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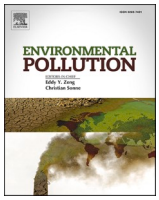

Long-term exposure to nitrogen dioxide air pollution and breast cancer risk: A nested case-control within the French E3N cohort study☆

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A B S T R A C T

Nitrogen dioxide (NO_2) is an important air pollutant due to its adverse effects on human health. Yet, current evidence on the association between NO_2 and the risk of breast cancer lacks consistency. In this study, we investigated the association between long-term exposure to NO_2 and breast cancer risk in the French E3N cohort study. Association of breast cancer risk with NO_2 exposure was assessed in a nested case-control study within the French E3N cohort including 5222 breast cancer cases identified over the 1990–2011 follow-up period and 5222 matched controls. Annual mean concentrations of NO_2 at participants' residential addresses for each year from recruitment 1990 through 2011, were estimated using a land use regression (LUR) model. Multivariable conditional logistic regression models were used to compute odds ratios (ORs) and their 95% confidence intervals (CIs). Additional analyses were performed using NO_2 concentrations estimated by CHIMERE, a chemistry transport model. Overall, the mean NO_2 exposure was associated with an increased risk of breast cancer. In all women, for each interquartile range (IQR) increase in NO_2 levels (LUR: 17.8 $\mu g/m^3$), the OR of the model adjusted for confounders was 1.09 (95% CI: 1.01–1.18). The corresponding OR in the fully adjusted model (additionally adjusted for established breast cancer risk factors) was 1.07 (95% CI: 0.98–1.15). By menopausal status, results for postmenopausal women were comparable to those for all women, while no association was observed among premenopausal women. By hormone receptor status, the OR of estrogen receptor positive breast cancer = 1.07 (95% CI: 0.97–1.19) in the fully adjusted model. Additional analyses using the CHIMERE model showed slight differences in ORs estimates. The results of this study indicate an increased risk of breast cancer associated with long-term exposure to NO_2 air pollution. Observing comparable effects of NO_2 exposure estimated by two different models, reinforces these findings.

Abbreviations: AFP, age at first full-term pregnancy; BaP, Benzo[a]pyrene; BMI, body mass index; CIs, confidence intervals; CNIL, commission for data protection and privacy; CTM, Chemistry Transport Model; DM, dispersion modeling; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ER, estrogen receptor; EPIC, European Prospective Investigation into Cancer and Nutrition; EDC, endocrine-disrupting-chemicals; FHBC, family history of breast cancer; IARC, International Agency for Research on Cancer; LUR, land use regression; MHT, menopausal hormone therapy; MET, metabolic equivalent task; NO_2, nitrogen dioxide; IGN, National Geographic Institute; ORs, odds ratios; PR, progesterone receptor; SD, standard deviation; TRAP, traffic-related air pollutants; TNM, tumor-node-metastasis.

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1. Introduction

Air pollution and breast cancer are highly prevalent public health concerns worldwide, including in France (Turner et al., 2020; White et al., 2018). In 2020, 2.3 million new breast cancer cases were estimated worldwide (Sun et al., 2017). According to the latest review on the health effects of air pollution by the World Health Organization (WHO) working group (WHO, 2013) and the International Agency for Research on Cancer (IARC) (Loomis et al., 2013), there is evidence that ambient air pollutants have several adverse effects on health including cancer. Among these pollutants, ambient nitrogen dioxide (NO_2) is strongly associated with an increased incidence and mortality of several diseases including lung cancer (Faustini et al., 2014; Hamra et al., 2015; Latza et al., 2009). However, currently available evidence regarding its association with breast cancer development remains sparse (Alotaibi et al., 2019; Huang et al., 2021). It is worth noting that NO_2 may be a marker for several other pollutants (Europe WRO for, 2013). For example, the spatial patterns of NO_2 may correlate with heavy metals from motor vehicles, which exert genotoxic, mutagenic, epigenetic, inflammatory, and endocrine-disrupting effects (Rodgers et al., 2018; White et al., 2016).

The major sources of emissions of NO_2 into the atmosphere are the combustion of fossil fuels (heating, power generation) and motor vehicle emission (Krzyzanowski and Cohen, 2008; World Health Organization, 2020). There are several nitrogen oxides (NOx) that can be found in the ambient air, namely nitrous oxide (N_2O), nitric oxide (NO), and NO_2. NO_2 is the most commonly used as a surrogate for the mixture of traffic-related pollutants in epidemiological studies (Alotaibi et al., 2019; Weuve et al., 2016). It is a strong oxidant, which absorbs visible solar radiation and contributes to impaired atmospheric visibility and the formation of photochemical smog, which can have significant impacts on human health (Krzyzanowski and Cohen, 2008; White et al., 2018; World Health Organization, 2005). Other contributions come from specific non-combustion industrial processes, such as the manufacture of nitric acid, the use of explosives and welding. To a lesser extent, NO_2 is also of concern as an indoor air pollutant, emitted from tobacco smoking and the use of gas-fired appliances and oil stoves (Braun et al., 2021; Krzyzanowski and Cohen, 2008). The main route of human exposure is inhalation, whether the source is outdoor or indoor air. However, as compared to outdoor and domestic exposures, occupational exposure is infrequent and limited to a few industrial processes (Krzyzanowski and Cohen, 2008; World Health Organization, 2005).

Although the association of NO_2 ambient air exposure has been widely studied in relation to other chronic diseases, including lung cancer, current evidence regarding breast cancer risk lacks consistency. Some supported a statistically significant increased risk of breast cancer associated with higher NO_2 exposure (Crouse et al., 2010; Hystad et al., 2015), while others reported no evidence of the association (Andersen et al., 2017a; Bai et al., 2020; Goldberg et al., 2017). In a meta-analysis of individual data from 15 European prospective cohorts, a borderline positive association with postmenopausal breast cancer was observed for ambient NO_2 (hazard ratio (HR) = 1.02 (95% CI: 0.98–1.07) per 10 $\mu g/m^3$) (Andersen et al., 2017b). A recent random-effects meta-analysis of associations between atmospheric NO_2 exposure and breast cancer incidence showed a pooled RR estimate of 1.023 (95% CI: 1.005–1.041) and estimated that 1677 (95% CI: 374–2914) new breast cancer cases were attributable to NO_2 annually in France (Gabet et al., 2021). This study suggested that decreasing long-term NO_2 exposure exposures could lower breast cancer risk (Gabet et al., 2021). Another meta-analysis of three ecological studies reported a tendency toward a weak correlation between exposure to ambient air NO_2 and breast cancer, with a pooled estimate of correlation coefficient r = 0.89 (95% CI: 0.84 to 0.95) (Keramatinia et al., 2016). Moreover, a review by White et al., (2018) reported a positive association between NO_2 and breast cancer risk, which may vary according to hormone receptor subtype (estrogen receptor/progesterone receptor (ER/PR)). The divergent results from published studies could be partially explained by heterogeneity in NO_2 exposure assessment methods, and their ability to reliably reflect the high spatial variability of NO_2 concentrations, as well as the evolution of concentrations over time; heterogeneity in study design, as well as insufficient statistical power (small sample size) in some studies. Furthermore, the differential effects of menopausal status and hormone receptor and clinicopathological subtypes on breast cancer risk have been insufficiently explored. Additionally, less is known that other factors (e.g tobacco smoking) may modify the association of BC with NO_2 exposure.

To address limitations of previous studies and improve the knowledge on the impact of chronic NO_2 exposure on breast cancer risk, this study investigated whether long-term exposure levels of ambient NO_2 estimated at the subject residential addresses, were associated with breast cancer risk, in a large nested case-control study.

2. Material and methods

2.1. The E3N cohort study

This study was based on a nested case-control study within the French national E3N cohort study (Amadou et al., 2020, 2021; Deygas et al., 2021). E3N (Etude Epidémiologique après de femmes de l'Education Nationale) is an ongoing French prospective cohort study involving 98,995 French women, between 40 and 65 years of age at inclusion in 1990, and insured by the national health insurance covering employees from the French National Education System (Mutuelle Générale de l'Education Nationale, MGEN). Details on the E3N study have been provided previously (Clavel-Chapelon, 2015). In brief, the study was initially conducted in order to investigate the etiology of cancer and severe chronic diseases in women. At time at entry, participants filled a baseline self-administered questionnaire, comprising data on socio-demographic characteristics, lifestyle (smoking and physical activity), reproductive factors (ages at menarche and menopause, use of exogenous hormones, number of children, age at first full-term pregnancy, and breastfeeding), anthropometry (height, weight, waist and hip circumference), past medical history (benign breast disease and gynecological screening), familial history of cancer, as well as an urban/rural status area (Binachon et al., 2014a). Follow-up questionnaires were sent to the women every 2–3 years thereafter (with a total of thirteen questionnaires to date, and an average participation rate of around 83%). Breast cancer cases were identified through self-reports in the questionnaires from the MGEN system or through information from death certificates. The pathological confirmation was obtained for 93% of incident breast cancer cases. Since the false-positive rate of self-reports was low in the cohort population (<5%), the present study also included the cases that were not pathologically confirmed. Women provided their fully residential addresses at the baseline (1990) and during the follow-up (from the 5th to the 10th follow-up questionnaires, corresponding to years 1997, 2000, 2002, 2005, 2008, and 2011), whereas only postal codes were provided in the 3rd and the 4th follow-up questionnaires (years 1993 and 1995). An informed consent was obtained from each participant, and the study was approved by the French National Commission for Data Protection and Privacy (CNIL).

2.2. The nested case-control study design

A total of 6298 histologically confirmed incident invasive breast cancer cases were identified in the E3N cohort during the 1990–2011 follow-up period. Similar to most previous studies on breast cancer, only invasive cases are included in the present study. Ductal carcinoma in situ (DCIS) are generally considered to be benign disease, as they are non-invasive, and confined to duct and ductal. In France, DCIS represents 15% of all breast cancers in France, with a standard treatment of breast-conserving surgery (Cutuli et al., 2020). Women who completed their home address at baseline, lived in the metropolitan French territory

(except Corsica) during the follow-up time, and were not diagnosed with any cancer at baseline, were eligible for the present study (Amadou et al., 2020). After excluding women with phyllodes tumors (N = 19), those with missing data on matching variables (N = 3), those with at least two missing addresses, as well those living abroad during follow-up time (N = 1054 cases) (Amadou et al., 2021; Deygas et al., 2021), the current study was conducted in a subsample of 5222 women with invasive breast cancer. For each breast cancer case, one control free of cancer was randomly selected by incidence density sampling, among cohort participants at risk of breast cancer at the time of case diagnosis (Amadou et al., 2020). Women with DCIS were not eligible to be included as controls. Two matchings were done according to the availability of a biological sample (blood or saliva) (Amadou et al., 2020). Controls of the first group (with a blood sample) were matched to cases on the department of residence, age (±1 year), date (±3 months), and menopausal status at blood collection. Controls of the second group (without a blood sample) were matched on the same criteria but considered at baseline, and additionally matched on the existence or not of a saliva sample. Information on ER and PR status were obtained from pathology reports (Clavel-Chapelon, 2015). ER and PR status were available for 79.8% (ER- = 760; ER+ = 3405; and unknown = 1057) and 77.4% (PR- = 1439; PR+ = 2602; and unknown = 1181) of cases, respectively. Information on the tumor-node-metastasis (TNM) stage and the breast cancer grade of differentiation were extracted from pathological reports, and were available for a total of 4733 (90.6%), and 4164 (79.7%) breast cancer cases, respectively.

2.3. NO_2 exposure assessment

This study has been conducted within the framework of the XENAIR project aiming at assessing associations between chronic exposure to selected ambient air pollutants (PM, NO_2, O_3, BaP, dioxins, PCB 153, and cadmium) and the breast cancer risk (Amadou et al., 2020). Pollutant concentrations were estimated at each residential address of each study subject from 1990 to 2011. NO_2 levels were estimated by two different models, a LUR model and a chemical transport model (CHIMERE) (Amadou et al., 2020).

LUR is a common approach used in epidemiology studies of air pollution, to model the spatial variability of air pollutants (Lee et al., 2017; Ryan and LeMasters, 2007). The model uses proximity measures such as circular buffers of varying sizes to summarize geographical features (*eg.* land use, road networks, traffic, or terrain), which explain variability in monitored concentrations around point locations (*i.e.* monitoring sites or addresses) (de Hoogh et al., 2016; Eeftens et al., 2016; Gulliver et al., 2013). In the present study, a LUR model (50 × 50 m) was developed based on average NO_2 measurements for the 2010 to 2012 period. This "baseline" model combined inputs from COPERNIC (a chemical transport model providing NO_2 background concentrations over France) and localized variables describing road traffic and land use, available nationwide (Gulliver et al., 2013; Levy et al., 2015). The LUR model has been validated against measurements across France by performing a hold-out validation (i.e. independent monitoring sites) (Gulliver et al., 2013; Levy et al., 2015). This LUR model was then back-extrapolated until 1990, using trends observed at the regional scale in NO_2 concentrations and local concentrations estimated by the above CHIMERE model for the period 2010 to 1990.

CHIMERE is a chemistry-transport model used to simulate pollutant transport from local to continental scales, with a spatial resolution of 0.125° × 0.0625° (around 7 × 7 km) (Guerreiro et al., 2016, 2014). For the present study, the model was developed by the National Institute for Industrial Environment and Risks (INERIS) (Guerreiro et al., 2016; Menut et al., 2013). This model uses emission data, meteorological fields, and boundary conditions as inputs and computes a set of equations representing the physical and chemical processes involved in the evolution of concentrations. CHIMERE simulates the gas-phase chemistry to provide concentrations of several compounds. CHIMERE considers primary particles (directly emitted as particles) that can be anthropogenic or natural, and simulates the concentrations of particles with aerodynamic diameters (ranging from a few nanometers to 10 μm) (Guerreiro et al., 2016, 2014).

Since NO_2 concentrations vary over very short distances (de Hoogh et al., 2016; Eeftens et al., 2016; Gulliver et al., 2013), the LUR model with its high spatial resolution (50 × 50 m) was used for the main analyses in the present study. Concentrations estimated by the CHIMERE model (7 × 7km) were further used for sensitivity analyses.

The ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute - ESRI, Redlands, CA, USA) and its reference street network database, BD Adresse®, from the National Geographic Institute (IGN) were used to geocode participants' residential addresses (Faure et al., 2017). Annual estimates of NO_2 concentrations from LUR and CHIMERE models were assigned to the geocoded residential addresses of subjects for each year of the 1990–2011 follow-up period. For each woman, annual mean concentration levels ($\mu g/m^3$) of NO_2 exposure at the residential address were further calculated, from their entry into the cohort to their index date. Entry into the E3N (1990) cohort is thus the starting point for the exposure assessment in the present nested case-control study. Exposure assessment is performed until the index date (corresponding to the date of breast cancer diagnosis for cases and date of selection for controls). The main analyses were based on the annual mean NO_2 concentration estimates prior to breast cancer diagnosis. The cumulative NO_2 concentration, i.e. $\sum$ of annual concentrations from entry into the cohort to the index date, was used only for sensitivity analyses to examine the robustness of the association observed.

2.4. Statistical analysis

Atmospheric exposure to NO_2, socio-demographic characteristics, and other covariates were described using mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Subject characteristics were compared between cases and controls using univariate conditional logistic regression models, in pre-menopausal and post-menopausal women at index date. The associations with the breast cancer risk were modelled using conditional logistic regression models to calculate odds ratios (OR) and their 95% confidence intervals (95% CI). The shape of the exposure-response curve between NO_2 levels and breast cancer risk was estimated using restricted cubic splines (Durrleman and Simon, 1989), with four knots (at 5th, 35th, 65th, and 95th percentiles) (Harrell, 2001). For all models the relationships were consistent with linearity, therefore continuous analyses were implemented for an increment of 1 interquartile range (IQR) level of the annual mean NO_2 in controls. Three adjusted models were considered. The first model (crude model) was conditioned on the matching factors including age, date, department of residence, and menopausal status at blood collection or baseline, and the existence of biological sample (blood, saliva, none) (model 1). French departments are administrative divisions of territories ("NUTS-3" in the classification of territorial divisions of the European Union) (Eurostat, 2021), with surface areas ranging from 105 to 10,000 km^2 (with 25th, 50th, and 75th percentiles of 5147 km^2, 5954 km^2, and 6775 km^2 respectively); and population size varying from 76,604 to 2,608,346 persons (with 25th, 50th, and 75th percentiles of 296,715, 539,049, and 850,837 persons respectively) (INSEE, 2022). Consequently, areas were considered sufficiently large to have heterogeneous NO_2 exposures levels. The second model (model 2) was adjusted for a *priori* factors that could potentially confound the association between NO_2 and breast cancer, including physical activity (<25.3, 25.3–35.5, 35.6–51.8, and ≥51.8 MET-h/w), smoking status (never, current, and former), level of education (undergraduate, 1 to 2-year university degree, ≥ 3-year university degree) and the rural/urban status at inclusion (rural, urban), selected on the basis of the literature (Andersen et al., 2017b; Braun et al., 2021; Cheng et al., 2020; Hajat et al., 2021; Hwang et al., 2020;

Milojevic et al., 2017; White et al., 2021). These variables have also been consistently used as confounders in published studies on the associations between NO_2 exposure and breast cancer (Andersen et al., 2017b; Cheng et al., 2020; Hwang et al., 2020; Reding et al., 2015; White et al., 2019). Education level was considered a confounding factor in the relation between NO_2 exposure and breast cancer risk, because it is related to socioeconomic status (Hajat et al., 2015, 2021). Similarly, the urban/-rural is both associated with air pollution (Milojevic et al., 2017) and risk of breast cancer (Binachon et al., 2014b). Concerning tobacco smoke, it contains several chemical, which have been linked to breast cancer risk (White et al., 2017). As Tobacco smoke contains NO_2 (Braun et al., 2021), people who smoke may have a higher level of NO_2 exposure as compared to non-smokers. Moreover, there is an increasing number of epidemiological studies highlighting a significant effect of smoking on the risk of breast cancer (Jones et al., 2017; Macacu et al., 2015; Reynolds, 2013). Regarding physical activity, it has been associated with levels of NO_2 exposure (Cepeda et al., 2017; Hahad et al., 2021), as well as inversely associated with risk of breast cancer (Spei et al., 2019). Doing physical activity could increase individual exposure to NO_2 air pollution, as it may increase the uptake and deposition of air pollutants in the lungs/airways and circulation, due to increased breathing frequency (Cepeda et al., 2017; Hahad et al., 2021). The third model (model 3) was further adjusted for known and important breast cancer risk factors that could potentially impact the breast cancer risk estimates (including BMI ($<$25, 25–30, and $\geq$30 kg/m^2), previous family history of breast cancer (FHBC) (yes, no), history of personal benign breast disease (yes, no), age at menarche ($<$12, 12–14, and $\geq$14 years), parity, age at first full-term pregnancy (AFP) (0, 1–2 children & AFP $<$30 years, 1–2 children & AFP $\geq$30 years, and $\geq$3 children), breastfeeding (nulliparous, ever, never), oral contraceptive use (ever, never), and menopausal hormone therapy use (MHT, ever, never)). As in the previous E3n studies, simple imputation was used (Garcia-Acosta and Clavel-Chapelon, 1999). More precisely, covariates with less than 5% of missing data of the study population, were imputed to the median (for continuous variables) or modal value (for categorical variables) of the control population data; while covariates with greater than 5% of missing values were included as a separate category (Garcia-Acosta and Clavel-Chapelon, 1999). All variables have less than 5% of missing value, except alcohol for which a category of missing data was created. Of note, alcohol consumption was collected in 1993 (at questionnaire 3 of the follow-up). Thus, the proportion of missing values (28.9%) concerned mainly women diagnosed with breast cancer before 1993, and their matched controls. Analyses were conducted for all subjects and separately according to menopausal status (pre- and post-menopausal) at the index date. Given the long etiologic window for breast cancer development and the long-term follow-up period in the present study, analyses according to menopausal status at the index date seem more relevant. However, for comparison, additional analyses according to menopausal status at inclusion were performed.

Further subgroup analyses were conducted according to hormone receptor (ER, PR) status, stage, and histology of breast cancer at diagnosis. Heterogeneity through these subgroups was evaluated using multinomial logistic regression and P values for heterogeneity were determined from Wald tests (Wang et al., 2016).

The potential effect modification by tobacco smoking status (Braun et al., 2021), urban/rural area (Milojevic et al., 2017) and family history of breast cancer history (Niehoff et al., 2022) were evaluated. The interaction tests were conducted using the likelihood ratio tests comparing models with and without the interaction term between NO_2 exposure and the putative effect modifiers.

Similar to most of the previous studies, further analyses were conducted using a standardized size increase of NO_2 exposure levels (10 μg/m^3). Additional sensitivity analyses were performed using the cumulative NO_2 exposure, obtained by cumulating women's annual NO_2 concentration levels from the entry into the cohort to their index date. We assessed the breast cancer risk associated with the exposure estimated at the baseline address (1990–1991), similar to several previous studies (Andersen et al., 2017b; Datzmann et al., 2018; Goldberg et al., 2017). To assess whether imputation of missing values affected observed associations, we repeated analyses after excluding participants with missing values in any covariate (complete-case analysis). Finally, as sensitivity analyses, we additionally performed multiple imputation to handle missing data, in order to compare findings from simple imputation. The multiple imputation takes into account the uncertainty of missing data, by creating several different sets of imputed data and suitably combining the results from each set (Sterne et al., 2009).

The statistical analyses were performed using STATA version 14 (College Station, Texas, USA). The threshold for statistical significance was set at 5%. All statistical tests were two-sided.

3. Results

3.1. Characteristics of the study population

The selection of the 10,444 subjects involved in our nested case-control study is presented in a flow chart in Supplemental Material (Fig. S1). Table 1 provides the characteristics of study participants (5222 breast cancer cases/5222 matched controls) according to the menopausal status at index date. The average age (±SD) of premenopausal and postmenopausal breast cancer cases was 44.1 (±3.0) and 50.7 (±6.2) years, respectively, as compared to 43.9 (±2.9) and 50.6 (±6.2) years for premenopausal and postmenopausal controls. In postmenopausal women, compared to controls, breast cancer cases were more likely to have a higher level of alcohol intake, to be born in an urban area, to have higher education, and to be MHT users. The proportions of women having a history of personal benign breast disease, having a family history of breast cancer, and receiving routine mammography screenings were significantly higher for postmenopausal cases as compared to postmenopausal controls. In premenopausal women, with the exception of alcohol intake, history of personal benign breast disease, family history of breast cancer, and routine mammography screenings, that were significantly higher in breast cancer cases compared to controls, the distribution of individual's characteristics were generally similar between the cases and controls.

3.2. Distribution and Evolution of NO_2 exposure estimated by LUR and CHIMERE models

The average (±SD) of annual means of NO_2 concentrations determined by the LUR model was 30.3 (±15.3) μg/m^3 during the follow-up period, ranging from 9.2 to 94.8 μg/m^3 (Fig. 1). Fig. S2 shows the evolution of annual means of NO_2 levels estimated at subjects' residences during the period of 1990–2011. Overall, the annual mean decreased over time during the study period, with the mean (±SD) ranging from 31.2 (±15.8) μg/m^3 in 1990 to 20.2 (±10.1) μg/m^3 in 2011.

The average (±SD) of annual means of NO_2 levels estimated from the CHIMERE model was 24.7 (±17.4) μg/m^3, ranging from 2.11 to 75.7 μg/m^3 (Fig. S3) and varying from 25.6 (±17.9) μg/m^3 in 1990 to 13.8 (±11.4) μg/m^3 in 2011 (Fig. 1). Overall, there was a strong correlation between the two models, with the coefficient of correlation of 0.94 between the average annual means at the individual subject level of LUR and CHIMERE models.

Fig. 2 illustrates the spatial pattern of the NO_2 concentrations estimated at baseline and at index date. According to both LUR and CHIMERE models, there is an important geographic variability of individual exposure levels, with the highest estimated NO_2 concentrations observed in the dense urban areas.

3.3. NO_2 exposure and breast cancer risk

The non-linear modeling of the relation between NO_2 exposure and

Table 1
Distribution of breast cancer risk factors among study participants by case-control and menopausal status at index date in the XENAIR case-control study nested within the E3N cohort, France, 1990–2011.

Characteristics	Premenopausal			Postmenopausal		
	Cases	Controls	P value	Cases	Controls	P value
LUR airborne NO_2 ($\mu g/m^3$), mean ± SD	31.3 ± 16.0	30.9 ± 15.4	0.424	30.4 ± 15.4	29.9 ± 15.0	0.008
CHIMERE airborne NO_2 ($\mu g/m^3$), mean ± SD	25.6 ± 18.0	25.4 ± 17.5	0.615	24.9 ± 17.6	24.1 ± 17.0	<0.001
Age (years), mean ± SD	44.1 ± 3.0	43.9 ± 2.9		50.7 ± 6.2	50.6 ± 6.2	
Alcohol drinking (g/day)						
0	49 (5.6)	51 (6.3)		353 (8.1)	422 (9.6)	
> 0–6.7	165 (18.9)	130 (16.1)		1127 (25.9)	1261 (28.5)	
≥ 6.7	218 (24.9)	181 (22.5)		1784 (41.0)	1686 (38.2)	
Missing	442 (50.6)	444 (55.1)	0.048	1086 (25.0)	1049 (23.7)	<0.001
Body Mass Index (kg/m^2)						
< 25	774 (88.6)	700 (86.9)		3556 (81.8)	3647 (82.5)	
25-30	86 (9.8)	84 (10.4)		631 (15.1)	658 (14.3)	
≥ 30	14 (1.6)	22 (2.7)	0.265	140 (3.1)	136 (3.2)	0.619
Smoking status, n (%)						
Never	448 (51.3)	413 (51.2)		2369 (54.4)	2464 (55.8)	
Current	143 (16.3)	138 (17.2)		638 (14.7)	605 (13.7)	
Former	283 (32.4)	255 (31.6)	0.672	1343 (30.9)	1349 (30.5)	0.271
Status of birthplace, n (%)						
Rural	219 (25.1)	201 (24.9)		1150 (26.4)	1229 (27.8)	
Urban	578 (66.1)	532 (66.0)		2723 (62.6)	2659 (60.2)	
Missing	77 (8.8)	73 (9.1)	0.778	477 (11.0)	530 (12.0)	0.015
Residential status at inclusion, n (%)						
Rural	279 (31.9)	282 (35.0)		1279 (29.4)	1310 (29.7)	
Urban	595 (68.1)	524 (65.0)	0.419	3069 (70.6)	3106 (70.3)	0.787
Physical activity (METs-h/week), n (%)						
< 25.3	229 (26.2)	210 (26.1)		1075 (24.7)	1019 (23.1)	
25.3–35.5	266 (30.2)	209 (25.9)		1124 (25.8)	1150 (26.0)	
35.6–51.8	226 (25.9)	209 (25.9)		1116 (25.7)	1126 (25.5)	
≥ 51.8	153 (17.5)	178 (22.1)	0.679	1035 (23.8)	1123 (25.4)	0.143
Education, n (%)						
Secondary	104 (11.9)	104 (12.9)		698 (16.1)	770 (17.4)	
1- to 2-year university degree	387 (44.3)	381 (47.3)		2111 (48.5)	2242 (50.8)	
≥ 3 year university degree	383 (43.8)	321 (39.8)	0.289	1541 (35.4)	1406 (31.8)	0.002
Use of oral contraceptives, n (%)						
No	211 (24.1)	194 (24.1)		1936 (44.5)	1964 (44.5)	
Yes	663 (75.9)	612 (75.9)	0.675	2414 (55.5)	2454 (55.5)	0.713
Use of menopausal hormone therapy, n (%)						
No	–	–		1178 (27.1)	1390 (31.5)	
Yes	–	–		3062 (70.4)	2914 (65.9)	
Missing	–	–		110 (2.5)	114 (2.6)	<0.001
Parity, n (%)						
Nulliparous	99 (11.3)	81 (10.0)		575 (13.2)	481 (10.9)	
1-2	582 (66.6)	523 (64.9)		2616 (60.1)	2579 (58.4)	
≥ 3	193 (22.1)	202 (25.1)	0.348	1159 (26.6)	1358 (30.7)	0.348
Age at First Pregnancy (years), n (%)						
Nulliparous	99 (11.3)	81 (10.0)		575 (13.2)	481 (10.9)	
< 30	636 (72.8)	625 (77.5)		3233 (74.3)	3478 (78.7)	
≥ 30	139 (15.9)	100 (12.4)	0.340	459 (12.5)	542 (10.4)	0.341
Age at menarche (years), n (%)						
< 12	194 (22.2)	180 (22.3)		904 (20.8)	870 (19.7)	
12-14	474 (54.2)	413 (51.2)		2231 (51.3)	2290 (51.8)	
≥ 14	206 (23.6)	213 (26.4)	0.701	1215 (27.9)	1258 (28.5)	0.412
Breastfeeding, n (%)						
No	419 (47.9)	384 (47.6)		1964 (45.2)	1989 (45.0)	
Yes	455 (52.1)	422 (52.4)	0.395	2386 (54.8)	2429 (55.0)	0.637
Family history of breast cancer, n (%)						
No	719 (82.3)	725 (89.9)		3619 (83.2)	3944 (89.3)	
Yes	155 (17.7)	81 (10.1)	<0.001	731 (16.8)	474 (10.7)	<0.001
History of personal benign breast disease, n (%)						
No	598 (68.4)	612 (75.9)		3092 (71.1)	3433 (77.7)	
Yes	276 (31.6)	194 (24.1)	<0.001	1258 (28.9)	985 (22.3)	<0.001
Mammography, n (%)						
No	240 (27.5)	278 (34.5)		956 (22.0)	1149 (26.0)	
Yes	634 (72.5)	528 (65.5)	<0.001	3394 (78.0)	3269 (74.0)	<0.001

P value from univariate conditional logistic regression models (except for age and menopausal status which were matching factors) comparing the distribution of the baseline characteristics of the study subjects according to the case-control status.
SD: Standard deviation, MET: Metabolic Equivalent of Task, NO_2: nitrogen dioxide, Menopausal status at index date: date of diagnosis in the case in the case-control pair.

overall breast cancer risk using four-knot cubic splines with the mean value as the reference category is shown in Fig. S4. Overall, the association between NO_2 levels and breast cancer risk was linear, with P for linear relation of 0.029 for LUR estimates.

The results of the association between NO_2 levels estimated at subjects' residences and breast cancer risk using three adjusted models are shown in Table 2. Among all women, breast cancer risk was positively associated with NO_2 levels. In the model 1 (crude model conditioned on matching variables), the OR for each 1 IQR increase in estimated NO_2 concentrations (LUR: 17.8 $\mu g/m^3$) was 1.12 (95% CI: 1.04–1.20). In the model 2 (adjusted for confounding variables), the OR for an increment of 1 IQR in estimated NO_2 concentrations was slightly attenuated (OR = 1.09; 95% CI: 1.01–1.18). The OR of model 3 (additionally adjusted for other known and established breast cancer risk factors) was 1.07 (95% CI: 0.98–1.15). By menopausal status at index date, results for postmenopausal women were comparable with those for all women (Table 2), while no association was observed among premenopausal

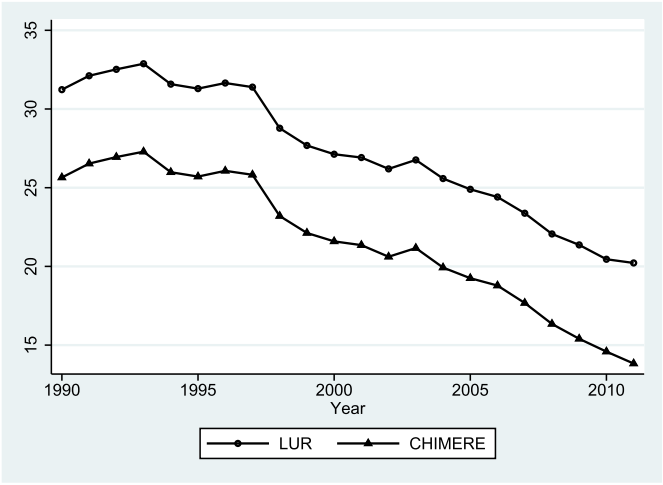

Fig. 1. Evolution of the annual mean NO_2 levels estimated at the subject's residence during the 1990–2011 follow up period in the XENAIR case-control study nested within the E3N cohort, France, 1990–2011.

women.

By hormone receptor status, there was a borderline increased risk of ER + breast cancer for NO_2 levels assessed by the LUR, with the OR of 1.07 (95% CI: 0.97–1.19) per 1 IQR increase in the fully adjusted model. Nevertheless, the associations did not significantly vary by PR, and ERPR status (Table 3). There was some heterogeneity when stratifying by breast cancer histology, with a stronger association for ductal-lobular breast cancer (Table 3). The corresponding ORs were 1.89 (95% CI: 1.11–3.21) for model 2 and 1.77 (95% CI: 0.90–3.47) (P heterogeneity = 0.007) for model 3. We did not find any differences in results by stage of disease or grade of differentiation at diagnosis.

3.4. *Effect modification and additional analyses*

Although there was no statistical interaction of effect by smoking status, an elevated association was observed among current smokers as compared to non-smokers. For each 1 IQR increase in LUR NO_2 levels, the ORs for model 3 were 1.21 (95% CI: 0.91–1.63) and 1.04 (95% CI: 0.87–1.23) among current smokers and never smokers, respectively (Table S1). Results of additional analyses by urban/rural area and family history of breast cancer history for each 1 IQR increase in LUR NO_2 levels, were also shown in Table S1. Even though the OR estimates were greater among women living in urban area, there were no evidence for effect modification (P interaction = 0.582). The ORs was 1.08 (95% CI: 0.98–1.19) for women living in an urban area, while it was 1.01 (95% CI: 0.64–1.58) for those living in rural area. Similarly, the association remained higher among women with family history of breast cancer, but the effect did not differ significantly (P interaction = 0.119). The ORs

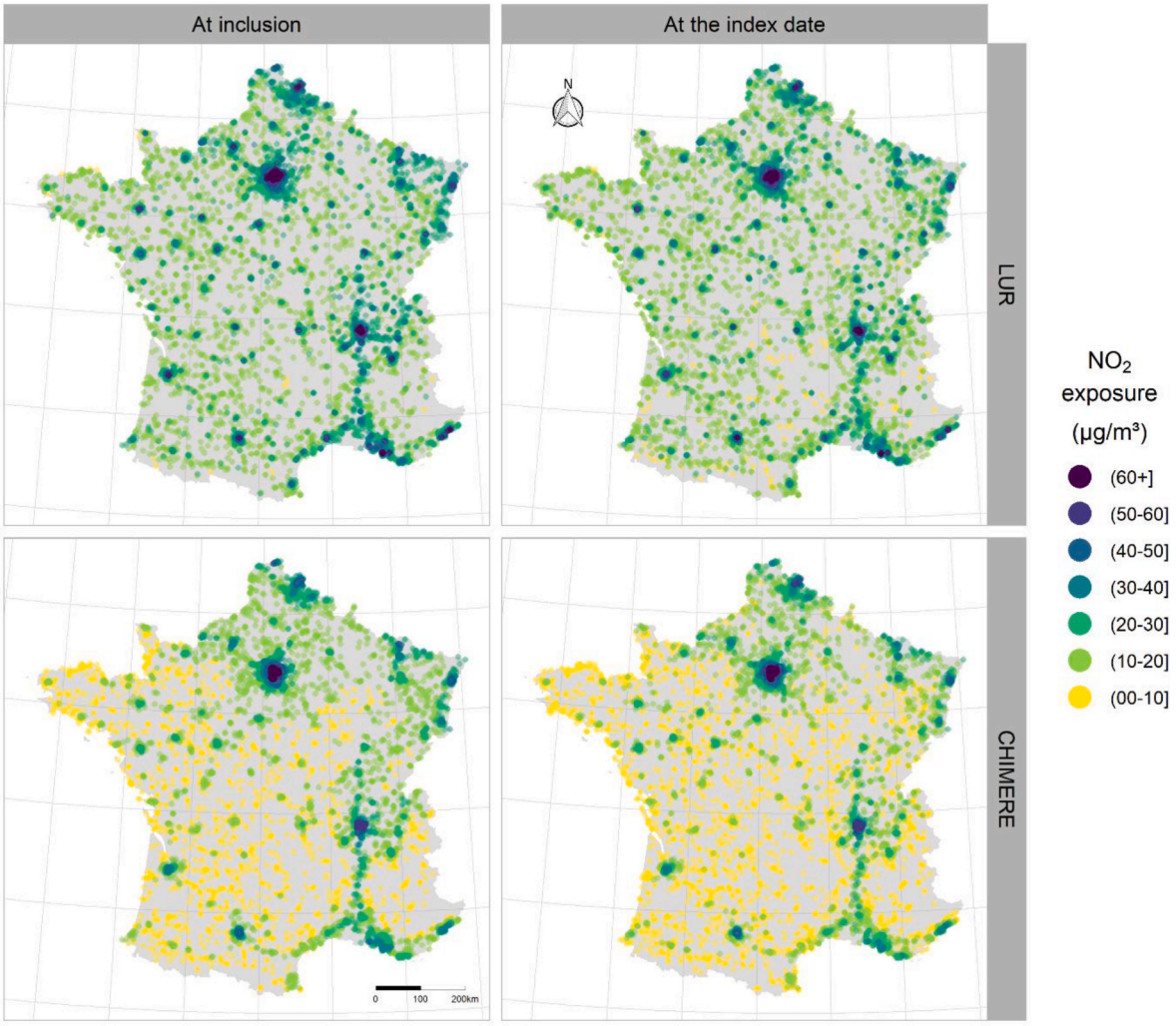

Fig. 2. Spatial pattern of estimated NO_2 levels at the subject's residence at inclusion and at index date using CHIMERE and LUR models in the XENAIR case-control study nested within the E3N cohort, France, 1990–2011. Index date: date at breast cancer diagnosis for cases or the selection for controls.

Table 2
Association for breast cancer risk with mean airborne NO_2 exposure overall, by menopausal status at index date and according to exposure assessment models in the XENAIR case-control study nested within the E3N cohort, France, 1990–2011.

Exposure assessment models	Matched cases/ controls (n)	Crude OR (95% CI)[a]	Multivariable OR (95% CI) [b]	Multivariable OR (95% CI) [c]
LUR				
Overall	5222/ 5222	1.12 (1.04–1.20)	1.09 (1.01–1.18)	1.07 (0.98–1.15)
Premenopausal	591/591	1.09 (0.89–1.33)	1.03 (0.82–1.28)	1.02 (0.81–1.29)
Postmenopausal	4133/ 4133	1.12 (1.03–1.22)	1.10 (1.01–1.21)	1.07 (0.97–1.17)
P interaction				<0.001
CHIMERE				
Overall	5222/ 5222	1.18 (1.08–1.28)	1.15 (1.06–1.26)	1.13 (1.03–1.23)
Premenopausal	591/591	1.06 (0.84–1.34)	1.00 (0.77–1.28)	1.00 (0.76–1.30)
Postmenopausal	4133/ 4133	1.21 (1.10–1.33)	1.20 (1.08–1.32)	1.17 (1.05–1.29)
P interaction				0.002

The OR (95% CI) corresponds to an increment of 1 IQR level of NO_2 in controls (LUR: 17.8 μg/m^3, CHIMERE: 20.8 μg/m^3).

[a] Models conditioned on the matching factors including age, date, department of residence, and menopausal status at blood collection or at baseline, and existence of a biological sample.

[b] Multivariable models adjusted for confounding variables including physical activity, smoking status, level of education and the rural urban status at inclusion.

[c] Models additionally adjusted for known and established breast cancer risk factors including body mass index, previous family history of breast cancer, history of personal benign breast disease, age at menarche, parity and age at first full-term pregnancy, breastfeeding, oral contraceptive use, and menopausal hormone therapy use.

were 1.68 (95% CI: 0.85–3.35) and 1.05 (95% CI: 0.96–1.16) for women with and without family history of breast cancer, respectively.

Additional analyses using a standardized increase of NO_2 estimates (10 μg/m^3) showed an OR of 1.04 (95% CI: 0.99–1.08) in the fully adjusted model (model 3) (Table S2). Moreover, sensitivity analyses using cumulative NO_2 estimates instead of the annual mean of NO_2 levels showed no significant differences, with an OR of 1.06 (95% CI: 0.95–1.17) for each IQR increase in NO_2 levels (LUR: 275.9 μg/m^3) among all women in the fully adjusted model (Table S2). Finally, when computing ORs based solely on NO_2 estimates at the baseline address (in 1990 or 1991), similar to previous studies from the literature, the association with breast cancer risk was attenuated, showing that the ORs for each 1 IQR increase in NO_2 levels (LUR: 19.3 μg/m^3) were 1.06 (95% CI: 0.98–1.15) and 1.04 (95% CI: 0.95–1.13) for model 2 and model 3, respectively (Table S2). Results of a complete-case analysis without imputation were shown in Table S3. The OR estimates remained comparable to the analysis using simple median imputation. Further analyses using multiple imputation showed similar results to those using simple median imputation (Table S4).

Supplementary analyses using NO_2 estimates from the CHIMERE model showed ORs estimates slightly higher than ORs estimates using the LUR model. There was a linear association between CHIMERE NO_2 levels and overall breast cancer risk, with P for linear relation = 0.001 (Fig. S5). In all women, the ORs for each 1 IQR increase in estimated NO_2 concentrations (CHIMERE: 20.8 μg/m^3) were 1.18 (95% CI: 1.08–1.28) in the crude model, 1.15 (95% CI: 1.06–1.26) in the model 2 adjusted for confounding variables, and 1.13 (95% CI: 1.03–1.23) in model 3 additionally adjusted for other known and established breast cancer risk factors (Table 2). An increase of one IQR in estimated NO_2 concentrations (CHIMERE: 20.8 μg/m^3) was associated with increased risks of ER+, PR+, and ER + PR + breast cancer (Table S5). The ORs of model 2 were 1.19 (95% CI: 1.07–1.33), 1.16 (95% CI: 1.02–1.32), 1.16 (95% CI: 1.01–1.32) for ER+, PR+, and ER+ PR+, respectively. The corresponding ORs of model 3 were 1.16 (95% CI: 1.04–1.30), 1.12 (95% CI: 0.98–1.27), and 1.12 (95% CI: 0.97–1.28) for ER+, PR+, and ER+ PR+, respectively. There was a stronger association for ductal-lobular breast cancer, showing that the ORs for an increase in exposure by 1 IQR (20.8 μg/m^3) were 1.83 (95% CI: 1.04–3.24) and 1.74 (95% CI: 0.87–3.48) for the second and the third multivariable model, respectively. Further analyses using CHIMERE NO_2 estimates (standardized increase of NO_2 estimates (10 μg/m^3), cumulative NO_2 estimates instead of the annual mean NO_2, and NO_2 estimates at the baseline address) are presented in Table S2.

4. Discussion

This large nested case-control study is, to the best of our knowledge, the first study investigating long-term exposure to NO_2 over up to 22 years and its association with the risk of breast cancer. The breast cancer risk was positively associated with NO_2 levels using concentrations estimates from both the primary model (LUR) and the additional model (CHIMERE). Subgroup analyses by hormone receptor status showed an increased risk for ER + breast cancer. By histological subtypes, results suggest an association between NO_2 exposure and ductal-lobular breast cancer. Additional analyses using the CHIMERE model showed comparable results to those observed using LUR estimates. Overall, consistent associations were observed with the two exposure assessment methods.

Our findings are in line with two previous studies that have assessed the risk of breast cancer in relation to NO_2 exposure using more than one method of exposure assessment. The Canadian multi-site population-based case-control study (1569 breast cancer cases and 1872 population controls), using three different modeling approaches to estimate ambient NO_2 concentrations, found positive and comparable OR estimates across the three assessments methods, even if the associations were not statistically significant for all models. Their adjusted ORs were 1.26 (95%CI: 0.92–1.74), 1.32 (95% CI: 1.05–1.67), and 1.28 (95% CI: 0.92–1.79) for each 10 ppb (18.8 μg/m^3) increase in NO_2 concentrations estimated from satellite-derived observations, scaled satellite-derived observations, and a national LUR model, respectively (Hystad et al., 2015). Recently, Cheng et al. used two different exposure methods (kriging interpolation and LUR model) to investigate associations between air pollutant exposure to NO_2 and breast cancer risk. This study found a positive association with NO_2 ambient air exposure only among women residing near major roads for both kriging and LUR estimates. The HRs per 20 ppb (37.6 μg/m^3) were 1.44 (95% CI: 1.04–1.99) and 1.26 (95% CI: 1.00–1.59) among women who lived within 500 m of major roads, for kriging and LUR, respectively (Cheng et al., 2020). Among other studies investigating the association of NO_2 with breast cancer risk, the results were generally heterogeneous (Andersen et al., 2017b; Bai et al., 2020; Datzmann et al., 2018; Turner et al., 2020; White et al., 2018). Consistent with our overall results, the study by Hwang et al. reported that ambient NO_2 exposure was positively associated with breast cancer incidence per 10 ppb (18.8 μg/m^3) NO_2, with an OR of 1.14 (95% CI: 1.12–1.16) (Hwang et al., 2020). Likewise, a French population-based case-control study on breast cancer reported a higher risk of breast cancer in relation to NO_2 exposure in the 10-year period preceding diagnosis (Lemarchand et al., 2021). The ORs for breast cancer were 1.11 (95% CI, 0.98–1.26) for each 10 μg/m^3 increase in NO2, and 1.41 (95% CI 1.07, 1.86) in the highest exposure quintile, compared to the first quintile (Lemarchand et al., 2021). However, several other studies reported not or borderline significant associations between NO_2 exposure and breast cancer risk. For example, the study of Andersen et al. detected an HR of 1.02 (95%CI: 0.98–1.07) per each 10 μg/m^3 NO_2 increment (Andersen et al., 2017b). Similarly, the Sister Study cohort reported an OR of 1.02 (95%CI: 0.97–1.07) per 5.8 ppb (10.9 μg/m^3) NO_2 increment (Reding et al., 2015). It is important to note

Table 3
Association for BC risk with LUR mean airborne NO_2 exposure by hormone receptor status and histopathological types in the XENAIR case-control study nested within the E3N cohort, France, 1990–2011.

	Matched cases/controls (n)	Crude OR (95% CI) [a]	Multivariable OR (95% CI) [b]	Multivariable OR (95% CI) [c]
Hormone receptor status				
ER-	760/760	1.12 (0.91–1.37)	1.05 (0.84–1.31)	1.06 (0.84–1.34)
ER+	3405/3405	1.12 (1.02–1.23)	1.10 (1.00–1.22)	1.07 (0.97–1.19)
P heterogeneity				0.814
PR-	1439/1439	1.14 (0.99–1.31)	1.08 (0.93–1.26)	1.06 (0.91–1.24)
PR+	2602/2602	1.09 (0.98–1.21)	1.09 (0.97–1.23)	1.05 (0.93–1.18)
P heterogeneity				0.304
ER-PR-	612/612	1.05 (0.83–1.32)	0.98 (0.76–1.26)	0.98 (0.75–1.27)
ER + PR+	2459/2459	1.08 (0.96–1.20)	1.08 (0.96–1.22)	1.04 (0.92–1.18)
ER-PR+	140/140	1.29 (0.81–2.05)	1.29 (0.76–2.18)	1.33 (0.71–2.50)
ER + PR-	825/825	1.18 (0.99–1.41)	1.13 (0.93–1.38)	1.09 (0.89–1.34)
P heterogeneity				0.696
Stage at diagnosis				
Stage I	2919/2919	1.15 (1.04–1.27)	1.13 (1.02–1.26)	1.10 (0.99–1.23)
Stage II	1412/1412	1.08 (0.94–1.24)	1.06 (0.91–1.24)	1.05 (0.89–1.23)
Stages III-IV	402/402	0.97 (0.76–1.24)	0.85 (0.64–1.11)	0.84 (0.64–1.12)
P heterogeneity				0.925
Histology				
Invasive ductal	3568/3568	1.12 (1.02–1.22)	1.11 (1.01–1.22)	1.09 (0.99–1.21)
Invasive lobular	828/828	0.97 (0.81–1.16)	0.92 (0.76–1.11)	0.90 (0.74–1.10)
Invasive tubular	141/141	1.15 (0.77–1.74)	0.98 (0.62–1.55)	0.93 (0.55–1.56)
Ductal-lobular	123/123	1.66 (1.05–2.61)	1.86 (1.10–3.17)	1.77 (0.90–3.51)
P heterogeneity				0.007

The OR (95% CI) corresponds to an increment of 1 IQR level of NO_2 in controls (LUR: 17.8 $\mu g/m^3$)
Staging analyses were done on the four stages after excluding cases with missing stage information (489 cases) and their matched controls (489), Histology analyses were conducted on the four main subtypes

[a] Models conditioned on the matching factors including age, date, department of residence, and menopausal status at blood collection or at baseline and existence of a biological sample.

[b] Multivariable models adjusted for confounding variables including physical activity, smoking status, level of education and the rural urban status at inclusion.

[c] Models additionally adjusted for known and established breast cancer risk factors including body mass index, previous family history of breast cancer, history of personal benign breast disease, age at menarche, parity and age at first full-term pregnancy, breastfeeding, oral contraceptive use, and menopausal hormone therapy use.

that most of these previous studies have used a single residential location (address) at baseline (Andersen et al., 2017b; Datzmann et al., 2018; Goldberg et al., 2019). The lack of association reported by some studies might be attributable to the absence of NO_2 exposure assessment over a longer period. Noteworthy, in the present study, ORs were attenuated for both models when computing ORs solely based on NO_2 estimates at the baseline address. Furthermore, some previously published studies might also be limited by a small number of cases.

Subgroup analyses by menopausal status showed a significantly increased risk of breast cancer only in postmenopausal women. Yet, to date, it remains unclear whether the association between NO_2 and breast cancer differs by menopausal status (Lemarchand et al., 2021). In accordance with the present findings, some studies reported higher positive associations among postmenopausal women (Andersen et al., 2017b; Crouse et al., 2010), while others found positive associations only in premenopausal women (Hystad et al., 2015; Nie et al., 2007). In this study, we observed potential heterogeneity by hormone receptor status. To date, few epidemiological studies have investigated the association of chronic exposure to NO_2 with breast cancer risk according to hormone receptor subtypes (Goldberg et al., 2019; Lemarchand et al., 2021; Reding et al., 2015). Similar to the results of the present study, Reding et al. reported a statistically significant increased risk of ER+/PR + breast cancer, with a RR of 1.10 (95% CI: 1.02–1.19) for an IQR difference of 5.8 ppb in NO_2, while there was no significant association with ER-/PR-breast cancer (RR = 0.92; 95% CI: 0.77–1.09; P interaction = 0.04) (Reding et al., 2015). The study by Le Marchand et al. also reported higher OR of ER+/PR + breast cancer (OR 1.15, 95% CI: 1.00–1.31) as compared that of ER–/PR– tumors (OR 0.95, 95% CI: 0.72–1.26) for each 10 $\mu g/m^3$ increase in NO_2 (Lemarchand et al., 2021). These findings highlight a differential impact of NO_2 in the etiology of breast cancer development. In contrast, there was no evidence that the association of NO_2 and breast cancer risk varied by stage or grade of differentiation of breast cancer. No previous epidemiological study has considered the impact of NO_2 exposure on breast cancer risk according to clinicopathological characteristics. Additional subgroup analyses suggested trend towards an effect modification by smoking status, urban/rural status at baseline, and family history of breast cancer, with increased risk observed among current smokers, among women living in urban areas, and in those with family history of breast cancer, even if these interaction tests were not statistically significant.

The two models used in this study, despite their fundamental differences in their operating principles, input data, and performance, are complementary, with the LUR describing potential local exposures at a fine spatial scale (at 50m resolution), while the CHIMERE describing neighbourhood/community-level exposures (at 7km resolution). The LUR model is a statistical approach based on correlations between geographical indicators and pollutant-direct measurements. The CHIMERE model is a deterministic model that simulates atmospheric concentrations according to emission and meteorological data. In addition, the spatial resolutions of these two models are different, 50 × 50 m grids for the LUR model and 7 × 7km grids for the CHIMERE model. It seems clear that the LUR model is best suited to describe NO_2 exposure that varies over short distances. Moreover, the LUR model has been calibrated on NO_2 concentration measurements (from the year 2010) contrary to the CHIMERE model, which tends to underestimate NO_2 concentrations levels compared to the LUR model. Additional analyses using an increase of a fixed value of NO_2 (10 $\mu g/m^3$) showed slightly higher risk estimates with the CHIMERE model compared to the LUR model. In summary, observing comparable effects of NO_2 exposure estimated by two models with differences in terms of principles and resolutions, reinforces our results. CHIMERE, due to the lower resolution of the model, is less efficient in urban and suburban areas with important spatial variations of NO_2 within cities (Cyrys et al., 2012). In contrast, it might provide pertinent information on NO_2 concentrations

for the living area of subjects in zones with lower measurement station density, i.e. remote rural areas. Furthermore, it is worthy of note that previous epidemiological studies examining the association between NO_2 exposure and breast cancer risk usually used an increase of 1 IQR level of the distribution of NO_2 in controls (ranging from 10.9 μg/m^3 (Reding et al., 2015) to 37.6 μg/m^3 (Cheng et al., 2020), or a fixed value of 10 μg/m^3 (Andersen et al., 2017a; Datzmann et al., 2018; Lemarchand et al., 2021). Nevertheless, there is no evidence for a clearly defined dose-response relationship for NO_2. The current WHO guideline value of 10 μg/m^3 (annual mean) was set to protect the public effects. Of note, 99.75% of the study population in the present study were exposed to levels exceeding the WHO annual target value of 10 μg/m^3 using the LUR model (World Health Organization, 2021).

The specific mechanisms by which the NO_2 air pollutant may influence breast cancer development is not well understood. First, NO_2 may exert directly both endocrine-disrupting and carcinogenic properties (Callahan et al., 2018; Rodgers et al., 2018; Smith et al., 2016). Second, NO_2 can affect breast cancer development through increased breast density, a strong breast cancer risk factor, as suggested by Perry et al. reporting that women living in urban areas had greater breast density than those living in rural areas (Perry et al., 2008). Third, nitric oxide (NO), one of the two principal nitrogen oxides associated with combustion sources that is oxidized in air to form NO_2, has been reported to modulate several cancer-related events including angiogenesis, apoptosis, cell cycle, invasion, and metastasis (Choudhary et al., 2014; Hu et al., 2020; Mandal, 2018). An increase in the concentration of NO has been observed in the blood of breast cancer patients, and higher Nitric oxide synthase (NOS) activity has been found in invasive breast tumors when compared with benign or normal breast tissue (Basudhar et al., 2017; Loibl et al., 2002), suggesting a carcinogenic effect of NO. NO can directly inhibit the activity of caspases providing an efficient means to block apoptosis (Loibl et al., 2002; Thomsen et al., 1995; Wang et al., 2020) and can increase breast cancer development through estrogen and progesterone pathways, which are both involved in the carcinogenesis of breast cancer (Hu et al., 2020; Sahay et al., 2019). Fourth, exposure to NO_2 is believed to be a proxy of exposure to traffic-related air pollutants (TRAP). TRAP is a complex mixture containing numerous compounds, such as gaseous pollutants (carbon monoxide, NO_2, sulfur dioxide), particulate matter, metals, and organic compounds including benzene and polycyclic aromatic hydrocarbons. Most of these compounds have been reported to have directly carcinogenetic effects such as cytotoxic, genotoxic, mutagenic, epigenetic, and inflammatory effects, or to act as endocrine disruptors (Rodgers et al., 2018; White et al., 2016). A recent review suggested that TRAP may exert effects through the alteration of epigenetic regulatory mechanisms (Sahay et al., 2019). This study reported that traffic-related NO_2 may lower methylation of protumorigenic genes EPHB2 and LONP1. Similarly, Callahan et al. reported that exposure to ambient air pollution throughout life, measuring total suspended particulates (TSP) and traffic emissions (TE) during key windows of susceptibility (at menarche, at a woman's first birth, and 10 years prior to enrollment), may be associated with DNA methylation of some tumor suppressor genes in breast tumor tissue (Callahan et al., 2018). They demonstrated that higher exposure to TE during menarche was associated with higher methylation of a breast tumor suppressor gene spleen tyrosine kinase (*SYK*). They also observed that cases with higher levels of TE at first birth, and at years prior to enrollment had lower methylation of a breast tumorigenic gene Cyclin D2 (*CCND2*). This study suggested that these DNA methylation patterns earlier in carcinogenesis, can also persist until later life (Callahan et al., 2018).

One of the major strengths of our study is the use of an exposure assessment method with a fine spatial resolution (50 × 50 m) over 22 years to estimate the risk of breast cancer. Other strengths include the use of another model to perform additional analyses supporting our main results and a large number of cases (n = 5222). Also, the prospective cohort design and the long follow-up period allowed to evaluate the impact of long-term NO_2 exposure (up to 22 years) on breast cancer risk. The extensive prospectively collected information on covariates allowed to control for confounding factors that could potentially impact the association. Another strength of our study is the availability of information on breast cancer subtypes (ER and PR status) and clinicopathologic characteristics (stage, grade, and histology) to investigate whether NO_2 exposure contributes differently to breast cancer risk by subgroup. However, several limitations should be considered. One of the weaknesses of our study is the lack of NO_2 exposure data prior to cohort entry, to allow analyses during some relevant periods of exposure (specific windows of susceptibility, such as menarche and pregnancy), with respect to breast cancer etiology and latency, as the women were aged 45–60 at enrollment in the cohort, and NO_2 exposure estimates were not available before 1990 (Rodgers et al., 2018; Rudel et al., 2011; Zhai et al., 2021). The results observed when the baseline address only is used, suggest some influence of the more proximate exposures. However, even if recent exposure is not negligible, our results, similar to previous findings emphasize the importance to consider the long-term exposure (particularly the duration) when studying the risk of breast cancer. It should be noted that patterns of NO_2 have been decreasing during the 1990–2011 study follow up period, steadily since 1996, and given that the exposure duration vary according to each woman, for some women the estimate of exposure is based on only a few years, and for others it is based on up to 20 years. However, the choice of average annual concentrations as exposure summary would not introduce bias in the present study, as long as exposure is measured only up to the index date, given that the matched design of our study only compares individuals with the same follow-up duration (from their entry into the cohort to their index date) in each case-control pair. Furthermore, information on detailed occupational exposures potentially related to breast cancer risk was lacking. However, women from the E3N cohort were teachers or worked in affiliated occupations, thus workplace exposures could be relatively low and homogeneous across study participants. Also, despite the extensive efforts to adjust for potential confounding factors, we could not exclude some residual confounders such as noise or other pollutants. Confounding from dietary exposure was not expected since inhalation is the only route of exposure to NO_2 in the general population that could impact the health effects. While the analysis of the entire cohort or case-cohort could have been pertinent, a nested case-control design is more efficient in terms of human and financial burden for data collection and characterization of environmental exposures. Thus, given the sufficient statistical power with the nested case-control study, and human resources required for the manual geocoding (to avoid misclassification bias due to positional errors) (Faure et al., 2017), balancing number of subjects versus precision of exposure characterization, we selected a matched case-control design nested in the cohort. Study designs, which would allow estimating of time-varying risks, such as case-cohort analyses, might be of interest in future studies.

Conclusions

This study shows that long-term exposure to ambient air NO_2 was positively associated with breast cancer risk overall. Subgroup analyses show a differential effect, with NO_2 being positively associated with postmenopausal, hormone receptor-positive, and ductal-lobular breast cancer. Overall, these results reinforce the existing evidence for an association between NO_2 exposure and breast cancer risk. However, as NO_2 is a proxy of TRAP, future studies should take into account workplace and commuting exposures (from home to work).

Credit author Statement

Amina Amadou: Visualization, Formal analysis, Conceptualization, Writing – original draft, Project administration, Supervision. **Delphine Praud**: Formal analysis, Conceptualization, Writing – review & editing.

Thomas Coudon: Conceptualization, Methodology, Writing – review & editing. **Floriane Deygas**: Conceptualization, Writing – review & editing. **Lény Grassot**: Conceptualization, Methodology, Writing – review & editing. **Mathieu Dubuis**: Methodology, Writing – review & editing. **Elodie Faure:** Resources, Investigation, Methodology, Writing – review & editing. **Florian Couvidat**: Resources, Investigation, Writing – review & editing. **Julien Caudeville**: Resources, Investigation, Writing – review & editing. **Bertrand Bessagnet**: Resources, Investigation, Writing – review & editing. **Pietro Salizzoni**: Conceptualization, Writing – review & editing. **Karen Leffondré**;: Formal analysis, Conceptualization, Writing – review & editing. **John Gulliver**: Conceptualization, Writing – review & editing. **Gianluca Severi**: Resources, Investigation, Conceptualization, Writing – review & editing. **Francesca Romana Mancini**: Resources, Investigation, Conceptualization Writing – review & editing. **Béatrice Fervers**: Investigation, Supervision, Writing – review & editing, Funding acquisition, Project administration.

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Ethical approval

The study was approved by the French National Commission for Data Protection and Privacy (CNIL).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Information about data sharing

Not applicable for that section. The datasets generated and/or analyzed during the current study are not publicly available for ethical reasons, permission by the participants to use their data, according to the signed informed consent, and from the MGEN, their insurance company, is restricted to the team in charge of the cohort, which can be extended to collaborators with a specific research agreement, but are available from the corresponding author on reasonable request.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.120719.

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