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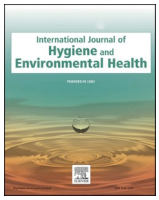

Association between chronic long-term exposure to airborne dioxins and breast cancer

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ABSTRACT

Breast cancer is the most common type of cancer among women. Environmental pollutants, specifically those with endocrine disrupting properties like dioxins, may impact breast cancer development. Current epidemiological studies on the association between exposure to dioxins and the risk of breast cancer show inconsistent results. To address these uncertainties, our objective was to investigate the impact of airborne dioxin exposure on breast cancer risk within the E3N cohort, encompassing 5222 cases identified during the 1990–2011 follow-up and 5222 matched controls. Airborne dioxin exposure was assessed using a Geographic Information System-based metric considering residential proximity to dioxin emitting sources, their technical characteristics, exposure duration and wind direction. Additional analyses were performed using dioxin concentrations estimated by a chemistry transport model, CHIMERE. The results suggest a slightly increased risk between cumulative dioxin exposure at the residential address and overall breast cancer risk (adjusted odds ratio (OR) = 1.03, 95% confidence interval (CI): 0.99–1.07, for a one standard deviation (SD) increment among controls (14.47 log-µg-TEQ/m^2). The associations remained consistent for sources within 3, 5, and 10 km, and when restricting exposure to dioxin emissions from household waste incinerators. Similar OR estimates (OR = 1.02, 95% CI: 0.97–1.07, for a one SD increment) were obtained using the CHIMERE model. The findings of this study suggest the possibility of an increased risk of breast cancer associated with long-term residential exposure to dioxins and emphasize the importance of efforts to mitigate air pollution exposure.

1. Introduction

Breast cancer is the most common type of cancer among women with particular elevated incidence in Western and Northern European countries, and it was one of the main cause of death from cancer among women in 2020 (Carioli et al., 2017; Sung et al., 2021). Considerable research has been carried out on lifestyle-related and hormonal risk factors, but the contribution of other potential risk factors such as environmental pollutants has also been suggested (Wan et al., 2021; White et al., 2018). Air pollution is a leading environmental risk factor globally. The World Health Organization estimates showed that around 7 million deaths, mainly from noncommunicable diseases, were

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attributable to the joint effects of ambient and household air pollution in 2016 (World Health Organization, 2018). The Global Burden of Disease (GBD) Study (2019) estimated that all forms of air pollution account for about 11.3% of total deaths worldwide for women (GBD 2019 Cancer Risk Factors Collaborators, 2022).

Epidemiological and biological studies have suggested that exposure to chemical compounds with endocrine disrupting properties may have an effect on breast cancer (Rodgers et al., 2018). There is evidence that endocrine disrupting chemicals (EDCs) can impact all pathways of major hallmarks associated with breast cancer development (including sustained proliferative signaling, growth suppressor evasion, cell death resistance, replicative immortality, angiogenesis induction, invasion activation, metastasis, genome instability, inflammation, immune destruction evasion and metabolism reprogramming) (Calaf et al., 2020; Darbre, 2021; Das et al., 2023; Cano-Sánchez et al., 2023; Wang et al., 2024).

Dioxins (combining polychlorinated dibenzo-para-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF)) are generated by combustion processes and their main sources of release are the chemical manufacturing of chlorinated products and industrial activities including metallurgy, steel production and municipal solid waste incineration (Coudon et al., 2019). TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin), the most potent compound of PCDD, has been classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC), with sufficient evidence for all cancers combined (IARC, 2012). Several epidemiological studies have evaluated the association between TCDD and breast cancer incidence, but the results remain inconsistent (Baek et al., 2022; Cong et al., 2023; Haghighi et al., 2021; Xu et al., 2016). Most of them were conducted on occupational exposures (Kogevinas et al., 1997; Manuwald et al., 2012; Revich et al., 2001) and the accidental exposure of residents living near industrial sites (namely the Seveso accident in Italy) (Bertazzi et al., 1993, 2001, 1997; Warner et al., 2002, 2011). However, only very few studies have been conducted on ambient TCCD exposure (Danjou et al., 2019; Rhee et al., 2023; Viel et al., 2008; VoPham et al., 2020). The recent meta-analysis of two EDCs (including TCDD) in relation to breast cancer reported no statistically significant association between ambient TCCD and breast cancer risk (odds ratio, OR = 1.00, 95% confidence intervals (95% CI) = 0.89–1.12) (Cong et al., 2023). Similarly, the Nurses' Health Study II showed no association between residential proximity to any dioxin facilities (all facilities combined) and breast cancer risk overall (VoPham et al., 2020). However, this study found an increased risk of breast cancer for women who resided within 10 km of any (≥1) municipal solid waste incinerator (MSWI) compared to none (adjusted hazard ratio, HR = 1.15, 95% CI: 1.03–1.28), with higher estimates for women who lived within 5 km (adjusted HR = 1.25, 95% CI: 1.04–1.52). In the Sister study including 2670 incident breast cancer cases, Rhee et al. also showed an increased risk of breast cancer associated with exposure to ambient PCDD assessed using distance- and toxic equivalency quotient (TEQ)-weighted average emission indices, with elevated risks observed for individuals living in close proximity to these sources (HR = 1.18, 95% CI = 0.99–1.40, for exposure higher than the fourth quartile *versus* exposure equal to 0, exposure was estimated within 3 km of participants' residential addresses), and for emissions from MSWIs, as well as among ever smokers (Rhee et al., 2023). In contrast, in a previous study conducted within the French E3N cohort but restricted to the Rhône-Alpes region (429 breast cancer cases diagnosed in 1990–2008 and 716 matched controls), no evidence of an association was observed between the overall risk of breast cancer and exposure to dioxins (based on a Geographic Information System (GIS)-based metric, and estimated within 10 km of participants' residential addresses) (OR = 1.12, 95% CI = 0.69–1.82, for the highest quintiles *versus* the lowest (Danjou et al., 2019).

In summary, findings from previous studies remain inconsistent, and evidence of effect modification by menopausal status, tumor subtypes, stage, grade, or histology remains sparse. Also, statistical power and exposure assessment issues may explain some of these inconsistent findings.

To overcome to current limitations, the aim of this study was to investigate the effect of chronic exposure to airborne dioxins on breast cancer risk overall, and taking into account menopausal status, tumor subtypes, stage, grade, and histology in a large nationwide nested case-control study using two distinct models to assess dioxin exposure.

2. Methods

2.1. Population and study design

We analyzed data from the XENAIR study, a case-control study of breast cancer nested in the French national E3N cohort study.

2.2. The E3N cohort study

Briefly the E3N study is an ongoing prospective cohort whose purpose is to identify female cancer and other chronic diseases risk factors (Clavel-Chapelon and E3N Study Group, 2015). The cohort involves 98,995 French female volunteers, born between 1925 and 1950 and insured by the national health insurance plan MGEN, mostly covering teachers. The female participants, who live in France were included between June 1990 and November 1991, after having completed a self-administered questionnaire (including data on health status, medical history and a large number of potential lifestyle factors) and providing written informed consent for data collection. Follow-up questionnaires were sent every 2–3 years thereafter. Breast cancers were first self-declared in each questionnaire, and then confirmed by pathology report for 93% of the cases. The proportion of false-positive was less than 5%. In addition to the questionnaires, blood samples were collected for 25,000 participants between 1994 and 1999, and saliva samples for 47,000 participants between 2009 and 2011. Overall, 13 questionnaires had been sent since 1990 and the participants' residential addresses were recorded in the first and fifth to the tenth questionnaires (*i.e.* in 1990, 1997, 2000, 2002, 2005, 2008, 2010). For the third and the fourth questionnaires (in 1993 and 1994), only the postal code was recorded. Addresses' management has already been described (Deygas et al., 2021). In addition, for each participant's place of birth (postal code and commune recorded from the first questionnaire) an urban/rural status was assigned using data from the closest national census (Binachon et al., 2014). The study was approved by the French National Commission for Data protection and privacy (CNIL).

2.3. The XENAIR nested case-control study

As has been described previously (Amadou et al., 2020a, 2020b, 2021a, 2021b; Deygas et al., 2021), the present study is a case-control study nested within the E3N cohort. Histologically confirmed breast cancer cases were identified in the cohort during the follow-up from entry into the E3N cohort (1990) to the tenth questionnaire (2011). Women with Paget's disease, phyllodes tumors or tumors with missing morphological codes were excluded. For each breast cancer case, one control was randomly selected using incidence density sampling, among cohort participants at risk of breast cancer at the time of the case diagnosis, with the delay since enrollment into the cohort as time axis. Two groups of controls were formed, according to the presence of a biological sample (blood or saliva) of the cases. For the group with blood sampling, controls were matched to cases on department of residence (area corresponding to the French administrative division of the territory), age (±1 year), calendar date (±3 months) and menopausal status at the time of blood sampling, while controls without blood sampling were matched on the same criteria at baseline, and additionally on the existence of a saliva sample (yes, no). Women were included in the present case-control study if they had completed their home address at baseline, lived in French metropolitan territory during the follow-up

time, and had never been diagnosed with any cancer at baseline. Women with more than one missing, incomplete or foreign address during follow up, were also excluded. After these exclusions, incomplete case-control pairs were excluded.

Information on estrogen receptor (ER) and progesterone receptor (PR) status was obtained from the pathology report. ER and PR status were available for 79.7% (ER- = 760 ER+ = 3405, and unknown = 1057) and 77.4% (PR- = 1439, PR+ = 2602, and unknown = 1181) of cases, respectively.

2.4. Assessment of airborne dioxin exposure

2.4.1. Addresses' geocoding

The participants' residential history from the beginning of the follow-up until the index date (breast cancer diagnosis of the case in the case-control pair) and emitting sources addresses were geocoded (X and Y coordinates, addresses) using the Arc GIS 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) (Deygas et al., 2021; Faure et al., 2017).

2.4.2. Exposure assessment

For each participants' address, we estimated the airborne dioxin exposure using two different approaches, a GIS and the CHIMERE model. The methodologies have been described in detail previously (Coudon et al., 2018; Danjou et al., 2019; Amadou et al., 2020b).

Briefly, for the GIS-based metric, a detailed retrospective inventory of industrial sources likely to have emitted dioxins during the study period in metropolitan France was performed. Multiple and varied sources of information were employed to establish this inventory, including institutional sources, contacts with labor unions, municipal and legislative decrees, measurement data, etc. In addition, a structured questionnaire was sent to the facilities to collect additional information on their technical characteristics and activity rates. The technical and activity characteristics collected include: emission intensity, stack height, operating periods, the emission reduction techniques implemented and geographic location of the facilities A total of 3185 sources were inventoried from 1990 to 2011 in metropolitan France (Coudon et al., 2019). Industrial emitting sources were repositioned at the location of the flue-gas stack using historical aerial photography from National Institute of Geographic and Forest Information.

Exposure to dioxins was estimated using the following parameters: j, the place of residence (j = 1, …,J); i, the industrial source (i = 1, …,I), EI_i, the annual dioxin emission intensity of each industrial source *i* (in g-TEQ/year); t_i, the emission period duration of each industrial source *i* (in years); d_{ij}, the residence-to-source distance (in m); Fi, the factor taking into account the percentage of time during which the wind was blowing in a direction leading to ~~a~~ transport from the industrial source *i* to the participant's residence *j* (accounting for the weighted contribution of the sector of the buffer in which the participant was located); h_i, the stack height of each industrial source *i* (in m); h_{median}, the median value of the other sources' stack heights (in m) in a 10-km buffer, taken into account only when h_i was higher than 90 m. For each individual and for each calendar year, a cumulative index of estimated exposure to dioxins was calculated by cumulating their estimated annual exposure index (AEI) from their entry into the cohort to the index date (breast cancer diagnosis of the case in the case-control pair). For sensitivity analyses, additional AEIs were calculated using 3- and 5-km buffers (i.e. considering dioxin sources located at 3 and 5 km from the participant's residence).

$$AEI\ (gTEQ/m^2year) = \sum_{j}^{J}\sum_{i}^{I} t_j \times \frac{1}{d_{ij}^2} \times EI_i \times F_i \times \left(\frac{h_{median}}{h_i}\right)^a$$

CHIMERE is a Eulerian deterministic model, developed by the National Institute for the Industrial Environment and Risks (INERIS) (Guerreiro et al., 2014, 2016), that simulates pollutant atmospheric dispersion and other physical and chemical processes using emission data, meteorological fields, and boundary conditions as inputs and provides hourly averaged concentrations (Guerreiro et al., 2014, 2016). For this study, dioxin concentrations were simulated with a spatial resolution of 0.125° × 0.0625° (around 7 × 7 km) considering both anthropogenic and natural emissions.

2.5. Statistical methods

The characteristics of the participants were described by case-control status and according to quintiles of the cumulative airborne dioxin exposure assessed by a GIS-based metric, using mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. The evolution of dioxin exposure between 1990 and 2011 corresponding to the different addresses of the participants included in our analysis have been described graphically (1st quartile, median, 3rd quartile). The variability of cumulative exposure among participants is represented in a histogram.

Odds ratios (OR) and corresponding 95% confidence intervals (CIs) for invasive breast cancer were estimated for cumulative exposure as continuous variables whereas for the quintiles of cumulative exposure, the first quintile served as the reference category, using multivariate conditional logistic regression. All the models were conditioned for matching variables (age, department of residence, menopausal status and date at blood collection or at baseline and the existence of a biological sample (blood, saliva, none). We used a directed acyclic graph (DAG) to identify the minimally sufficient adjustment set of variables (Supplementary Fig. 1). We adjusted for level of education (secondary, 1 to 2-year university degree, ≥ 3-year university degree) and urban/rural status at the cohort entry (Rural, Urban) (Model 1).

For the sensitivity analyses, we considered two further models. A second model emerged from the DAG including urban/rural status at cohort entry (rural, urban), urban/rural status at birth, body mass index (BMI, <25.0, 25.0–29.9, ≥30 kg/m^2), total physical activity (<25.3, 25.3–35.5, 35.6–51.8, ≥51.8 METs-h/week), smoking status (never, current, former), alcohol intake (Never, <6.7, ≥6.7 g/day, missing), previous use of oral contraceptives (yes, no), use of menopausal hormone treatment (yes, no), mammography at previous follow-up (yes, no), parity and age at the first full-term pregnancy (no child/1–2 children and age <30 years, 1–2 children and age ≥30 years, >3 children), breastfeeding (yes, no) and follow-up duration (Model 2). We considered an additional model adding to our first model other well-known factors of breast cancer frequently found in the literature: age at menarche (<13, ≥13 years old), menopausal status at index date (premenopausal, postmenopausal at the date of the breast cancer diagnosis of the case in the case-control pair), history of personal benign breast disease (yes, no), family history of breast cancer (yes, no) (Model 3).

We investigated whether the effect of the cumulative GIS-based metric of airborne dioxin exposure on breast cancer risk was homogeneous across strata of selected covariates. These variables (menopausal status, level of education, total physical activity, BMI, smoking status, and breastfeeding) were chosen based on their potential effect modification on the association of dioxin exposure with breast cancer risk. Heterogeneity across strata was assessed with likelihood ratio tests comparing the nested models including and excluding interaction terms. For each adjustment model, the linearity of cumulative dioxin exposure (considered as a continuous variable) on the logit of breast cancer was checked using fractional polynomials of degree 2. Subgroup~~s~~ analyses were conducted according to the hormone receptor status, stage, grade of differentiation and histological subtype.

All the adjustment variables were taken at cohort entry with the exception of alcohol consumption which was collected at the time of questionnaire 3 (1993) through the dietary questionnaire, and hormonal treatments which were selected from the last questionnaire before the

index date (date of the breast cancer diagnosis of the case in the case-control pair). Simple imputation methods were used for missing data, with covariates with less than 5% missing data replaced by their modal or median value in the control population, while for those with more than 5% missing data, a "missing data" category was generated (Garcia-Acosta and Clavel-Chapelon, 1999). Regarding the use of menopausal hormone therapy, no imputation was made, although less than 5% of data were missing, as this variable is highly dependent on age and time (Deygas et al., 2021).

A further analysis was performed using average annual dioxin exposure estimates between 1990 and the index date (date of the breast cancer diagnosis of the case in the case-control pair). Sensitivity analyses were performed on the GIS-based metric using AEIs calculated on the basis of 3 and 5 km buffers (maximal exposure distance from the source considered as exposed). Additional analyses were carried out on two main sources of dioxins (metallurgical and household waste incinerator sources). Also, sensitivity analyses excluding participants with the first two years of follow-up were conducted in order to control for potential reverse causation. Finally, to account for high outliers in dioxin exposure, we conducted additional analyses using log1p-transformed dioxin exposure data (log1p was chosen due to the presence of zero values).

All the *P*-values were two-sided and the nominal level of statistical significance was set at 0.05. All the analyses were performed with R studio software version 4.2.0.

3. Results

3.1. Characteristics of the study population

Table 1 shows the distribution of the study participants' characteristics by quintiles of cumulative dioxin exposure. In comparison to women in the lower quintile, women in the upper quintile had a lower BMI (83.1% *vs.* 78.7%), a higher level of alcohol consumption (42.8% *vs.* 30.2%), a higher level of education (48.5% *vs.* 22.1%), and were less physically active. In addition, they were more likely to be ever smokers (53.0% *vs.* 42.9%), to be in an urban area at inclusion (92.2% *vs.* 31.7%), to be postmenopausal at index date (88.2% *vs.* 78.6%), to be MHT users (63.3% *vs.* 51.5%), to be nulliparous (17.2% *vs.* 9.2%) and to have had a mammography before inclusion (77.7% *vs.* 71.0%).

The median cumulative exposure to dioxins was 0.38 (1st quartile: 0.04, 3rd quartile: 1.79) µg-TEQ/m^2 (min-max range: 0–586.73) for cases and 0.35 (1st quartile: 0.04, 3rd quartile: 1.69) µg-TEQ/m^2 (min-max range: 0–776.85) for controls, using the GIS-based metric approach. Using the CHIMERE model, the median cumulative exposure to dioxins was 74.49 (1st quartile: 45.89, 3rd quartile: 125.05) fg-TEQ/m^3 (min-max range: 0.11–3059.80) and 74.21 (1st quartile: 46.09, 3rd quartile: 125.48) fg-TEQ/m^3 (min-max range: 0.11–2732.34) for cases and controls, respectively. The distribution of cumulative exposures showed high variability between women (Supplementary Fig. 2). It should be noted that 90% of women were on average exposed to a level below 6.3 µg-TEQ/m^2 and 189.5 fg-TEQ/m^3, using the GIS-based metric approach and CHIMERE model, respectively, during the study period (Supplementary Fig. 2).

The evolution of the annual mean GIS-based airborne dioxin level estimates at subjects' residences during the period of 1990–2011, showed a decrease over time, with a sharp decline between 1995 and 1998. Trends were broadly similar with the CHIMERE model. The means (±SD) ranged from 6.98 (±2.36) log-10ng-TEQ/m^2 1990 to 1.31 (±2.17 log-10ng-TEQ/m^2 in 2011 for the GIS-based metric, and from 13.0 (±10.3) fg-TEQ/m^3 in 1990 to 1.6 (±1.3) fg-TEQ/m^3 in 2011 for the CHIMERE model (Fig. 1).

3.2. Dioxin exposure and breast cancer risk

The associations between cumulative dioxin exposure estimates and breast cancer risk, overall, are shown in Table 2. Overall, there was a

Table 1
Characteristics of 5222 cases and 5222 controls according to the quintiles distributions of the cumulative dioxins exposure in the XENAIR case-control study nested in the E3N cohort, France, 1990–2011.

Characteristics	Quintiles[a] of cumulative dioxins exposure (µg-TEQ/m^2)				
	I (N = 2069)[a]	II (N = 2059)[a]	III (N = 2091)[a]	IV (N = 2081)[a]	V (N = 2144)[a]
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Case/control status					
Control	1045 (49.9)	1044 (50.8)	1044 (50.0)	1044 (49.6)	1045 (49.8)
Case	1024 (49.5)	1015 (49.3)	1047 (50.1)	1037 (49.8)	1099 (51.3)
Age at baseline (years)	49.3 (6.3)	49.4 (6.2)	49.5 (6.2)	49.8 (6.3)	49.7 (6.5)
Age at diagnosis (years)	59.4 (8.5)	59.6 (8.1)	60.5 (8.0)	61.5 (7.9)	61.9 (7.9)
Time to diagnosis (years)	10.1 (6.2)	10.2 (5.9)	11.0 (5.7)	11.7 (5.4)	12.2 (5.1)
Body Mass Index (kg/m^2)					
<25	1629 (78.7)	1670 (81.1)	1706 (81.6)	1688 (81.1)	1782 (83.1)
25-29	330 (15.9)	275 (13.4)	296 (14.2)	301 (14.5)	257 (12.0)
≥30	67 (3.2)	73 (3.5)	49 (2.3)	58 (2.8)	64 (3.0)
Missing	43 (2.1)	41 (2.0)	40 (1.9)	34 (1.6)	41 (1.9)
Alcohol drinking (g/day)[b]					
Never drinker	179 (8.7)	168 (8.2)	176 (8.4)	184 (8.8)	168 (7.8)
≤6.7 (g/day)	547 (26.4)	522 (25.4)	500 (23.9)	549 (26.4)	564 (26.3)
>6.7 (g/day)	624 (30.2)	703 (34.1)	807 (38.6)	816 (39.2)	917 (42.8)
Missing	719 (34.8)	666 (32.3)	608 (29.1)	532 (25.6)	495 (23.1)
Smoking status					
Never smoker	1172 (56.6)	1167 (56.7)	1163 (55.6)	1157 (55.6)	1002 (46.7)
Current smoker	248 (12.0)	268 (13.0)	302 (14.4)	307 (14.8)	399 (18.6)
Former smoker	640 (30.9)	619 (30.1)	619 (29.6)	613 (29.5)	738 (34.4)
Missing	9 (0.4)	5 (0.2)	7 (0.3)	4 (0.2)	5 (0.2)
Status of the birthplace					
Rural	800 (38.7)	597 (29.0)	504 (24.1)	459 (22.1)	438 (20.4)
Urban	1103 (53.3)	1243 (60.4)	1342 (64.2)	1349 (64.8)	1452 (67.7)
Missing	166 (8.0)	219 (10.6)	245 (11.7)	273 (13.1)	254 (11.8)
Status at inclusion					
Rural	1414 (68.3)	793 (38.5)	479 (22.9)	296 (14.2)	168 (7.8)
Urban	655 (31.7)	1266 (61.5)	1612 (77.1)	1785 (85.8)	1976 (92.2)
Total physical activity (METs-h/week)					
<25.3	360 (17.4)	455 (22.1)	519 (24.8)	549 (26.4)	650 (30.3)
25.3–35.5	514 (24.8)	489 (23.7)	552 (26.4)	562 (27.0)	630 (29.4)
35.6–51.8	578 (27.9)	538 (26.1)	540 (25.8)	515 (24.7)	492 (22.9)
≥51.8	615 (29.7)	575 (27.9)	476 (22.8)	450 (21.6)	370 (17.3)
Missing	2 (0.1)	2 (0.1)	4 (0.2)	5 (0.2)	2 (0.1)
Education level					
Secondary	346 (16.7)	341 (16.6)	375 (17.9)	342 (16.4)	272 (12.7)
1- to 2-year university degree	1252 (60.5)	1088 (52.8)	986 (47.2)	901 (43.3)	817 (38.1)
≥3-year university degree	458 (22.1)	622 (30.2)	714 (34.1)	816 (39.2)	1040 (48.5)
Missing	13 (0.6)	8 (0.4)	16 (0.8)	22 (1.1)	15 (0.7)
Age at menarche (years)					

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Quintiles[a] of cumulative dioxins exposure (µg-TEQ/m^2)				
	I (N = 2069)[a]	II (N = 2059)[a]	III (N = 2091)[a]	IV (N = 2081)[a]	V (N = 2144)[a]
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
<12	415 (20.1)	432 (21.0)	409 (19.6)	427 (20.5)	465 (21.7)
12-13	1027 (49.6)	1004 (48.8)	1065 (50.9)	1040 (50.0)	1056 (49.3)
≥14	584 (28.2)	582 (28.3)	578 (27.6)	570 (27.4)	576 (26.9)
Missing	43 (2.1)	41 (2.0)	39 (1.9)	44 (2.1)	47 (2.2)
Previous use of oral contraceptives[c]					
Yes	1251 (60.5)	1237 (60.1)	1199 (57.3)	1165 (56.0)	1287 (60.0)
No	797 (38.5)	805 (39.1)	872 (41.7)	900 (43.2)	839 (39.1)
Missing	21 (1.0)	17 (0.8)	20 (1.0)	16 (0.8)	18 (0.8)
Menopausal status at inclusion					
Premenopausal	1272 (61.5)	1247 (60.6)	1220 (58.3)	1217 (58.5)	1278 (59.6)
Postmenopausal	781 (37.7)	802 (39.0)	857 (41.0)	849 (40.8)	852 (39.7)
Missing	16 (0.8)	10 (0.5)	14 (0.7)	15 (0.7)	14 (0.7)
Menopausal status at index date					
Premenopausal	427 (20.6)	397 (19.3)	340 (16.3)	274 (13.2)	239 (11.1)
Postmenopausal	1626 (78.6)	1652 (80.2)	1737 (83.1)	1792 (86.1)	1891 (88.2)
Missing	16 (0.8)	10 (0.5)	14 (0.7)	15 (0.7)	14 (0.7)
Use of hormone replacement therapy[d]					
Yes	1065 (51.5)	1107 (53.8)	1215 (58.1)	1232 (59.2)	1358 (63.3)
No	961 (46.4)	908 (44.1)	824 (39.4)	790 (38.0)	733 (34.2)
Missing	43 (2.1)	44 (2.1)	52 (2.5)	59 (2.8)	53 (2.5)
Parity and age at first full-term pregnancy (years)					
No child	190 (9.2)	168 (8.2)	242 (11.6)	268 (12.9)	368 (17.2)
1–2 child and AFP <30	1055 (51.0)	1073 (52.1)	1026 (49.1)	985 (47.3)	972 (45.3)
1–2 child and AFP >30	172 (8.3)	203 (9.9)	214 (10.2)	215 (10.3)	265 (12.4)
>3	630 (30.4)	599 (29.1)	581 (27.8)	584 (28.1)	515 (24.0)
Missing	22 (1.1)	16 (0.8)	28 (1.3)	29 (1.4)	24 (1.1)
Breastfeeding					
Ever	1109 (53.6)	1142 (55.5)	1131 (54.1)	1091 (52.4)	1068 (49.8)
Never	929 (44.9)	897 (43.6)	935 (44.7)	948 (45.6)	1047 (48.8)
Missing	31 (1.5)	20 (1.0)	25 (1.2)	42 (2.0)	29 (1.4)
Mammography during the previous follow-up period					
Yes	1469 (71.0)	1511 (73.4)	1591 (76.1)	1584 (76.1)	1666 (77.7)
No	600 (29.0)	548 (26.6)	500 (23.9)	497 (23.9)	478 (22.3)
Previous family history of breast cancer					
Yes	272 (13.1)	271 (13.2)	288 (13.8)	278 (13.4)	332 (15.5)
No	1759 (85.0)	1767 (85.8)	1758 (84.1)	1764 (84.8)	1784 (83.2)
Missing	38 (1.8)	21 (1.0)	45 (2.2)	39 (1.9)	28 (1.3)
Previous history of personal benign breast disease[e]					
Yes	518 (25.0)	546 (26.5)	582 (27.8)	548 (26.3)	517 (24.1)
No	1551 (75.0)	1513 (73.5)	1509 (72.2)	1533 (73.7)	1627 (75.9)

SD, standard deviation; MET, metabolic equivalent of task, TEQ, toxic equivalent quantity.

[a] Quintiles' cut offs based on the distribution among controls: ≤0.02, ≤0.20, ≤0.78, ≤2.52 µg-TEQ/m.^{2}.

[b] Alcohol consumption collected during the food questionnaire (Q3).

[c] Use of oral contraceptive collected between Q1 and index date.

[d] Use of menopausal replacement therapy collected between Q2 and index date.

[e] Breast cancer among parents, siblings or children.

borderline positive association between continuous cumulative exposure to dioxins and the risk of breast cancer. With the model 1 (adjusted for confounding variables), for each 1 SD increment in dioxin exposure (GIS-based metric: 14.47 µg-TEQ/m^2) the OR was 1.03 (95% CI: 0.99–1.07). A similar OR estimate was obtained when using dioxin exposure estimated by the CHIMERE model (OR = 1.02, 95% CI: 0.97–1.07, Model 1) for each 1 SD (91.3 fg-TEQ/m^3). No increased risk of breast cancer was observed across quintiles of cumulative dioxin exposure neither with the GIS-based metric (OR $_{Q5\ vs.\ Q1}$ = 1.08, 95% CI: 0.93–1.24, Model 1) nor with the CHIMERE model (OR $_{Q5\ vs.\ Q1}$ = 1.10, 95% CI: 0.78–1.56, Model 1). Comparable results were found when considering the two other adjustment models (Table 2).

There was no association observed when limiting the analyses to either premenopausal, postmenopausal breast cancer (p-value for interaction = 0.84 and 0.59, using the GIS-based metric and the CHIMERE model, respectively) (Supplementary Table 1).

When considering the hormone receptor status of breast cancer, there was a slight but imprecise increase of risk of hormone receptor positive breast cancers, for each 1 SD increment (14.47 µg-TEQ/m^2) in dioxin exposure (GIS-based metric), the ORs were 1.03 (95% CI: 0.99–1.08), 1.05 (95% CI: 0.99–1.12) and 1.05 (95% CI: 0.99–1.13) for ER+, PR+ and ER + PR + breast cancer, respectively (Table 3). The association appeared higher but not statistically significant for invasive lobular breast cancer, with an OR of 1.22 (95% CI: 0.97–1.53), for each 1 SD (14.47 µg-TEQ/m^2) increase in cumulative dioxin exposure estimated with the GIS-based metric (Table 3). There was no evidence of associations with risk of breast cancer subtypes in relation to dioxin exposure estimated by the CHIMERE model. Also, associations did not significantly vary by stage or grade of breast cancer for either exposure assessment approach (Table 3).

There was no evidence of effect modification by education, total physical activity, BMI, tobacco smoking or breastfeeding (Supplementary Table 2).

3.3. Sensitivity analysis

Further analyses using the average of the annual mean dioxin exposure estimates showed similar findings to those observed using the cumulative exposure. The ORs were 1.02 (95% CI: 0.99–1.06) and 1.02 (95% CI: 0.97–1.07) for each 1 SD increase in dioxins exposure estimated with the GIS-based metric (1.42 µg-TEQ/m^2) and with the CHIMERE model (8.2 fg-TEQ/m^3), respectively (Supplementary Table 3). Similar results were obtained when varying the buffer around sources, of the GIS-based metric to 3 km and 5 km, instead of 10 km; with OR = 1.02 (95% CI: 0.98–1.06) for an increase of 1 SD (1.43 µg-TEQ/m^2) for a buffer at 3 km; and 1.03 (95% CI: 0.99–1.07) for an increase of 1 SD (1.43 µg-TEQ/m^2) for a buffer of 5 km (Supplementary Table 4). Moreover, the results remained comparable when the GIS-based dioxin exposure estimates were restricted to specific emission sources. The ORs were 1.02 (95% CI: 0.99–1.07), for an increase of 1 SD (1.59 µg-TEQ/m^2), when only household waste incinerator sources were considered, and 1.00 (95% CI: 0.98–1.03) for an increase of 1 SD (7.43 µg-TEQ/m^2), when only metallurgical sources were included (Supplementary Table 5). Estimates did not change materially when considering only participants with more than two years of follow-up (4864 case-control pairs, OR = 1.03; 95% CI: 0.99–1.07 for each 1 SD increase; 1.44 µg-TEQ/m^2) (Supplementary Table 6). Finally, when dioxin exposure estimates were based on a log1p-transformed measure the analyses yielded ORs comparable to the main findings without transformation (Supplementary Table 7).

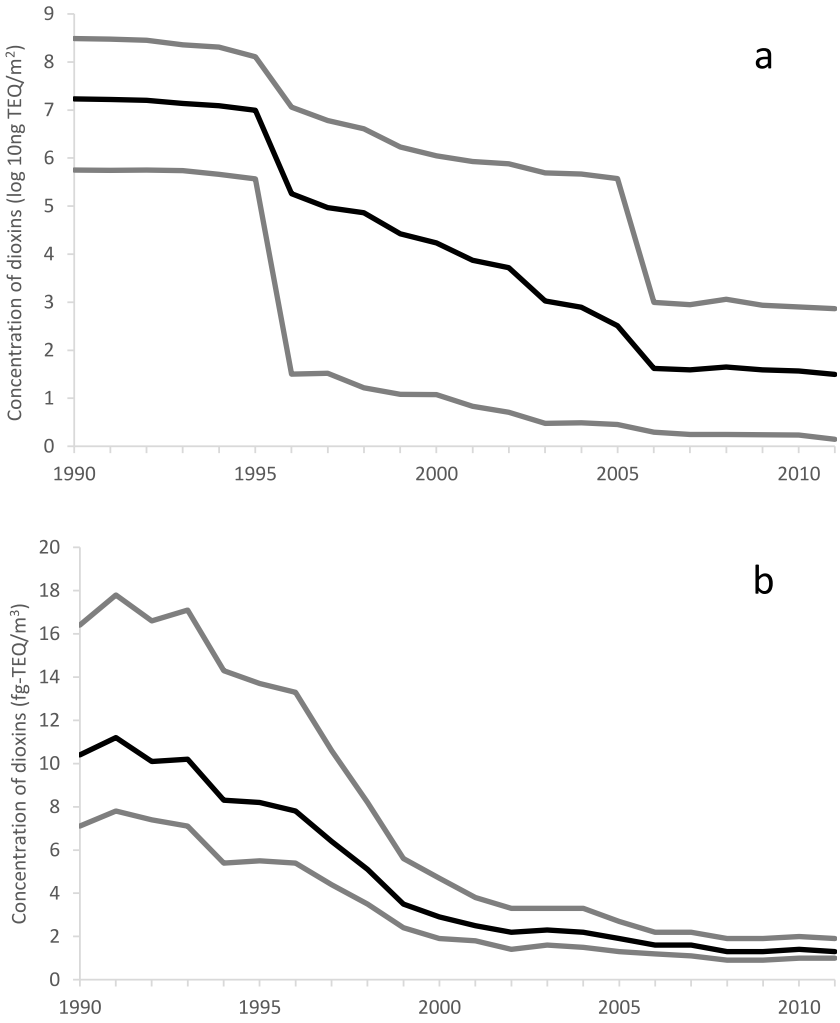

Fig. 1. Average annual evolution of dioxin concentration (median, 1st and 3rd quartiles) at the addresses of the study subjects by year from 1990 to 2011, estimated by the GIS-based metric (log-transformed) (a) and CHIMERE (b). XENAIR case-control study nested in the E3N cohort, France, 1990–2011.

4. Discussion

This study is the largest epidemiological study internationally investigating dioxin exposure and breast cancer risk in a non-occupational population. In this study, the results suggested a weak non-significant positive association between cumulative exposure to dioxins at the residential address and the risk of breast cancer. The associations were similar when restricting the analyses to dioxins emitting sources located within 3, 5 and 10 km and when considering only dioxin exposure estimates from household waste incinerators.

Dioxins, due to their endocrine-disrupting properties, are suspected to increase breast cancer risk, however, despite an increasing number of studies investigating these associations, the epidemiological results obtained have generally been heterogeneous and inconsistent.

Overall, we found little evidence that increased exposure to dioxins was associated with a higher risk of breast cancer. Consistent with our findings, few studies have reported positive associations between dioxin exposure and breast cancer (VoPham et al., 2020). In a case-control study (429 breast cancer cases/716 matched controls, selected from the Rhône-Alpes region) nested within the E3N cohort, no increased risk of breast cancer was found for higher exposure to ambient dioxins overall or by hormone receptor status (Danjou et al., 2019). Conversely, the study by VoPham et al. observed an increased risk of breast cancer only among women living near municipal solid waste incinerators (one of the major sources of dioxin emissions), with the risk being stronger for women who lived within 5 km (VoPham et al., 2020), whereas a recent meta-analysis by Baeck et al., in 2022 did not provide evidence of an increased risk for breast cancer in women living near waste incinerators (Baek et al., 2022). Rhee et al. suggested that residential exposure to PCDD/F emissions may increase the risk of breast cancer, with a higher risk observed among women living within 3 km of the emission sources (Rhee et al., 2023). Warner et al. also reported a non-significant increase in breast cancer risk in women with higher serum levels of TCDD, the most potent dioxin congener (Warner et al., 2011). Moreover, a study based on dietary exposure to dioxins reported no overall association between dietary exposure to dioxins and breast cancer risk, although a decreased risk in some subtypes of breast cancer has been observed (Danjou et al., 2015). Similarly, the last study from the large EPIC European prospective study showed no evidence of an increased risk of breast cancer related to dietary dioxin intake (Fiolet et al., 2024).

The lack of consistent associations reported by some studies could be due to the method of exposure assessment, particularly when a single-point estimate is used instead of a longer period. Additionally, some studies might also be limited by a small number of cases. Although TCDD is often used and considered the most toxic dioxin (IARC, 2012; Coudon et al., 2018), the heterogeneity of dioxins remains a key element that may contribute to the variations of observed in study results. Taken together, these findings highlight the complex relationship between

Table 2
Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the association between invasive breast cancer and cumulative exposure to dioxins, overall. XENAIR case-control study nested in the E3N cohort, France, 1990–2011.

Cumulative dioxins exposure	Matched cases/controls	Model 1[a]		Model 2[b]		Model 3[c]	
		OR	95% CI	OR	95% CI	OR	95% CI
GIS-based metric							
Continuous (for an increment of 14.47 µg-TEQ/m^2)	5222/5222	1.03	0.99–1.07	1.02	0.98–1.07	1.03	0.99–1.07
Quintiles							
≤0.02	1024/1045	1.00		1.00		1.00	
>0.02–0.20	1015/1044	0.99	0.87–1.12	0.99	0.87–1.12	0.97	0.85–1.11
>0.20–0.78	1047/1044	1.02	0.90–1.16	1.01	0.88–1.15	1.00	0.87–1.14
>0.78–2.52	1037/1044	1.01	0.89–1.15	1.00	0.87–1.15	0.99	0.86–1.14
>2.52	1099/1045	1.08	0.93–1.24	1.06	0.91–1.23	1.05	0.90–1.22
CHIMERE							
Continuous (for an increment of 91.3 fg-TEQ/m^3)	5222/5222	1.02	0.97–1.07	1.02	0.98–1.08	1.02	0.97–1.07
Quintiles							
≤40.1	1049/1045	1.00		1.00		1.00	
>40.1–62.5	1013/1044	0.95	0.76–1.20	0.94	0.74–1.18	0.96	0.76–1.22
>62.5–89.5	1045/1044	1.04	0.79–1.37	1.01	0.77–1.34	1.06	0.79–1.40
>89.5–141.8	1061/1044	1.13	0.83–1.54	1.09	0.79–1.50	1.13	0.82–1.56
>141.8	1054/1045	1.13	0.81–1.59	1.10	0.77–1.55	1.13	0.79–1.60

OR, odds ratio; 95% CI, 95% confidence intervals, TEQ, toxic equivalent quantity.

[a] Conditioned for matching variables (age at inclusion or at blood collection, date of return of inclusion questionnaire or at blood collection, menopausal status at inclusion or at blood collection, department of residence at inclusion or at blood collection, availability of a salivary sample), and adjusted for level of education and urban/rural status at inclusion.

[b] Conditioned for matching variables (age at inclusion or at blood collection, date of return of inclusion questionnaire or at blood collection, menopausal status at inclusion or at blood collection, department of residence at inclusion or at blood collection, availability of a salivary sample), and adjusted for physical activity, body mass index, alcohol intake, smoking status, oral contraceptive use, menopausal hormone therapy use, mammography, parity and age at the first full-term pregnancy, breastfeeding, urban/rural status of birthplace and urban/rural status at inclusion.

[c] Model 1 further adjusted for age at menarche, previous family of breast cancer, personal history of benign breast cancer and menopausal status at index date.

dioxin exposure and breast cancer development.

The two methods of dioxin exposure estimation are difficult to compare, firstly because the units of exposure are different (g-TEQ/m2 *vs.* g-TEQ/m^3) and secondly because the objectives of these two methods are different, even opposed. The GIS-based metric is based on the idea that industrial sources are the dominant sources of exposure to dioxins and are sufficient to separate subjects according to their exposure. In a previous study, we showed that this was the case for most of the study period, even when considering the decrease of industrial emission (Coudon et al., 2018). This tool was originally developed specifically for the French E3N cohort population, and has been validated in comparison with a reference model in 3 areas of France. The CHIMERE model, on the other hand, was designed by INERIS to process all types of emissions over a wide area and produce global estimates on a European scale with coarse resolution. This model has the advantage of considering types of emission that are neglected by the GIS-based metric (traffic, heating, cable burning). However, these global emission data come from the European EMEP database (50 × 50km resolution) and are estimated based on macroeconomic indicators. This illustrates the difference with the GIS-based metric which, on the contrary, is based on ultra-local input data (nearly 3185 industrial sources located mainly at the stack).

In summary, the CHIMERE model is relevant for describing background exposure to dioxins, whereas the GIS-based metric better describes exposure to industrials dioxin emissions.

In terms of breast cancer risk assessment, the difference between the two methods seems to indicate that exposure to industrial dioxin emissions has a more significant impact on the risk of breast cancer than exposure to ambient background dioxin concentration. Several hypotheses can be considered to explain these results. Industrial emissions may consist of a specific combination of dioxins. However, the use of the TEQ system by both methods theoretically allows weighting exposures based on the toxicity of different dioxin congeners present in the mixture. It is possible that the TEQ weighting may not be suitable for breast cancer risk. Another hypothesis for explaining the observed difference is that industrial emissions of dioxins may be associated with other types of industrial emissions (such as cadmium and particles). The estimates provided by the GIS-based metric would therefore be representative of a "general" exposure to various industrial emissions that could increase the risk of breast cancer. Indeed, dioxins have been used several times as "tracer" pollutants for overall exposure related to industrial emissions such as those from domestic waste incinerators (Cordioli et al., 2013; Ranzi et al., 2011).

Several biological mechanisms have been proposed to explain the potential association between dioxins and breast cancer (Modica et al., 2023). Evidence from cell line and receptor assay studies shows that, to exert their carcinogenic effects, dioxins can bind to and activate the aryl hydrocarbon receptor (AhR), which can modulate the activation of several genes involved in cell proliferation, progression, inflammation, and in turn contribute to the development of breast cancer cells (Sweeney et al., 2022; Wang et al., 2020). Moreover, long-term exposure can cause DNA damage, notably by regulating estradiol-induced DNA damage in breast cancer cells, resulting in the altered expression of cytochrome P450 A1 and B1 (CYP1A1 and CYP1B1 (Das et al., 2017). Dioxin exposure is also linked to changes in epigenetic patterns, which can modify gene expression and contribute to both the development and progression of breast cancer (Singh et al., 2023). Additionally, another biological mechanism by which dioxins may influence breast cancer development is its endocrine disruption property (Rodgers et al., 2018; Smith et al., 2016). Dioxins are known to disrupt the endocrine system and interfere with estrogen signaling pathways, which can promote the growth of hormone-sensitive breast cancer cells (Eve et al., 2020; Wan et al., 2022). Moreover, a varying effect of TCDD according to windows of exposure has been observed in animal studies reporting increased susceptibility to carcinogen-induced mammary tumor formation associated with prenatal TCDD exposure, while exposure during pregnancy delayed mammary tumor formation (Safe, 1995).

One of the strengths of our study is the large number of cases, facilitated by the large E3N cohort. The cohort also provided extensive information on women's characteristics, enabling us to adjust for potential confounding factors and effect modifiers, and conduct subgroup analyses. The present analysis is also the first national study to have been performed in France. Additionally, one of the novelties of this

Table 3
Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for the association between invasive breast cancer and cumulative exposure to dioxins according to the hormone receptors status and histopathological types. XENAIR case-control study nested in the E3N cohort, France, 1990–2011.

Cumulative dioxins exposure	Matched cases/controls	OR[a]	95% CI
GIS-based metric (for an increment of 14.47 µg-TEQ/m^2)			
Hormone receptor			
ER-	760/760	1.00	0.84–1.19
ER+	3405/3405	1.03	0.99–1.08
PR-	1439/1439	1.06	0.95–1.19
PR+	2602/2602	1.05	0.99–1.12
ER-PR-	612/612	0.98	0.80–1.20
ER + PR+	2459/2459	1.05	0.99–1.13
Missing	1186/1186	0.99	0.93–1.05
Stage			
Stage I	2919/2919	1.05	0.99–1.11
Stage II	1412/1412	0.98	0.92–1.05
Stage III-IV	402/402	1.12	0.90–1.38
Missing	489/489	1.08	0.85–1.38
Grade of differentiation			
Grade I	614/614	1.06	0.94–1.19
Grade II	1483/1483	1.03	0.94–1.14
Grade III-IV	2067/2067	1.01	0.95–1.06
Missing	1058/1058	1.06	0.96–1.16
Histology			
Invasive ductal	3568/3568	1.02	0.98–1.06
Invasive lobular	828/828	1.22	0.97–1.53
Invasive tubular	141/141	1.32	0.79–2.20
Ductal-lobular	123/123	0.96	0.75–1.24
Missing	281/281	1.13	0.82–1.55
CHIMERE (for an increment of 91.3 fg-TEQ/m^3)			
Hormone receptor			
ER-	760/760	1.12	0.91–1.37
ER+	3405/3405	1.01	0.94–1.09
PR-	1439/1439	1.02	0.92–1.13
PR+	2602/2602	0.95	0.85–1.08
ER-PR-	612/612	1.10	0.91–1.32
ER + PR+	2459/2459	0.95	0.84–1.07
Missing	1186/1186	1.04	0.97–1.11
Stage			
Stage I	2919/2919	1.03	0.96–1.11
Stage II	1412/1412	1.00	0.89–1.12
Stage III-IV	402/402	0.83	0.56–1.12
Missing	489/489	1.03	0.94–1.12
Grade of differentiation			
Grade I	614/614	1.07	0.86–1.33
Grade II	1483/1483	0.99	0.87–1.12
Grade III-IV	2067/2067	1.02	0.95–1.10
Missing	1058/1058	1.03	0.95–1.11
Histology			
Invasive ductal	3568/3568	1.01	0.94–1.09
Invasive lobular	828/828	1.16	0.92–1.47
Invasive tubular	141/141	1.14	0.71–1.85
Ductal-lobular	123/123	0.90	0.70–1.15
Missing	281/281	1.03	0.95–1.13

OR, odds ratio; 95% CI, 95% confidence intervals, TEQ, toxic equivalent quantity.

[a] Conditioned for matching variables (age at inclusion or at blood collection, date of return of inclusion questionnaire or at blood collection, menopausal status at inclusion or at blood collection, department of residence at inclusion or at blood collection, availability of a salivary sample), and adjusted for level of education and urban/rural status at inclusion (Model 1).

study was the use of two exposure assessment approaches considering participants' residential histories up to 22 years before the diagnosis of breast cancer cases. This methodology accounted for the residential mobility of the study participants and temporal variations in dioxin emissions throughout the study period. GIS-based methods have been increasingly employed as an alternative for assessing exposure to air pollutants in the absence of measured data, as evidenced by their growing use in epidemiological studies (Cordioli et al., 2013; Rodgers et al., 2018). In our study, we evaluated airborne dioxin exposure using a GIS-based metric that enabled the estimation of long-term exposure at the individual address level (Coudon et al., 2018). The GIS-based metric incorporated parameters identified in the literature as influencing individual airborne dioxin exposure, including residence-to-source proximity, dioxin emission intensity from industrial sources, exposure duration, and wind direction (Gulliver and Briggs, 2011; Hoek et al., 2001; Pronk et al., 2013; Vienneau et al., 2009; White et al., 2009; Yu et al., 2006). The exposure classification into quintiles, based on the GIS-based metric, demonstrated a good agreement with dioxin dispersion modeling (SIRANE) (Soulhac et al., 2011, 2012, 2017) across various settings (Coudon et al., 2018; Viera and Garrett, 2005). Furthermore, the use of an additional model (CHIMERE) for exposure assessment supports our primary findings.

Overall, our findings should be interpreted in the light of certain limitations. Firstly, our study included women aged between 45 and 60 years old; assessing dioxin exposure before 1990 was not feasible. Consequently, we were unable to investigate exposure throughout the entire lifespan of the participants or conduct analyses during key periods of sensitivity, such as puberty and pregnancy. Additionally, dioxin emissions decreased over the study period, and the exposure levels were likely higher before 1990, meaning that a portion of the exposure was missed. However, left truncation of dioxin emission estimates may be associated with the overestimation of the dose effect and should be interpreted with caution (Zhai et al., 2021). Nevertheless, due to the matched design of our study, cases and controls were compared over the same follow-up duration, from 1990 to the index date, within each case-control pair. Some cases had a shorter follow-up, but a sensitivity analysis carried out on women followed-up for at least two years showed no difference in the observed association. Despite considerable efforts to account for potential confounding factors, some residual confounders such as dietary exposure could not be entirely ruled out. However, investigation into dietary exposure to dioxins in the E3N study did not find an association with breast cancer (Danjou et al., 2015), a result confirmed by a recent analysis of the EPIC study (a consortium including the E3N cohort) (Fiolet et al., 2024). Finally, our study focused only on airborne exposure to dioxins, and we cannot exclude confusion with or interaction between other air pollutants. Further epidemiological studies are needed to consider multi-exposures using appropriate statistical methods.

5. Conclusions

Our study suggests the possibility of a weak association between exposure to dioxin pollution and breast cancer risk in the XENAIR study, a case-control study nested within the E3N cohort. These findings contribute to understanding the effect of air pollution on breast cancer risk and highlight the need for future studies in general, and with particular focus on exposure during specific critical windows (e.g., prenatal, puberty and during pregnancy), given the major structural and functional changes in the breast during these periods, and the greater impact of dioxins observed in animal studies.

10. IARC disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organisation, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organisation.

CRediT authorship contribution statement

Delphine Praud: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Amina Amadou:** Writing – original draft, Methodology. **Thomas Coudon:** Writing – review & editing, Funding acquisition, Data curation. **Margaux Duboeuf:** Writing – review & editing, Software, Formal analysis. **Benoît Mercoeur:** Writing – review & editing, Formal analysis. **Elodie Faure:** Writing – review & editing, Project administration, Data curation. **Lény Grassot:** Writing – review & editing, Data curation. **Aurélie MN. Danjou:** Writing – review & editing, Methodology. **Pietro Salizzoni:** Writing – review & editing, Data curation. **Florian Couvidat:** Writing – review & editing, Data curation. **Laure Dossus:** Writing – review & editing, Project administration. **Gianluca Severi:** Writing – review & editing. **Francesca Romana Mancini:** Writing – review & editing. **Béatrice Fervers:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Ethical considerations

The study was approved by the French National Commission for Data Protection and Privacy (CNIL). Informed consent was obtained from all the individuals included in the study.

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Declaration of competing interests

The authors declare that they have no competing financial or non-financial interests that could appear to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114489.

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