controls. We elicited information on demographic and sociodemographic characteristics, reproductive history, family history of cancer, hormonal treatments, lifestyle, occupational history, and residential history over the lifetime.

2.3. Assessment of exposure to air pollutants

Exposure to air pollution at the women's home address was assessed over the 10 years prior to a reference date, set at the date of diagnosis for the cases and at a concomitant date for frequency-matched controls. The reference date for the controls was chosen in accordance with incidence density sampling principles (Vandenbroucke and Pearce 2012), which require selecting controls at each occurrence of a case. To account for the delay between case diagnosis and control interview during recruitment of study subjects, the controls reference date was set by moving the date of interview to the nearest earlier date of a case diagnosis. Only exposures that occurred prior to a woman's reference date were included in the analysis, so that air pollution was assessed during the same 10-year time period in cases and in controls.

During the 10-year period before reference date, 5,489 home addresses were occupied by the cases and the controls. Each home address was geocoded using the street network database BD Adresse® (*Institut Géographique National, IGN, Saint Mandé, France*), which includes 26 million addresses in metropolitan France. Women with one or more missing addresses and those who lived at any time outside metropolitan France during the last 10 years were excluded from the analysis (31 cases and 25 controls), leaving 1,201 breast cancer cases and 1,292 controls in the analyses.

NO_2, PM_{10} and $PM_{2.5}$ concentrations at each home address were obtained during the corresponding period of occupancy using the nationwide Gazel-Air model (Bentayeb et al. 2014, 2015). This model provides annual estimates of each pollutant from 1989 to 2008 at a 2-km resolution scale in France. It is based on the CHIMERE chemistry-transport model, which provides pollutants concentrations at a 10-km resolution in France (Menut et al. 2012). To improve the spatial resolution from 10 to 2 km, a mesh refinement was performed using topography, land use, and road traffic data, that accounts for concentrations gradients around emission sources and variability of sources in a given mesh. Data assimilation and geostatistical analyses were also used to improve the accuracy of pollutants concentrations using local measurements (Bentayeb et al. 2014) (Fig. 1).

The mean of the annual concentrations of NO_2, PM_{10} and $PM_{2.5}$ over the 10-year period before the reference date of each woman was calculated to serve as the main exposure metric in the analyses.

2.4. Correction for possible selection bias assigning weights to cases and controls

Any difference between cases and controls in the probability of inclusion in the study based on their place of residence at the time of recruitment, particularly whether they lived in an urban or rural area, could lead to a biased estimate of the association between air pollution and breast cancer risk. To avoid such bias, each woman was assigned a weight inversely proportional to her probability of participation in the study, based on her canton of residence during recruitment. The *départements* of *Côte d'Or* and *Ille-et-Vilaine* are subdivided in 18 and 20

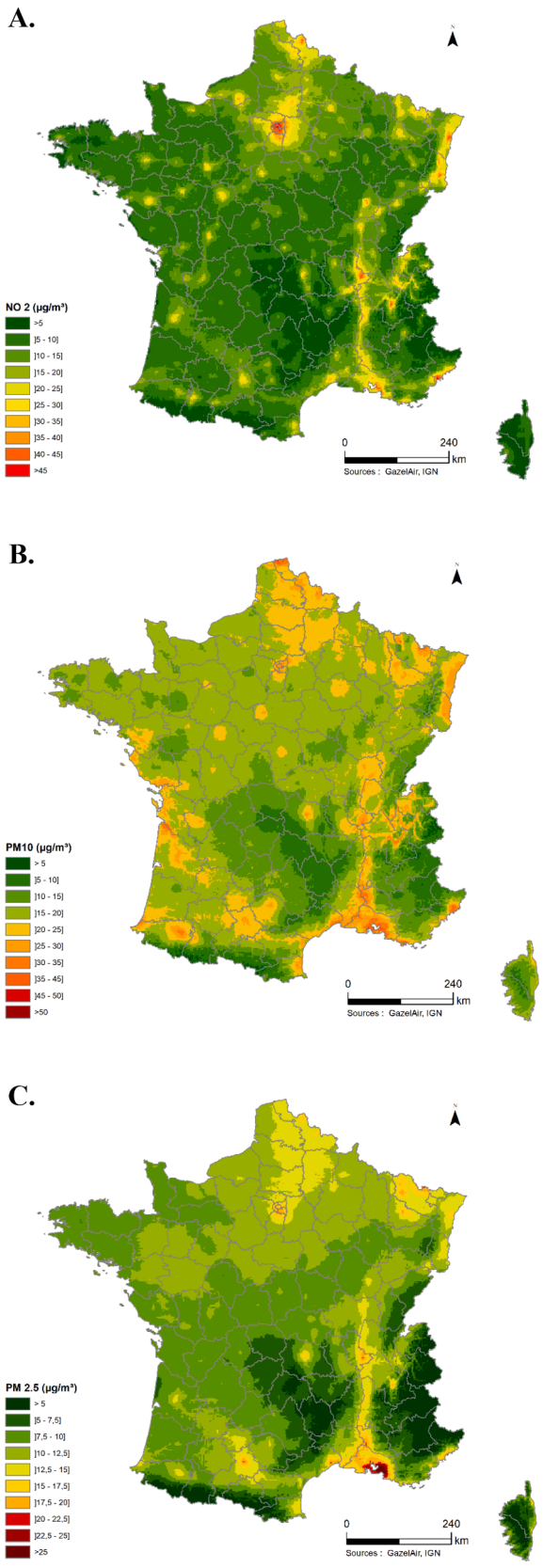

Fig. 1. Air pollutant concentrations (annual averages for NO_2 (A), PM_{10} (B) and $PM_{2.5}$ (C)). Estimates were derived from the Gazel-air model for the year 2000 (France).

cantons, respectively. The weights were calculated for each *département* and for the cases and controls separately, as the ratio between the proportion of women living in a given canton in the general population and the proportion of women living in that *canton* in the study sample. The weight assigned to a woman was thus greater than 1 if she lived in a *canton* that was under-represented in the study sample, and <1 if she lived in a *canton* that was over-represented. To assign weights to the cases in *Côte d'Or*, the distribution by canton of all incident breast cancer cases in the study period was made available from the local cancer registry. In *Ille-et-Vilaine*, where no cancer registry was available, incident breast cancer cases were actively searched in the medical records of all public hospitals and private clinics treating breast cancer patients, leading to a high inclusion rate of incident breast cancer patients into the study. Because the probability of recruitment of the cases was unlikely to vary greatly by canton of residence in Ille-et-Vilaine, a weight of 1 was assigned to all cases in this area. To assign weights to the controls in both *Ille-et-Vilaine* and *Côte d'Or*, we used the distribution by age and canton of the general female population in 2010, available from the Population Census (https://www.insee.fr/fr/statistiques/1893204).

2.5. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (95% CI) for breast cancer associated with 10-year mean annual exposures to NO_2, PM_{10} and $PM_{2.5}$ were estimated from unconditional logistic regression models, using the woman-specific weights as mentioned above. Exposure to each pollutant was categorized using quintiles of exposure among controls as cut-offs and trend tests were performed by fitting models where the median value of each quintile was introduced as a quantitative variable. We also expressed exposure as a continuous variable in multivariate models and estimated odds ratios for each increment of 10 $\mu g/m^3$ for NO_2 and 1 $\mu g/m^3$ for PM_{10} and $PM_{2.5}$, consistent with the interquartile ranges of pollutant levels among controls. ORs were adjusted for the matching variables (i.e., age (continuous) and study area (*Côte d'Or*, *Ille-et-Vilaine*)). Models were further adjusted for potential confounders selected among established breast cancer risk factors using stepwise logistic regression models to avoid collinearity between variables (history of breast cancer in first degree relatives, parity, age at first full-term pregnancy, current use of hormone replacement therapy and physical activity). Stratified analyses according to menopausal status were also conducted, and interactions were tested using likelihood ratio tests comparing models with and without an interaction term. To analyze possible differences by tumor subtype, we conducted multinomial logistic regressions by dichotomizing breast cancers as hormone positive (ER+ or PR+) or hormone negative (ER- and PR-) tumors. These subtypes were further subdivided according to HER2 status (HER2+ or HER2-), which was however missing in 214 cases (17%).

Sensitivity analyses using alternative methods to control for potential selection bias by place of residence were also conducted from logistic regression models using no weight but adjusting for urbanization level of the place residence at recruitment. Urbanization level was defined in four classes (main city center, suburb, medium-sized town, rural area) (https://www.insee.fr/fr/information/2571258).

3. Results

The distribution of breast cancer risk factors among cases and controls are presented in Table 1. As expected, the distributions by age and study area (the matching variables) were similar in the two groups. Cases had more often than controls a family history of breast cancer, had later age at first child birth, earlier age at menarche, lower parity, were more often current users of hormone replacement therapy and were more often physically inactive.

The mean and median concentrations of air pollutants during the last 10 years are presented in Table 2. NO_2 concentrations were higher in

Table 1
Distribution of breast cancer risk factors among study participants by case-control status.

	Cases (n = 1,201)		Controls (n = 1,292)		p†
	N	%	*N*	%	
Study area (département)					
Côte d'Or	379	31.6%	449	34.8%	
Ille-et-Vilaine	822	68.4%	843	65.2%	*0.10*
Mean age (sd)	55.4 (10.6)		55.4 (11.0)		*0.94*
Family history of cancer in first degree relatives					
No	996	82.9%	1153	89.2%	
Yes	205	17.1%	139	10.8%	*<0.01*
Mean age at menarche (sd)	12.9 (1.6)		13.1 (1.7)		*0.01*
Parity					
0	129	10.7%	84	6.5%	
1	186	15.5%	169	13.1%	
2	475	39.6%	460	35.6%	
≥3	411	34.2%	579	44.8%	*<0.01*
Mean age at first child birth(sd)*	24.7 (4.3)		24.0 (3.9)		*<0.01*
Duration of breastfeeding (weeks)*					
Never	531	49.9%	578	48.0%	
<26	392	36.8%	446	37.0%	
26–52	92	8.7%	114	9.5%	
≥52	49	4.6%	67	5.5%	*0.60*
Oral contraceptive use					
Never	381	31.7%	378	29.3%	
Ever	820	68.3%	913	70.7%	*0.19*
Hormone replacement therapy**					
Never	356	49.2%	389	48.1%	
Current user	147	20.3%	124	15.4%	
Former user	221	30.5%	295	36.5%	*0.01*
Body Mass Index (kg/m²)					
Premenopausal women					
<24.9	356	74.8%	314	65.0%	
25.0–29.9	84	17.6%	117	24.2%	
≥30	36	7.6%	52	10.8%	*<0.01*
Postmenopausal women					
<24.9	378	52.3%	430	53.3%	
25.0–29.9	223	30.9%	237	29.4%	
≥30	121	16.8%	140	16.3%	*0.81*
Smoking status					
Never smoker	738	61.5%	791	61.3%	
Former smoker	255	21.2%	292	22.6%	
Current smoker	208	17.3%	207	16.1%	*0.56*
Lifetime alcohol consumption (drinks/week)					
0–3	936	77.9%	976	75.5%	
4–7	152	12.7%	183	14.2%	
≥8	113	9.4%	133	10.3%	*0.42*
Physical activity					
Inactive	390	32.8%	365	28.3%	
Active	800	67.2%	924	71.7%	*0.02*

**among parous women.*
***among postmenopausal women.*
† p-*values derived from* χ^2 *for categorical variables* and from *t-test for continuous variables.*

Table 2
Mean concentrations (μg/m³) of NO_2, PM_{10} and $PM_{2.5}$ among cases and controls by study area and urbanization level.

	Cases			Controls		
Pollutant (μg/m³)	n	Mean (sd)	Q2 (Q1-Q3)	n	Mean (sd)	Q2 (Q1-Q3)
NO_2	1,201	17.2 (6.9)	16.0 (11.1-21.9)	1,292	16.8 (7.0)	15.2 (10.8-21.5)
NO_2 by study area						
Côte d'Or	379	21.0 (8.1)	21.9 (14.8–25.9)	449	20.4 (8.1)	20.2 (13.7–25.4)
Ille&Vilaine	822	15.4 (5.5)	14.0 (10.7–19.6)	843	14.9 (5.4)	13.2 (10.5–18.9)
NO_2 by urbanization level						
Main city	405	21.2 (6.8)	21.8 (16.3–25.1)	360	21.3 (6.9)	21.6 (16.1–25.1)
Suburb	214	20.5 (6.0)	19.6 (17.2–24.4)	188	20.7 (6.8)	19.8 (16.8–24.5)
Small town	256	13.9 (4.0)	13.2 (10.7–16.2)	280	14.1 (4.1)	13.3 (10.9–16.5)
Rural area	326	12.6 (5.0)	10.7 (9.4–14.5)	464	12.6 (4.7)	10.7 (9.5–14.5)
PM_{10}	1,201	21.7 (1.6)	21.5 (21.1-22.2)	1,292	21.6 (1.6)	21.6 (21.1-22.2)
PM_{10} by study area						
Côte d'Or	379	21.6 (2.4)	21.9 (20.3–23.4)	449	21.6 (2.4)	21.8 (19.9–23.6)
Ille&Vilaine	822	21.7 (1.0)	21.5 (21.2–21.9)	843	21.7 (1.0)	21.5 (21.2–21.9)
PM_{10} by urbanization level						
Main city	405	21.9 (1.5)	21.4 (21.1–22.4)	360	21.9 (1.6)	21.4 (21.1–22.5)
Suburb	214	21.8 (1.2)	21.5 (21.2–22.1)	188	22.0 (1.4)	21.5 (21.2–22.6)
Small town	256	21.7 (1.1)	21.5 (21.0–21.9)	280	21.6 (1.3)	21.5 (21.1–21.9)
Rural area	326	21.3 (2.0)	21.8 (21.1–22.2)	464	21.2 (1.8)	21.7 (20.8–22.2)
$PM_{2.5}$	1,201	13.7 (1.3)	13.8 (12.9-14.7)	1,292	13.6 (1.3)	13.7 (12.9-14.6)
$PM_{2.5}$ by study area						
Côte d'Or	379	13.3 (1.6)	13.5 (12.6–14.5)	449	13.2 (1.5)	13.4 (12.3–14.4)
Ille&Vilaine	822	13.8 (1.1)	13.9 (13.0–14.7)	843	13.8 (1.1)	13.8 (13.1–14.6)
$PM_{2.5}$ by urbanization level						
Main city	405	14.2 (1.2)	14.6 (13.6–14.9)	360	14.2 (1.2)	14.7 (13.6–14.9)
Suburb	214	14.2 (0.9)	14.5 (13.9–14.8)	188	14.2 (1.0)	14.4 (13.7–14.8)
Small town	256	13.2 (1.1)	13.3 (12.3–13.9)	280	13.3 (1.1)	13.5 (12.7–14.0)
Rural area	326	13.0 (1.3)	13.1 (12.5–13.7)	464	12.9 (1.2)	13.1 (12.3–13.6)

Côte d'Or than in *Ille-et-Vilaine* regardless of the case-control status, and were higher in the main cities than in rural areas in both *départements*. Overall, exposure to NO_2 was slightly higher among cases (17.2 μg/m³) than controls (16.8 μg/m³). Exposure to PM_{10} and $PM_{2.5}$ was similar in the two groups (21.7 vs 21.6 and 13.7 vs 13.6 μg/m³ respectively) and in the two study areas, and did not change noticeably with urbanization level. Spearman correlation coefficients were 0.74 between NO_2 and $PM_{2.5}$ exposures, 0.21 between NO_2 and PM_{10}, and 0.38 between PM_{10} and $PM_{2.5}$.

The odds ratios associated with NO_2, PM_{10} and $PM_{2.5}$ are presented in Table 3. Odds ratios were adjusted for the matching variables only (age and *département*) in Model 1, and further adjusted for selected breast cancer risk factors in Model 2. The odds ratios decreased only slightly in Model 2. In this model, the odds ratio for breast cancer in the highest NO_2 quintile vs the lowest was 1.41 (95% CI, 1.07, 1.86) (p trend 0.04), and the odds ratio per 10-μg/m³ increment of NO_2 was 1.11 (95% CI, 0.98, 1.26). For PM_{10}, the odds ratio in the highest exposure quintile was 1.20 (95% CI, 0.93, 1.55) and the odds ratio per 1-μg/m³ PM_{10} exposure increment was 1.01 (95% CI, 0.96, 1.06). For $PM_{2.5}$ the corresponding odds ratios were 1.00 (95% CI, 0.77, 1.31) and 1.02 (95% CI, 0.95, 1.08), respectively.

In Table 4 the odds ratios are shown for pre- and post-menopausal women separately. The odds ratio per 10-μg/m³ increment of NO_2 was slightly higher in post-menopausal (1.14; 95% CI, 0.97, 1.33), than in pre-menopausal women (1.09; 95% CI, 0.89, 1.35) (interaction p-value 0.46). No association of PM_{10} or $PM_{2.5}$ exposure levels with breast cancer was apparent in either pre- or post-menopausal women.

Table 5 shows the odds ratios for specific breast cancer subtypes defined as either hormone receptor positive (ER+ or PR+) or hormone receptor negative (ER– and PR–). Odds ratios associated with NO_2 were increased for ER+/PR+ tumors (OR 1.15, 95% CI 1.00, 1.31), particularly in post-menopausal women (OR 1.19, 95% CI 1.01, 1.42), but not

Table 3
Odds ratios associated with mean exposure to NO_2, PM_{10} and $PM_{2.5}$ during the last 10 years, derived from models using weights inversely proportional to selection probability of study subjects.

Variable	Cases /controls	Model 1† OR	95% CI	p trend	Model 2‡ OR	95% CI	p trend
NO_2 (μg/m^3)							
<10.4	197/275	1.00			1.00		
10.4–13.0	234/282	1.15	0.89, 1.49		1.20	0.93, 1.56	
13.1–17.7	246/261	1.22	0.94, 1.57		1.20	0.92, 1.56	
17.8–22.4	254/236	1.26	0.98, 1.62		1.19	0.91, 1.55	
≥22.5	270/238	1.45	1.11, 1.89	*0.01*	1.41	1.07, 1.86	*0.04*
Per 10 μg/m^3		*1.15*	*1.02, 1.30*		*1.11*	*0.98, 1.26*	
PM_{10} (μg/m^3)							
<21.0	209/299	1.00			1.00		
21.0–21.3	285/219	1.49	1.14, 1.94		1.45	1.11, 1.91	
21.4–21.6	200/246	0.97	0.74, 1.27		0.95	0.72, 1.26	
21.7–22.3	238/267	1.11	0.85, 1.44		1.15	0.88, 1.51	
≥22.4	269/261	1.25	0.97, 1.60	*0.26*	1.20	0.93, 1.55	*0.36*
Per 1 μg/m^3		*1.01*	*0.96, 1.06*		*1.01*	*0.96, 1.06*	
$PM_{2.5}$ (μg/m^3)							
<12.6	212/283	1.00			1.00		
12.6–13.3	228/295	0.90	0.70, 1.16		0.92	0.71, 1.19	
13.4–13.9	233/243	1.08	0.83, 1.39		1.06	0.82, 1.38	
14.0–14.7	303/267	1.13	0.88, 1.45		1.09	0.85, 1.40	
≥14.8	225/204	1.10	0.85, 1.42	*0.18*	1.00	0.77, 1.31	*0.56*
Per 1 μg/m^3		*1.04*	*0.98, 1.11*		*1.02*	*0.95, 1.08*	

†*Model 1: odds ratios adjusted for age* and *study area.*
‡*Model 2: odds ratios further adjusted for family history of breast cancer in first degree relatives, age at menarche, parity, age at first full-term pregnancy, current use of hormone replacement therapy for postmenopausal women, physical activity.*

for ER–/PR– tumors (OR 0.87, 95% CI 0.60, 1.28). Further breakdown by HER2+ or HER2– status did not reveal a higher risk of breast cancer with either of these subtypes. No association with PM_{10} or $PM_{2.5}$ emerged regardless of the breast cancer subtype.

We also examined the association with air pollution for invasive and *in situ* breast tumors separately (Supplemental **Table S1**). Invasive tumors included 1,066 cases (89% of the total sample) and odds ratios were similar to those for the total sample. For *in situ* breast tumors (135 cases), the odds ratio per 10-μg/m^3 NO_2 was close to 1 with wide confidence interval (OR 1.02; 95% CI 0.77, 1.35) and no association was apparent for PM_{10} or $PM_{2.5}$.

To see whether breast cancer risk was more specifically associated with a specific exposure window during the 10-year period before diagnosis, we calculated the mean exposure to air pollutants in the two successive 5-year periods before the reference date. The odds ratios were similar for the two 5-year exposure periods considered. They revealed no relevant etiologic window, and provide no evidence of a lag-time period between exposure and breast cancer incidence (Supplemental **Table S2**).

4. Discussion

We found that exposure to NO_2 in the last 10-year period before diagnosis was associated with increased incidence of breast cancer. Although the association was slightly higher in post-menopausal than in premenopausal women, the evidence that the risk differed by menopausal status was weak. However, we found that exposure to NO_2 was associated with an increased risk of hormone-dependent breast tumors (ER+/PR+), while no association was seen with tumors that were negative for both ER and PR. There was no evidence of an association between exposure to PM_{10} or $PM_{2.5}$ and breast cancer risk.

4.1. Nitrogen oxides

A major source of NO_x/NO_2 in air is fossil fuel combustion arising from power generation plants and heat-engine vehicle traffic. As such, NO_x and NO_2 are considered as good road traffic tracers. Although the intrinsic carcinogenicity of NO_2 is still unclear (Huynh et al. 2015; Yaghjyan et al. 2017), it may represent a marker of exposure to mixtures of components with hormonal or carcinogenic properties, such as PAHs, benzo(a)pyrene (BaP), benzene, metals and other chemicals, some of these possibly acting on breast tissue.

Breast cancer in relation to NO_2 was investigated in case-control studies, all of them from Canada (Crouse et al. 2010; Hystad et al. 2015; Goldberg et al. 2017), in cohort studies (Raaschou-Nielsen et al. 2011; Reding et al. 2015; Andersen et al. 2017b; a; Goldberg et al. 2019; White et al. 2019; Cheng et al. 2020), and in studies based on population registers (Hwang et al., 2020; Bai et al., 2020) or on health care system databases (Datzmann et al. 2018). In the case-control studies, exposure to NO_2 was estimated from Land Use Regression (LUR) modeling at the time of diagnosis (Crouse et al. 2010; Goldberg et al. 2017), or during the preceding 20-year period (Hystad et al. 2015). In the later study, NO_2 was also assessed using satellite-derived observations and historical fixed-site measurements (Hystad et al. 2015). The odds ratios for breast cancer were 1.33 (95% CI, 1.00, 1.77) in Crouse et al. (Crouse et al. 2010), 1.07 (95% CI, 0.83, 1.39) in Goldberg et al. (Goldberg et al. 2017), and 1.04 (95% CI, 0.95, 1.14) in Hystad et al. (Hystad et al. 2015) per increase of 10 μg/m^3. These results are in line with our estimated odds ratio of 1.11 (95% CI, 0.98, 1.26) estimated over the 10-year period before diagnosis.

Cohort studies assessed NO_2 exposure using LUR modeling and reported mixed findings. In the ESCAPE study on post-menopausal women recruited in 15 cohort studies in 9 European countries, the hazard ratios were 1.02 per 10-μg/m^3 increase of NO_2 (95% CI, 0.98, 1.07), and 1.04 per 20-μg/m^3 increase of NO_x (95% CI, 1.00, 1.08) (Andersen et al. 2017b). No significant association was observed between NO_2 and breast cancer risk in cohort studies from Denmark (Raaschou-Nielsen et al. 2011; Andersen et al. 2017a) and in the Multiethnic cohort (Cheng et al. 2020). However, NO_2 was associated with breast cancer in the Sister Study cohort (White et al. 2019) and with pre-menopausal breast cancer in the Canadian National Breast Screening Study (Goldberg et al. 2019). Among studies based on population-registers of cancer incidence, a positive association of NO_2 with breast cancer incidence was reported in the nationwide ecological study in South-Korea (Hwang et al. 2020), and in study based on health care register databases from Saxony, Germany (Datzmann et al. 2018) but not from Ontario, Canada (Bai et al., 2020).

Overall, the findings from cohort or case-control studies, including our own, are suggestive of an association between NO_2 exposure and breast cancer. Exposure to NO_2 can be seen as a proxy for exposure to traffic-related air pollutants and may not be a direct cause of breast cancer. Additional evidence for a role of traffic-related air pollution is provided by studies showing that breast cancer risk increases with proximity to roadways and traffic volume (Hart et al. 2016; Shmuel et al. 2017; Cheng et al. 2020). Further studies are needed to identify the pollutants emitted by car traffic or their mixtures that could explain the

Table 4
Odds ratios associated with mean exposure to NO_2, PM_{10} and $PM_{2.5}$ during the last 10 years by menopausal status (odds ratios are derived from models using weights inversely proportional to selection probability of study subjects)

	Premenopausal women					Postmenopausal women				
Variable	Cases	Controls	OR†	95% CI	p trend	Cases	Controls	OR†	95% CI	p trend
NO_2 (μg/m^3)										
<10.4	82	93	1.00			115	182	1.00		
10.4–13.0	96	103	1.12	0.73, 1.72		138	179	1.29	0.92, 1.81	
13.1–17.7	87	104	0.91	0.59, 1.40		159	157	1.46	1.04, 2.04	
17.8–22.4	103	92	0.99	0.64, 1.52		151	144	1.35	0.96, 1.89	
≥22.5	109	92	1.35	0.85, 2.13	*0.29*	161	146	1.51	1.07, 2.15	*0.06*
Per 10 μg/m^3			*1.09*	*0.89, 1.35*				1.14	0.97, 1.33	
PM_{10} (μg/m^3)										
<21.0	72	94	1.00			137	205	1.00		
21.0–21.3	98	80	1.20	0.74, 1.93		187	139	1.61	1.15, 2.25	
21.4–21.6	80	90	0.93	0.58, 1.48		120	156	0.96	0.68, 1.36	
21.7–22.3	105	105	1.17	0.75, 1.83		133	162	1.12	0.80, 1.58	
≥22.4	122	115	1.19	0.78, 1.80	*0.44*	147	146	1.22	0.88, 1.68	*0.56*
Per 1 μg/m^3			*1.03*	*0.95,1.12*				*0.99*	*0.93, 1.06*	
$PM_{2.5}$ (μg/m^3)										
<12.6	77	94	1.00			135	189	1.00		
12.6–13.3	82	102	0.92	0.59, 1.43		146	193	0.92	0.67, 1.27	
13.4–13.9	98	100	1.03	0.67, 1.57		135	143	1.09	0.78, 1.53	
14.0–14.7	134	109	1.17	0.77, 1.77		169	158	1.05	0.76, 1.44	
≥14.8	86	79	0.96	0.61, 1.50	*0.70*	139	125	1.05	0.75, 1.47	*0.55*
Per 1 μg/m^3			*1.05*	*0.94, 1.16*				1.00	*0.92, 1.09*	

†*Odds ratios adjusted for age, study area, family history of breast cancer in first degree relatives, age at menarche, parity, age at first full-term pregnancy, current use of hormone replacement therapy (in postmenopausal women), physical activity.*

Table 5
Odds ratios of breast cancer by tumor subtypes defined according to estrogen (ER), progesterone (PR) and Human Epidermal growth factor Receptor 2 (HER2) associated with mean exposure to NO_2, PM_{10}, $PM_{2.5}$ during the past 10 years.

	All women			Premenopausal women			Postmenopausal women		
Variable	Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
NO_2 (per 10 μg/m^3)									
ER+/PR+	955	1.15	1.00, 1.31	367	1.09	0.87, 1.37	588	1.19	1.01, 1.42
Her2+	*92*	*1.21*	*0.88, 1.67*	*44*	*1.11*	*0.66, 1.84*	*48*	*1.34*	*0.88, 2.06*
Her2–	*733*	*1.17*	*1.02, 1.36*	*275*	*1.11*	*0.87, 1.42*	*458*	*1.23*	*1.02, 1.48*
ER-/PR-	163	0.95	0.72, 1.26	74	1.07	0.70, 1.64	89	0.87	0.60, 1.28
Her2+	*41*	*0.71*	*0.40, 1.26*	*19*	*0.56*	*0.23, 1.38*	*22*	*0.88*	*0.41, 1.86*
Her2–	*100*	*1.05*	*0.75, 1.48*	*47*	*1.29*	*0.79, 2.11*	*53*	*0.85*	*0.53, 1.38*
PM_{10} (per 1 μg/m^3)									
ER+/PR+	955	1.00	0.95, 1.06	367	1.04	0.95, 1.14	588	0.98	0.91, 1.05
Her2+	*92*	*1.04*	*0.92, 1.18*	*44*	*1.18*	*0.98, 1.42*	*48*	*0.96*	*0.81, 1.14*
Her2–	*733*	*1.00*	*0.94, 1.06*	*275*	*1.03*	*0.93, 1.13*	*458*	*0.99*	*0.91, 1.06*
ER-/PR-	163	1.01	0.90, 1.13	74	0.98	0.82, 1.17	89	1.03	0.89, 1.21
Her2+	*41*	*0.94*	*0.74, 1.18*	*19*	*0.80*	*0.55, 1.16*	*22*	*1.06*	*0.78, 1.43*
Her2–	*100*	*1.06*	*0.92, 1.21*	*47*	*1.05*	*0.86, 1.28*	*53*	*1.05*	*0.87, 1.27*
$PM_{2.5}$ (per 1 μg/m^3)									
ER+/PR+	955	1.03	0.96, 1.10	367	1.06	0.94, 1.18	588	1.02	0.93, 1.11
Her2+	*92*	*1.10*	*0.93, 1.30*	*44*	*1.20*	*0.94, 1.53*	*48*	*1.05*	*0.84, 1.32*
Her2–	*733*	*1.05*	*0.97, 1.13*	*275*	*1.07*	*0.94, 1.21*	*458*	*1.04*	*0.95, 1.14*
ER-/PR-	163	0.98	0.85, 1.12	74	1.01	0.82, 1.24	89	0.96	0.79, 1.15
Her2+	*41*	*0.79*	*0.60, 1.03*	*19*	*0.63*	*0.42, 0.95*	*22*	*0.94*	*0.65, 1.36*
Her2–	*100*	*1.05*	*0.89, 1.24*	*47*	*1.15*	*0.91, 1.46*	*53*	*0.95*	*0.75, 1.20*

ER+/PR+ = ER positive or PR positive; ER-/PR- = ER negative and PR negative; HER2 status is missing in 130 ER+/PR + breast tumors and in 22 ER-/PR- breast tumors. Odds ratios adjusted for age, study area, family history of breast cancer in first degree relatives, age at menarche, parity, age at first full-term pregnancy, current use of hormone replacement therapy for postmenopausal women, physical activity.

link with breast cancer risk.

4.2. Particulate matter

PM may be anthropogenic and produced from heating, traffic (particularly diesel-engine vehicles), industry, agriculture, or may be of natural origin. As a mixture, carcinogenic chemicals such as benzo[a] pyrene (B[a]P) and other polycyclic aromatic hydrocarbons (PAHs) can also bind to PM (Ravindra et al. 2001). Particulate matter was classified as carcinogenic by IARC, based on epidemiological studies showing a

consistent association with lung cancer risk (IARC 2016). To our knowledge, breast cancer risk in relation to PM exposure was investigated only in cohort studies (Reding et al. 2015; Hart et al. 2016; Andersen et al. 2017b; a; Villeneuve et al. 2018; White et al. 2019; Hwang et al. 2020; Cheng et al. 2020; Bai et al., 2020), based on LUR modeling (Reding et al. 2015; Hart et al. 2016; Andersen et al. 2017b; White et al., 2019), kriging (Cheng et al. 2020), dispersion modeling (Andersen et al. 2017a; Cheng et al. 2020), or satellite-based estimates (Villeneuve et al. 2018). In the ESCAPE project, a modest non-significant increase of breast cancer incidence was observed for $PM_{2.5}$ (HR 1.08, 95% CI, 0.77, 1.51 per 5-μg/m^3 increase) and PM_{10} (HR 1.07, 95% CI, 0.89, 1.30 per 10-μg/m^3 increase) (Andersen et al. 2017b). In the Multiethnic cohort study (Cheng et al. 2020), breast cancer was positively associated with PM_{10} and $PM_{2.5}$, particularly in women living within 500 m of major roads. The South-Korean study reported an odds ratio of 1.13 (95% CI, 1.09, 1.17) per 10-μg/m^3 PM_{10}, but consideration of covariates at the ecological level was a strong limitation in this study (Hwang et al. 2020). PM_{10} and $PM_{2.5}$ were not found to be associated with breast cancer in other cohort studies.

Unlike NO_2, only weak and inconsistent increases in breast cancer risk associated with PM were reported in the literature. This could be explained by the low spatial variability of PM (compared to NO_2) that strongly limits its potential as a proxy for assessing causal exposure and hence that does not make it a sensitive marker for identifying chronic effects. Because only certain specific components of PM may be responsible for an increase in breast cancer incidence, the inconsistent findings may be explained by the variable composition of PM between studies. In the US nationwide Sister Study, breast cancer risk varied according to geographic location in the US and clusters defined by $PM_{2.5}$ composition (White et al. 2019). In the ESCAPE project, the analysis of the elemental composition of PM showed that the nickel and vanadium components of both PM_{10} and $PM_{2.5}$ were associated with increased breast cancer risk (Andersen et al. 2017b). Further investigation is thus warranted to investigate in more details the role of PM components in breast cancer incidence.

4.3. Menopausal status

In our study, the association between NO_2 and breast cancer was slightly higher in postmenopausal than in premenopausal women, but the difference was very small (interaction p-value, 0.46). While some studies reported no increased risk associated with NO_2 in either group (White et al. 2019; Bai et al., 2020), a few others reported an association with breast cancer in premenopausal women (Hystad et al. 2015; Goldberg et al. 2019). Exposure to $PM_{2.5}$ was also associated with higher breast cancer risk in pre- than in post-menopausal women (Hart et al. 2016; Andersen et al. 2017a; Villeneuve et al. 2018), but the findings have been inconsistent. Whether air pollution affects breast cancer risk differently according to menopausal status remains unclear and requires further scrutiny.

4.4. Hormone receptor status and plausible biological mechanisms

We found that NO_2 increased the risk of hormone-dependent ER+/PR + breast tumors, but not ER-/PR- tumors. To our knowledge, our study is the first to examine the relationship between air pollutants and breast cancer subtypes defined by the HER2 receptor status, but the existence of a specific risk profile in relation to HER2 expression was not found. Because the breast cancer tumor subtype seems to be determined at the time of tumor initiation (Lacroix et al. 2004), the receptor status of the breast tumor might reflect the etiologic pathway that led from exposure to cancer development. The finding of an association with hormone-dependent tumors in our study is in line with previous studies reporting an association between NO_x/NO_2 and ER+/PR + breast cancer subtypes (Reding et al. 2015; Goldberg et al. 2017; Cheng et al. 2020), suggesting that traffic-related air pollutants associated with NO_2 might act as mammary carcinogens through hormonal mechanisms. Besides, ER-/PR- breast tumors have been associated with exposure to benzene (Garcia et al. 2015), traffic-related benzo(a)pyrene (Mordukhovich et al. 2016a), or long-term low-dose exposure to ambient cadmium compounds (Liu et al. 2015), suggesting that some pollutants may also affect breast cancer risk through non-hormonal mechanisms.

Although the precise mechanism by which air pollutants may affect breast cancer incidence are not known, exposure to PAHs represents a possible cause of mammary carcinogenesis. PAHs are present in ambient air and are lipophilic compounds that accumulate in breast tissue (Morris and Seifter 1992). They have estrogenic or anti-estrogenic properties (Darbre 2018) and induce mammary tumors in animal studies (Rodgers et al. 2018). They are also genotoxic and cause DNA damage through the formation of PAH-DNA adducts (Gray et al. 2017; Rodgers et al. 2018). An increase in breast cancer risk has been associated with traffic-related benzo[a]pyrene used as a proxy of traffic-related PAHs (Mordukhovich et al. 2016a; White et al. 2016), particularly among women with selected biologically plausible DNA repair genotypes (Mordukhovich et al. 2016b). It is also possible that traffic-related air pollutants lead to high risk of breast cancer through DNA-methylation processes. This hypothesis is supported by studies showing that global hypomethylation was associated with NO_x and NO_2 (Plusquin et al. 2017) and that high epigenome-wide DNA methylation in pre-diagnostic blood samples was associated with lower risk of breast cancer (van Veldhoven et al. 2015).

4.5. Invasive vs in situ breast tumors

Exposure to air pollutants was not associated with *in situ* breast tumors in our data. The odds ratios were close to 1 with wide confidence intervals and did not significantly differ from those for invasive tumors. Our results do not confirm the findings of the Sister Study cohort that reported associations of NO_2 and $PM_{2.5}$ with ductal carcinomas *in situ* (DCIS) but not with invasive tumors (White et al. 2019). In the Long Island Breast Cancer Study, exposure to traffic-related B[a]P was also stronger for *in situ* carcinomas than for invasive tumors (Mordukhovich et al. 2016a). The higher risk for DCIS in these studies remains unexplained and deserves further investigations.

4.6. Study strengths and weaknesses

Inherent to case-control studies is the potential for bias in the selection of cases and controls. This is of particular concern when the exposure of interest is strongly related to the place of residence or time, as is the case for atmospheric pollutants. To our knowledge, most former case-control studies relating atmospheric pollutants and breast cancer did not explicitly consider this issue. In our study, we were able to accurately control for a potential selection bias arising from differential recruitment probability of cases and controls with respect to their residential location within the *département*, by assigning a weight to each subject depending on the residence in one of the 18 cantons in *Côte d'Or* and 20 cantons in *Ille-et-Vilaine*. When using this weight, we considered the fact that the cases and the controls were more or less willing to participate depending on the urban or rural status of their area of residence. For cases, we were only able to calculate these weights in the *Côte d'Or* area, where a cancer registry exists, but not in *Ille-et-Vilaine*. In this area, however, incident cases were actively sought in all medical departments treating breast cancer patients with close involvement of the oncologists. We applied a weight of 1 to all cases in *Ille-et-Vilaine,* because the high inclusion rate of incident cases was likely to prevent substantial variations in recruitment probabilities between cantons.

The availability of detailed data on established breast cancer risk factors and other potential confounders, on hormonal receptors status of the cases' tumor as well as on lifetime residential history in 2,500 French women constitute other strengths of our study.

Regarding exposure characterization to air pollutants, we used the

Gazel-Air model, which provides annual averages of air pollutant levels in France from 1989 to 2008 at a scale of 2 km. We were thus able to assess exposure over a 10-year period prior to the date of cancer diagnosis, avoiding biased estimations related to particular conditions of air pollution for a given year and accounted for all residential changes during that period. A limitation of our study is that we were not able to assess air pollution in early life periods, which may be another etiologically relevant period (Fenton and Birnbaum 2015). Although the adult period remains a relevant time period to study, previous investigations also reported associations between breast cancer risk and exposure to air pollutants or vehicular traffic-related air pollution at birth (Bonner et al. 2005), during childhood (Shmuel et al. 2017), or adolescence (Nie et al. 2007). Another limitation of the study includes the lack of time-activity pattern information, that did not allow us to consider exposure to air pollutants at work and in transport.

5. Conclusion

Our results indicate that exposure to NO_2, a marker of motor-vehicle traffic pollution, may increase the risk of breast cancer. The stronger association with hormone receptor-positive breast tumors suggests a role in disease etiology of specific airborne pollutants with hormonal effects. These results confirm the importance of reducing air pollution, especially those related to road traffic emissions.

Declaration of Competing Interest

The authors 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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Author Contributions

Pascal Guénel: Study design and conceptualization, supervision, project administration and funding acquisition. **Rémy Slama:** Study conceptualization. **Nastassia Tvardik:** Data management. **Sylvie Cénée and Nastassia Tvardik:** Data geocoding. **Clémentine Lemarchand:** conducted the statistical analysis and wrote the original draft of the manuscript. **All authors:** Manuscript – review and editing, final draft approbation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106604.

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