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Author's draft

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Abstract

Background:

Dioxins, Group 1 carcinogens, are emitted by industrial chlorinated combustion processes and suspected to increase breast cancer risk through receptor-mediated pathways.

Objectives:

We estimated breast cancer risk associated with airborne dioxin exposure, using geographic information system (GIS) methods and historical exposure data.

Methods:

We designed a case-control study (429 breast cancer cases diagnosed between 1990 and 2008, matched to 716 controls) nested within the E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) cohort. Airborne dioxin exposure was assessed using a GIS-based metric including participants' residential history, technical characteristics of 222 dioxin sources, residential proximity to dioxin sources, exposure duration and wind direction. Odds ratios (OR) and 95% confidence intervals (CI) associated with quintiles of cumulative exposure were estimated using multivariate logistic regression models.

Results:

We observed no increased risk of breast cancer for higher dioxin exposure levels overall and according to hormone-receptor status. We however observed a statistically significant OR for Q2 *versus* Q1 overall (1.612, 95% CI: 1.042-2.493) and for estrogen-receptor (ER) positive breast cancer (1.843, 95% CI: 1.033-3.292).

Conclusions:

Overall, as well as according to hormone-receptor status, no increased risk was observed for higher airborne dioxin exposure. The increased risk for low exposure levels might be compatible with non-monotonic dose-response relationship. Confirmation of our findings is required. Our GIS-based metric may provide an alternative in absence of ambient dioxin monitoring and may allow assessing exposure to other pollutants.

Keywords

Breast cancer; endocrine disruptors; dioxins; geographic information system; tumor receptor

Abbreviations

AIC, Akaike information criteria; AhR, aryl hydrocarbon receptor; BMI, body mass index; CI, confidence interval; E3N, Étude Épidémiologique auprès de femmes de l'Éducation Nationale ; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, estrogen receptor; GIS, Geographical Information System; IARC, International Agency for Research Agency; IGN, National Geographic Institute; MET, metabolic equivalent task; MHT, menopausal hormone therapy; MSWI, municipal solid waste incinerator; OR, odds ratio; PCDD, polychlorinated dibenzo-*para*-dioxin; PCDF, polychlorinated dibenzofuran; PR, progesterone receptor; SD, standard deviation; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TEQ, toxic equivalent

1. Introduction

Dioxins are a mixture of related chemicals, namely polychlorinated dibenzo-*para*-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF), generated from combustion processes involving chlorine-bearing materials. The main sources of dioxin release in the environment include chemical manufacturing of chlorinated products such as herbicides and insecticides and industrial activities from metallurgy, steel and municipal solid waste incineration (MSWI) (Anzivino-Viricel et al., 2012; ATSDR, 1998; Travis and Hattemer-Frey, 1989; Zook and Rappe, 1994). Emissions of dioxins have greatly decreased since the 1990s, because of changes in regulation and technological processes (Anzivino-Viricel et al., 2012; Coudon et al., 2017; Nzihou et al., 2012). In France, emissions have been reduced by a factor of 1000 between 1990 and 2008 (CITEPA, 2015). Dioxins are persistent in the environment and bioaccumulate at high trophic levels, including livestock and humans. Although most of human exposure to dioxins occurs from consumption of contaminated fat-rich food in the general population (IARC, 2012), airborne dioxin exposure may also be a major exposure route, in particular for populations living in the vicinity of industrial dioxin sources.

TCDD (2,3,7,8-tetrachlorodibenzo-*para*-dioxin) is the most potent dioxin congener and 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). Experimental evidence showed that dioxins have no genotoxic activity, but rather act as tumor promoter through activation of cellular replication, interruption of apoptosis and increase in oxidative stress (IARC, 2012; Knerr and Schrenk, 2006; Mandal, 2005). As a persistent endocrine disruptor, TCDD may contribute to breast cancer by binding to the aryl hydrocarbon receptor (AhR), a nuclear transcription factor widely present in humans and animals that influences gene expression, enzyme metabolism and hormone signaling pathway, including estrogen- and progesterone-mediated pathways (Birnbaum and Fenton, 2002; Boverhof, 2006; Jenkins et al., 2012; Matthews and Gustafsson, 2006; Tsuchiya et al., 2005).

An increased risk of breast cancer associated with dioxin exposure has been suggested, but overall, epidemiological studies did not provide a consistent link between dioxin exposure and risk of breast cancer in women (Rodgers et al., 2018; Xu et al., 2016). Following the 1976 industrial accident in Seveso, Italy, results from the cohort of local residents in the contaminated zones showed no increase in breast cancer risk (Bertazzi et al., 1993; Pesatori et al., 2009). In addition, in the Seveso Women's Health Study (SWHS), no association was

observed between TCDD serum levels measured in blood samples provided after the accident and breast cancer risk among women who were 0-40 years old at the time of the accident and lived in the most contaminated zones (Warner et al., 2011). Positive associations were found in cohorts of herbicide and insecticide workers (Brody et al., 2007; Manuwald et al., 2012), among Russian women living near a chemical plant, compared with women from a non-contaminated area (Revich et al., 2001), and among women from a large French ecological study of residents exposed to dioxin emissions from several MSWIs (Fabre et al., 2008). On the contrary, a statistically significant decrease in breast cancer risk was found among women over 60 years of age and living in the most exposed zone around a French MSWI (Viel et al., 2008). The most recent meta-analysis, involving ten studies conducted on the association between external TCDD exposure and cancer incidence, reported no statistically significant increased risk for breast cancer (Xu et al., 2016).

The inconsistency in published results may be explained by differences in study population and methodology (*e.g.* study design and exposure assessment) as well as some specific study limitations, including the lack of adjustment for confounding by established risk factors, inadequate exposure assessment and small number of cases (Cordioli et al., 2013; Rodgers et al., 2018; Xu et al., 2016). The long-term nature of airborne dioxin exposure may imply variations in exposure intensities over time. Given their tumor-promoter properties, studying the association between airborne dioxin exposure and breast cancer risk should consider the impact of temporal variation in exposure, exposure proximal to time of diagnosis as well as hormone receptor subtypes of breast tumors (Rodgers et al., 2018).

Recently, we investigated the relationship between estimated dietary dioxin exposure and breast cancer risk in the French E3N (Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale) prospective cohort. No association was observed overall, except for a statistically significant decrease in postmenopausal hormone receptor-negative breast cancer risk among women most exposed (Danjou et al., 2015). Here, we estimated breast cancer risk associated with airborne dioxin exposure in a case-control study nested within the E3N cohort and restricted to the Rhône-Alpes region, France, using geographic information system (GIS) methods and historical exposure data for the assessment of airborne dioxin exposure.

2. Material and methods

2.1. The E3N cohort study

The E3N study is an ongoing prospective cohort, initiated to identify female cancer risk factors, such as dietary, hormonal and reproductive factors (Clavel-Chapelon, 2015). The cohort includes 98,995 French female volunteers, born between 1925 and 1950, subscribers of a national health insurance covering mostly teachers and recruited between 1989 and 1991. The study protocol was approved by the French National Commission for Data Protection and Privacy. The study was initiated when participants returned the first self-administered questionnaire and provided written informed consent for data collection. Since then, participants completed self-administered questionnaires, mailed every 2 to 3 years, on health status, medical history and a large number of lifestyle factors. Overall, nine questionnaires were sent between 1990 and 2008. Epidemiological data were enriched with 25,000 blood samples and 47,000 saliva samples. Participants' home addresses were recorded in the first and fifth to ninth questionnaires (years 1990, 1997, 2000, 2002, 2005 and 2008); their zip code was recorded in the third and fourth questionnaires (years 1993 and 1994); there was no address kept in the database for the second questionnaire (year 1992). Moreover, participants' place of birth (zip code and commune) was obtained from the first questionnaire and an urban/rural status was assigned; definition of the urban/rural status has been previously described (Binachon et al., 2014). The E3N cohort is the French component of the European Prospective Investigation into Cancer and nutrition (EPIC) study (Riboli, 1992; Riboli et al., 2002).

2.2. Study population

For this nested case-control study, we selected participants who filled in their home address at baseline (*i.e.* entry into the cohort), lived in the Rhône-Alpes region, France between 1990 and 2008 and had not reported cancer at baseline. The study population was selected from the Rhône-Alpes region because of its high population density (147.8 inhabitants/km² in 2014 (Insee, 2017)), its large area (43,700 km²), and its dense industrial network (2nd French industrial region, (Insee, 2012)). Data on health status and medical history of participants, including cancer occurrence, were collected and updated throughout the follow-up. Between 1990 and 2008, 429 primary invasive breast cancer cases were reported, of which 93.5% have been validated with pathology reports; not confirmed cases (N=28) were considered as breast cancer cases, as the proportion of false-positive self-reported breast cancer cases is less than 5% in the E3N cohort. Information on estrogen

receptor (ER) and progesterone receptor (PR) status was obtained from the pathology reports: n=244 breast tumors were ER positive (ER+); n=80 were ER-negative (ER-); n=215 were PR positive (PR+); and n=108 were PR-negative (PR-).

Using incidence density sampling, up to two controls per case were randomly selected and matched for age (± 1 year), department (French administrative divisions) of residence, menopausal status and date (± 3 months) at blood collection for participants who donated blood (N=325 (28.4%)), or at baseline for participants without a blood sample. The latter were matched for existence or not of a saliva sample (N=514 (44.9%) and N=306 (26.7%), respectively). A total of 716 controls were selected.

With matching on age and date of blood collection or date at baseline, we compared exposure of cases and controls having the same age, at the same time and the same timespan of exposure assessment since recruitment in the cohort. Existence of a biological sample was included in the matching protocol in perspective of future epi-genetic or gene-environment interaction studies.

2.3. Assessment of airborne dioxin exposure

The methodology for the assessment of airborne dioxin exposure has been previously described in detail (Coudon et al., 2018, 2017); a brief description is given below.

2.3.1. Inventory and characterization of industrial dioxin sources

A detailed retrospective inventory of industrial sources likely to emit or to have emitted dioxins between 1990 and 2008 in the Rhône-Alpes region, France was performed. The industrial sources were identified through national databases, institutional information sources and structured questionnaires. Information on technical and process characteristics (*e.g.* stack height, exhaust flow rate and flue gas cleaning technologies), operating periods and rates, input materials and geographic location of the facilities were collected. We also used data from an existing inventory of MSWIs that operated in the Rhône-Alpes region between 2001 and 2003, and for which technical characteristics and dioxin emissions have been collected (Cordier et al., 2004).

A total of 222 industrial dioxin sources operated in the Rhône-Alpes region from 1990 to 2008, corresponding to 286 distinct operation periods according to the evolution of technical characteristics. The predominant sector was waste incineration (N=119 distinct operation periods-sources), followed by production of mineral (N=87), heat and power generation (N=40), metal production (N=26), crematoria (N=13) and chemicals and consumer goods (N=1).

Using the 2013 Standardized Toolkit for Identification and Quantification of Dioxin and Furan Releases of the United Nation Environment Program (UNEP, 2013), the industrial sources were classified according to their main activity sector and technical characteristics to determine a dioxin emission factor (g-toxic equivalents (TEQ)/t). For each distinct operation period, the annual dioxin emission intensity (g-TEQ/year) was estimated by multiplying the emission factor by the operating rate.

2.3.2. Geocoding of the residential history and industrial sources

From 1990 to 2008, the residential history of the participants was extracted from the E3N follow-up questionnaires and geocoded (X and Y coordinates, addresses) using the ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute – ESRI, Redlands, CA, USA) and the address database, BD Adresse®, from the National Geographic Institute (IGN) (Faure et al., 2017). Geocoding was performed by a trained technician blinded to the case-control status of the participants. In addition, each industrial source inventoried was located in the GIS, based on collected geographic coordinates when available or addresses, and manually checked or repositioned at the location of the flue-gas stack.

2.3.3. Exposure assessment

Airborne dioxin exposure was estimated for each participant at the individual address level using a GIS-based metric. Relevant parameters to be integrated in the GIS-based metric were identified from the literature (Gulliver and Briggs, 2011; Hoek et al., 2001; Pronk et al., 2013; Vienneau et al., 2009; White et al., 2009; Yu, 2006) and from a previous work on dioxin dispersion modeling (Coudon et al., 2017). The definition and reliability of the GIS-based metric have been described in a previous publication (Coudon et al., 2018). Briefly, we considered that the impact zone of dioxin emissions was limited to a 10 km buffer zone (*i.e.* a circle of 10 km radius) around each industrial source. We determined the residence-to-source distance *d* for each participant's residence located in a buffer zone and the dioxin emissions' decline pattern. The buffer zone was divided into sectors of equal size, each of them characterized by a wind direction frequency (evaluated by means of hourly data registered at the nearest *Météo France* ® station, over the 1990-2008 period). The exposure of a participant to a given industrial source depended on its positioning, within the buffer zone, in one of these sectors. In order to take into account the effects of atmospheric turbulence on the dispersion of dioxin emissions over a wide area downwind the industrial source, we included two weighting factors: a higher one for the sector in which the participant was located in, and

a lower one for the two adjacent sectors. Theses parameters were combined with the Toolkit-based annual dioxin emission intensity and the exposure duration.

In the final GIS-based metric, the airborne dioxin exposure of each participant was computed as:

$$\text{GIS} - \text{based metric} = \sum_{j=1}^{J}\sum_{i=1}^{I}\left(EI_i \times t_i \times {d_{ij}}^{-2} \times F_{ij}\right) [1]$$

where the indices *j* and *i* indicate the places of residence (j=1,…,J) and the industrial sources (i=1,…,I), respectively, and where EI_i is the annual dioxin emission intensity of each industrial source (in g-TEQ/year), t_i is its emission period duration (in years), d_{ij} is the residence-to-source distance (in m) and F_{ij} is the factor taking into account the percentage of time during which the wind is blowing in a direction so as to induce a transport from the industrial source *i* to the location of the participant *j* (accounting for the weighted contribution of the sector of the buffer in which the participant is located in, *i.e.* 50% and that of the two adjacent sectors, *i.e.* 25% each). Airborne dioxin exposure was expressed in µg-TEQ/m² and computed for each calendar year from 1990 to 2008. The reliability of the GIS-based metric was assessed by comparing its exposure classification with that provided by an atmospheric dispersion modeling and showed weighted kappa coefficients ranging from 0.71 (0.67-0.76) to 0.84 (0.79-0.88) and R^2 ranging from 0.68 to 0.90; both consistent across time-periods and areas (rural/ urban/ coastal) (Coudon et al., 2018).

2.4. Statistical analyses

Airborne dioxin exposure was summarized into a cumulative exposure metric from baseline to the index date (date of diagnosis of the case in the case-control pair) by summing up the annual metric estimates. Based on the distribution of cumulative airborne dioxin exposure in our study population, exposure was *a priori* categorized according to quintiles of the control distribution.

Baseline characteristics of the participants were described by case-control status and according to quintiles of the cumulative metric of airborne dioxin exposure, using mean and SD for continuous covariates and frequency and percentage for categorical covariates. Baseline characteristics were compared between cases and controls with univariate conditional logistic regression models, and across quintiles of cumulative airborne dioxin exposure with Chi-square statistical test and analysis of variance.

Odds ratios (OR) and corresponding 95% CIs for invasive breast cancer were estimated for quintiles of the cumulative exposure metric with the first quintile as the

reference group, using multivariate conditional logistic regression models (Hosmer and Lemeshow, 2000). Tests for linear trend across quintiles were performed and derived from the Wald test of the models including quintiles of exposure as a continuous variable. All models were conditioned for matching factors (age, department of residence, menopausal status and date at blood collection or at baseline and existence of a biological sample (blood, saliva, none)). Models included terms for individual breast cancer risk factors and confounding factors selected through manual backward stepwise selection; covariates were retained if they were associated with breast cancer ($p<0.05$) or if they modified odds ratios by more than 10%: recreational physical activity at baseline (quartiles: <25.3, 25.3-37.2, 37.3-57.5, ≥57.6 metabolic equivalent task-hour per week (MET-h/w)); previous family history of breast cancer (no, yes); age at first full-term pregnancy (≤24, >24 years old; median value among controls); breastfeeding (never, ever) were found associated with breast cancer and status of birthplace (rural, urban) was considered as confounding factor. Although alcohol intake and education were differently distributed among cases and controls and quintiles of exposure (table 1 and table 2), they were not confounding factors in our study population. Simple imputation methods were used for missing data (Garcia-Acosta and Clavel-Chapelon, 1999): for covariates with less than 5% missing data, the latter were replaced by their modal or median value of the control population; age at first full-term pregnancy had more than 5% of missing data, thus a category "missing data" was generated.

We estimated invasive breast cancer odds ratios according to hormone-receptor status (ER and PR) of the breast tumors and tested heterogeneity of associations in these subgroups (ER-positive *versus* ER-negative, and PR-positive *versus* PR-negative) using polytomous logistic regression for nested case-control study (SAS macro *%subtype*) (Wang et al., 2016). *P*-values for heterogeneity were derived from the Likelihood Ratio Test (Wang et al., 2016). ER and PR status were missing for N=105 cases and N=106 cases, respectively. Models were further adjusted for estimated dietary dioxin intake, which was assessed in the E3N cohort (Danjou et al., 2015) by combining consumption data from a diet history questionnaire completed in 1993 by E3N the participants with food dioxin contamination data (CSHPF, 2000) according to the WHO recommended method (FAO/WHO, 2005). In addition, the relationship cumulative airborne dioxin exposure on breast cancer risk was investigated using a cubic spline function, with 10 knots evenly spaced over the range of values of dioxin exposure, in order to possibly highlight a non-linear effect of dioxins (Hastie and Tibshirani, 1990).

To investigate whether the effect of cumulative metric of airborne dioxin exposure was homogeneous across strata of selected covariates, we conducted stratified analyses. First, we estimated ORs for breast cancer according to menopausal status at index date (pre-menopause, post-menopause). Because of the bioaccumulation of dioxins in adipose tissue (Fries, 1995), dioxin exposure may vary depending on individual body composition, in particular fat mass; we conducted separate analysis in strata of body mass index (BMI) at baseline (≤21.9, >21.9 kg/m²; median value among controls) (Frery et al., 2007; Jackson et al., 2017). As breastfeeding has been shown to be negatively associated with dioxin body burden, we stratified the analysis according to breastfeeding (never, ever) (Caspersen et al., 2013; Humblet et al., 2010; Uemura et al., 2008). On the contrary, studies have reported positive associations of dioxins with age and maternal age due to dioxins' persistence and bioaccumulation in the human body (Caspersen et al., 2013; Humblet et al., 2010). We estimated OR for breast cancer separately among women aged 24 years old or less and over 24 years old at first full-term pregnancy (median value among controls). Due to negative associations between smoking habits and dioxin body burden, we conducted separate analyses according to smoking status at baseline (never, ever) (Arisawa et al., 2011; Frery et al., 2007; Hsu et al., 2009; Uemura et al., 2008). Association between invasive breast cancer risk and quintiles of the cumulative metric of airborne dioxin exposure was examined in the above-defined subgroups using unconditional logistic regression models adjusted for matching factors in order to retain all subjects in the models. Heterogeneity across strata was assessed with likelihood ratio tests comparing the nested models including and excluding interaction terms (Hosmer and Lemeshow, 2000). In addition, due to previously observed opposite associations between increased BMI and breast cancer risk in pre- and postmenopause, the interaction between BMI and menopausal status at baseline was tested in our study population (Chen et al., 2017; Schoemaker et al., 2018; Tehard et al., 2004).

We performed sensitivity analyses to test robustness of our findings. First, we estimated ORs for breast cancer according to quintiles of exposure using multiple imputation method for missing data on the following variables: age at first full-term pregnancy, status of birthplace and previous family history of breast cancer (Karahalios et al., 2012; Pedersen et al., 2017). Missing data were imputed 20 times using SAS procedures PROC MI and PROC MIANALYZE. Second, the cases not confirmed by pathology report (N=28, plus matched controls, N=44) were excluded and the models were run in this subgroup. In a third sensitivity analysis, participants that have been living more than 10 km away from any source between 1990 and 2008 (*i.e.* for which cumulative airborne dioxin exposure was estimated to be equal

to 0 over the study period by the cumulative metric and presented differences for several baseline characteristics) were separated from the first quintile, in order to assess differences in OR for breast cancer between participants with a cumulative null exposure and participants from the first quintile (first quintile as reference). In addition, we excluded cases diagnosed within the first five years after inclusion in the cohort (N=135, plus matched controls N=247) in order to exclude subjects with a high proportion of left truncated exposure information that might impact ORs for breast cancer (Hazelbag et al., 2015). Finally, we investigated the possible time-dependent impact of the annual intensity of airborne dioxin exposure on breast cancer risk, using a weighted cumulative index of exposure in logistic regression (Hauptmann et al., 2000; Lacourt et al., 2017; Lévêque et al., 2018). Weights were estimated from the data using a cubic B-spline with one interior knot minimizing the Akaike's information criteria (AIC). We calculated the ORs associated with the annual intensity of exposure at each year of exposure before the index date; nonparametric bootstrap sampling was performed to obtain 95% confidence intervals. Models included matching factors and covariates (recreational physical activity at baseline; previous family history of breast cancer; age at first full-term pregnancy; breastfeeding and status of birthplace).

All *P*-values were two-sided and the nominal level of statistical significance was set at 0.05. We used the SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) and the R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for data analysis.

3. Results

The baseline characteristics of the 429 cases of invasive breast cancer and the 716 matched controls are shown in Table 1. Cases reported less recreational physical activity than controls; they were more educated, younger at age at menarche and older at age at first full-term pregnancy. Performing a mammogram, family history of breast cancer and personal history of benign breast disease were more frequent among cases than controls. There was no difference in estimated dietary dioxin intake between breast cancer cases and matched controls (p=0.07; Table 1). The average cumulative metric of airborne dioxin exposure was estimated at 0.14 ± 1.20 µg-TEQ/m² (range: 0 to 24.43) for breast cancer cases and 0.12 ± 0.61 µg-TEQ/m² (range: 0 to 10.35) for controls. The average exposure duration between recruitment and diagnosis among cases was 8.7 ± 4.9 years (range: 1 month to 18 years) and the mean age at breast cancer diagnosis was 58.0 ± 7.8 years (range: 41.9 to 78.2).

Table 1. Baseline and clinical characteristics of 429 breast cancer cases and 716 controls, E3N study, Rhône-Alpes region, France, 1990-2008.

Characteristics	Cases		Controls		*P* [a]
Age at baseline (years), mean (SD)	49.4	6.1	49.5	6.2	0.81
Age at diagnosis (years), among breast cancer cases, mean (SD)	58.0	7.8	-	-	-
Time to diagnosis (years), among breast cancer cases, mean (SD)	8.7	4.9	-	-	-
Body Mass Index (kg/m²), median value among controls, n (%)					0.56
<=21.9	229	53.4	366	51.1	
>21.9	200	46.6	350	48.9	
Alcohol drinking, n (%)					0.11
Never drinker	37	8.6	85	11.9	
Drinker <5.9 g/day	144	33.6	229	32.0	
Drinker >= 5.9 g/day	217	50.6	309	43.2	
Missing data	*31*	*7.2*	*93*	*13.0*	
Smoking status, n (%)					0.30
Never smoker	235	54.8	416	58.1	
Current smoker	55	12.8	98	13.7	
Former smoker	139	32.4	202	28.2	
Status of birthplace, n (%)					0.07
Rural	89	20.7	180	25.1	
Urban	310	72.3	496	69.3	
Missing data	*30*	*7.0*	*40*	*5.6*	
Status of residence at baseline					0.12
Rural	120	28.0	237	33.1	
Urban	279	65.0	439	61.3	
Missing data	*30*	*7.0*	*40*	*5.6*	
Recreational physical activity (METs-h/week), n (%)					0.02
<25.3	105	24.5	141	19.7	
25.3-37.3	117	27.3	211	29.5	
37.4-56.9	132	30.8	191	26.7	
>=57.0	75	17.5	173	24.2	

Characteristics	Cases		Controls		*P* [a]
Education, n (%)					0.02
Undergraduate	44	10.3	88	12.3	
Post-graduate with a 1- to 2-year university degree	198	46.2	373	52.1	
Post-graduate with a >= 3 year university degree	187	43.6	255	35.6	
Age at menarche (years), modal value among controls, n (%)					0.01
<13	222	51.7	311	43.4	
>=13	207	48.3	405	56.6	
Previous use of oral contraceptives, n (%)	264	61.5	426	59.5	0.60
Previous use of progestin before menopause, n (%)	200	46.6	300	41.9	0.21
Menopausal status, n (%)					0.72
Premenopausal women	261	60.8	426	59.5	
Postmenopausal women	168	39.2	290	40.5	
Use of menopausal hormone treatment, among postmenopausal women, n (%)	62	13.5	94	20.5	0.42
Mammography during the previous follow-up period, n (%)	342	79.7	527	73.6	0.01
Age at first full-term pregnancy (years), median value among controls, n (%)					0.02
<=24	161	37.5	314	43.9	
>24	208	48.5	313	43.7	
Missing data	*60*	*14.0*	*89*	*12.4*	
Parity, n (%)					0.38
0	0	0.0	0	0.0	
1-2	260	60.6	413	57.7	
>=3	109	25.4	213	29.7	
Missing data	*60*	*14.0*	*90*	*12.6*	
Breastfeeding among parous women, n (%)	243	56.6	433	60.5	0.20
Previous family history of breast cancer, n (%)	76	17.7	67	9.4	<0.001
Previous history of personal benign breast disease, n (%)	166	38.7	206	28.8	<0.001
Estimated dietary dioxin intake (pg TEQ/kg body weight/day), mean (SD)	1.3	0.4	1.2	0.4	0.07
Missing data [b]	*119*	*27.7*	*135*	*18.9*	

[a] *P*-values from univariate conditional logistic regression models – except for age and menopausal status which were matching factors

[b] Missing data correspond to the participants that did not complete the E3N diet history questionnaire and for whom estimated dietary dioxin intake could not be assessed

A total of 105 participants (9.2%) had been living more than 10 km away from any dioxin source between 1990 and 2008, having therefore a cumulative airborne dioxin exposure of 0 µg-TEQ/m² according to our formula [1] (Table 2). Compared with participants with low exposure to airborne dioxins (in the first quintile), those non-exposed participants were more likely to be born and to live in rural areas, to be physically active and not consumer of alcohol; whereas participants in the first quintile of exposure were more likely to report familial history of breast cancer and former smokers, compared to non-exposed participants.

Table 2. Baseline characteristics of study participants (N=1,145) according to status of living more than 10 km from any source between 1990 and 2008 and quintiles [a] of cumulative metric of airborne dioxin exposure, E3N study, Rhône-Alpes region, France, 1990-2008.

	Living > 10 km from any source [b]		Cumulative metric of airborne dioxin exposure										*P* [c]
			I		II		III		IV		V		
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Case/Control status													0.21
Cases	32	(30.5)	33	(32.4)	101	(41.4)	87	(37.5)	100	(41.2)	76	(34.7)	
Controls	73	(69.5)	69	(67.6)	143	(58.6)	145	(62.5)	143	(58.8)	143	(65.3)	
Age (years), mean (SD)	50.2	(5.9)	50.4	(6.5)	49.1	(5.9)	49.6	(6.1)	48.8	(6.1)	49.4	(6.7)	0.20
Body Mass Index (kg/m²), median value among controls													0.80
<=21.9	52	(49.5)	52	(51.0)	129	(52.9)	113	(48.7)	134	(55.1)	115	(52.5)	
>21.9	53	(50.5)	50	(49.0)	115	(47.1)	119	(51.3)	109	(44.9)	104	(47.5)	
Alcohol drinking													0.07
Never drinker	9	(8.6)	16	(15.7)	30	(12.3)	22	(9.5)	17	(7.0)	28	(12.8)	
Drinker <5.9 g/day	40	(38.1)	33	(32.4)	78	(32.0)	71	(30.6)	87	(35.8)	64	(29.2)	
Drinker >=5.9 g/day	37	(35.2)	38	(37.3)	106	(43.4)	99	(42.7)	123	(50.6)	123	(56.2)	
Missing data	*19*	*(18.1)*	*15*	*(14.7)*	*30*	*(12.3)*	*40*	*(17.2)*	*16*	*(6.6)*	*4*	*(1.8)*	
Smoking status													0.01
Never smoker	69	(65.7)	64	(62.7)	156	(63.9)	118	(50.9)	129	(53.1)	115	(52.5)	
Current smoker	12	(11.4)	6	(5.9)	23	(9.4)	38	(16.4)	44	(18.1)	30	(13.7)	
Former smoker	24	(22.9)	32	(31.4)	65	(26.6)	76	(32.8)	70	(28.8)	74	(33.8)	
Status of birthplace													0.002
Rural	36	(34.3)	27	(26.5)	61	(25.0)	55	(23.7)	34	(14.0)	56	(25.6)	
Urban	65	(61.9)	72	(70.6)	174	(71.3)	161	(69.4)	190	(78.2)	144	(65.8)	
Missing data	*4*	*(3.8)*	*3*	*(2.9)*	*9*	*(3.7)*	*16*	*(6.9)*	*19*	*(7.8)*	*19*	*(8.7)*	
Status of residence at baseline													<0.0001
Rural	79	(75.2)	45	(44.1)	74	(30.3)	75	(32.3)	54	(22.2)	30	(13.7)	

Urban	22	(21.0)	54	(52.9)	161	(66.0)	141	(60.8)	170	(70.0)	170	(77.6)	
Missing data	*4*	*(3.8)*	*3*	*(2.9)*	*9*	*(3.7)*	*16*	*(6.9)*	*19*	*(7.8)*	*19*	*(8.7)*	
Recreational physical activity (METs-h/week)													0.11
<25.3	11	(10.5)	25	(24.5)	60	(24.6)	50	(21.6)	48	(19.8)	52	(23.7)	
25.3-37.3	25	(23.8)	23	(22.5)	72	(29.5)	74	(31.9)	72	(29.6)	62	(28.3)	
37.4-56.9	34	(32.4)	32	(31.4)	66	(27.0)	61	(26.3)	66	(27.2)	64	(29.2)	
>=57.0	35	(33.3)	22	(21.6)	46	(18.9)	47	(20.3)	57	(23.5)	41	(18.7)	
Education													0.0004
Undergraduate	16	(15.2)	12	(11.8)	26	(10.7)	22	(9.5)	30	(12.3)	26	(11.9)	
Post-graduate with a 1- to 2-year university degree	60	(57.1)	61	(59.8)	137	(56.1)	121	(52.2)	109	(44.9)	83	(37.9)	
Post-graduate with a >= 3 year university degree	29	(27.6)	29	(28.4)	81	(33.2)	89	(38.4)	104	(42.8)	110	(50.2)	
Age at menarche (years), modal value among controls													0.93
<13	46	(43.8)	43	(42.2)	115	(47.1)	109	(47.0)	116	(47.7)	104	(47.5)	
>=13	59	(56.2)	59	(57.8)	129	(52.9)	123	(53.0)	127	(52.3)	115	(52.5)	
Previous use of oral contraceptives	57	(54.3)	53	(52.0)	167	(68.4)	145	(62.5)	142	(58.4)	126	(57.5)	0.03
Previous use of progestin before menopause	51	(48.6)	29	(28.4)	108	(44.3)	109	(47.0)	112	(46.1)	91	(41.6)	0.03
Menopausal status at baseline													0.17
Premenopausal women	58	(55.2)	54	(52.9)	156	(63.9)	137	(59.1)	157	(64.6)	125	(57.1)	
Postmenopausal women	47	(44.8)	48	(47.1)	88	(36.1)	95	(40.9)	86	(35.4)	94	(42.9)	
Use of menopausal hormone treatment at baseline	16	(15.2)	10	(9.8)	32	(13.1)	29	(12.5)	34	(14.0)	35	(16.0)	0.72
Mammography during the previous follow-up period	82	(78.1)	67	(65.7)	192	(78.7)	178	(76.7)	188	(77.4)	162	(74.0)	0.16
Age at first full-term pregnancy (years), median value among controls													0.26
<=24	38	(36.2)	47	(46.1)	110	(45.1)	96	(41.4)	110	(45.3)	74	(33.8)	
>24	54	(51.4)	45	(44.1)	117	(48.0)	107	(46.1)	97	(39.9)	101	(46.1)	
Missing data	*13*	*(12.4)*	*10*	*(9.8)*	*17*	*(7.0)*	*29*	*(12.5)*	*36*	*(14.8)*	*44*	*(20.1)*	
Parity													0.23
<=2	63	(60.0)	63	(61.8)	161	(66.0)	128	(55.2)	131	(53.9)	127	(58.0)	
>=3	29	(27.6)	28	(27.5)	66	(27.0)	75	(32.3)	76	(31.3)	48	(21.9)	

Missing data	*13*	*(12.4)*	*11*	*(10.8)*	*17*	*(7.0)*	*29*	*(12.5)*	*36*	*(14.8)*	*44*	*(20.1)*	
Breastfeeding	54	(51.4)	57	(55.9)	154	(63.1)	130	(56.0)	145	(59.7)	136	(62.1)	0.27
Previous history of personal benign breast disease	28	(26.7)	29	(28.4)	101	(41.4)	74	(31.9)	78	(32.1)	62	(28.3)	0.03
Previous family history of breast cancer	9	(8.6)	13	(12.7)	29	(11.9)	29	(12.5)	31	(12.8)	32	(14.6)	0.78
Estimated dietary dioxin intake, mean (SD)	1.3	(0.5)	1.2	(0.4)	1.2	(0.4)	1.2	(0.4)	1.3	(0.4)	1.2	(0.4)	0.96
Missing data from the E3N diet history questionnaire of 1993	*32*	*(30.5)*	*30*	*(29.4)*	*63*	*(25.8)*	*67*	*(28.9)*	*41*	*(16.9)*	*21*	*(9.6)*	

[a] quintiles' cut offs: 1.7E-5, 2.2E-3, 1.9E-2 and 9.6E-2 µg-TEQ/m²

[b] All participants living ≥ 10 km for any dioxin source were included into the lowest exposure category (first quintile) for the main statistical analysis

[c] *P*-values derived from Chi-square statistical test and analysis of variance

Table 3 shows the distribution of breast cancer cases and matched controls and the odds ratios according to quintiles of the cumulative metric of airborne dioxin exposure, overall and for hormone-receptor status. We observed no increased risk of overall breast cancer for higher cumulative airborne dioxin exposure levels (OR for Q5 *versus* Q1: 1.124, 95% CI: 0.693-1.824, *P*-for-trend=0.81). We however observed a modest, statistically significant, increase in breast cancer risk for Q2 *versus* Q1 (OR: 1.612, 95% CI: 1.042-2.493). We found no evidence for heterogeneity in the associations for ER-positive *versus* ER-negative and PR-positive *versus* PR-negative tumors (P_{het}=0.49 and P_{het}=0.50, respectively). While we observed a statistically significant OR for Q2 *versus* Q1 for ER-positive breast cancer (1.843, 95% CI: 1.033-3.292), none of the other estimated ORs for specific breast cancer subtypes defined according to ER and PR status were statistically significant. Further adjustment for estimated dietary dioxin intake did not materially modify the odds ratios (data not shown). The modeling of the relationship between cumulative airborne dioxin exposure and overall breast cancer risk using a cubic spline function is shown in Figure 1 (supplementary material). The figure shows no association between cumulative airborne dioxin and breast cancer odds ratios, which confirms the overall findings observed with quintiles of exposure in statistical models, and suggests a multiphasic effect of dioxin exposure on breast cancer risk, although not statistically significant.

Table 3. Odds ratios (OR) [a] and 95% confidence intervals (CI) for the association between invasive breast cancer and quintiles [b] of cumulative metric of airborne dioxin exposure overall and according to hormone receptor status (N=1,145), E3N study, 1990-2008.

Populations		Cases, N (%)		Controls, N (%)		OR [a]	Lower 95%CI	Upper 95%CI	*P*-for-trend	*P*-het[e]
Overall									0.81	
	I	65	(15.2)	142	(19.8)	1.000				
	II	101	(23.5)	143	(20.0)	1.612	1.042	2.493		
	III	87	(20.3)	145	(20.3)	1.398	0.886	2.206		
	IV	100	(23.3)	143	(20.0)	1.506	0.953	2.380		
	V	76	(17.7)	143	(20.0)	1.124	0.693	1.824		
ER positive [c]									0.93	0.49
	I	34	(13.9)	81	(20.0)	1.000				
	II	60	(24.6)	75	(18.5)	1.843	1.033	3.292		
	III	48	(19.7)	83	(20.4)	1.322	0.723	2.416		
	IV	61	(25.0)	83	(20.4)	1.600	0.872	2.937		
	V	41	(16.8)	84	(20.7)	1.060	0.552	2.037		
ER negative [c]									0.35	0.49
	I	17	(21.3)	21	(16.2)	1.000				
	II	10	(12.5)	18	(13.8)	0.785	0.269	2.293		
	III	17	(21.3)	26	(20.0)	0.881	0.292	2.659		
	IV	20	(25.0)	35	(26.9)	0.597	0.206	1.729		

Populations		Cases, N (%)	Controls, N (%)	OR [a]	Lower 95%CI	Upper 95%CI	*P*-for-trend	*P*-het[e]
	V	16 (20.0)	30 (23.1)	0.637	0.226	1.794		
PR positive [d]							0.24	0.50
	I	34 (15.8)	64 (18.0)	1.000				
	II	48 (22.3)	61 (17.1)	1.394	0.771	2.524		
	III	41 (19.1)	75 (21.1)	0.922	0.500	1.713		
	IV	56 (26.0)	81 (22.8)	1.072	0.587	1.958		
	V	36 (16.7)	75 (21.1)	0.695	0.352	1.373		
PR negative [d]							0.47	0.50
	I	17 (15.7)	39 (21.8)	1.000				
	II	22 (20.4)	30 (16.8)	2.057	0.783	5.405		
	III	23 (21.3)	33 (18.4)	2.285	0.843	6.189		
	IV	24 (22.2)	37 (20.7)	1.845	0.649	5.248		
	V	22 (20.4)	40 (22.3)	1.733	0.668	4.494		

[a] adjusted for family history of breast cancer, age at first full-term pregnancy, recreational physical activity, status of birthplace and breastfeeding

[b] quintiles' cut offs: 1.7E-5, 2.2E-3, 1.9E-2 and 9.6E-2 µg-TEQ/m². The first quintile included all participants living ≥ 10 km for any dioxin source over the study period.

[c] n=105 invasive breast cancer cases with missing estrogen receptor status, and n=205 matched controls

[d] n=106 invasive breast cancer cases with missing progesterone receptor status, and n=251 matched controls

[e] *P*-heterogeneity derived from the Likelihood Ratio Test, comparing ER+ *versus* ER- and PR+ *versus* PR- breast tumors

Odds ratios for breast cancer according to quintiles of cumulative metric of airborne dioxin exposure in strata of selected covariates are presented in Table 4. Although no effect modification by menopausal status at index date was found (*P*-for-interaction=0.45), we observed a statistically significant increased OR for Q2 *versus* Q1 (1.594, 95% CI: 1.078-2.356) among postmenopausal women at index date, whereas no association was found in pre-menopause. We found a statistically significant effect modification by age at first full-term pregnancy (*P*-for-interaction=0.01). In the strata of women aged 24 years old or less at first full-term pregnancy, ORs were ≤ 1 and we observed a statistically significant decrease in breast cancer risk for the highest *versus* the lowest quintile of cumulative metric of airborne dioxin exposure with an OR of 0.400 (95% CI: 0.197-0.812; *P*-for-trend=0.03), whereas among women over 24 years old at first full-term pregnancy, ORs were ≥1 and we observed a statistically significant OR for Q2 *versus* Q1 (1.631, 95% CI: 1.003-2.653; *P*-for-trend=0.96). No association and no heterogeneity were found between cumulative metric of airborne dioxin exposure and breast cancer across strata of breastfeeding, BMI and smoking status. There was no effect modification by menopausal status at baseline and BMI on the

association between cumulative metric of airborne dioxin exposure and breast cancer risk (*P*-for-interaction=0.20).

Our findings were not materially modified using multiple imputation method for missing data on adjustment variables (data not shown). Excluding the cases not confirmed by pathology reports (and matched controls) did not modify our results (data not shown). When separating participants with a null estimated cumulative airborne dioxin exposure from the other participants categorized into quintiles, OR for 0 *versus* Q1 was 1.014 (95% CI: 0.544-1.891), and the association previously observed for Q2 *versus* Q1 was no longer statistically significant (OR: 1.622, 95% CI: 0.952-2.765) (data not shown). In the sub-population excluding cases diagnosed within the first five years after inclusion in the cohort, OR for Q2 *versus* Q1 for overall and ER-positive breast cancers remained statistically significant (OR: 2.059, 95% CI: 1.142-3.713; *P*-for-trend=0.51 and OR:2.421, 95% CI: 1.947-4.908; *P*-for-trend=0.48, respectively), as well as among postmenopausal women at index date (OR for Q2 *versus* Q1:1.605, 95% CI: 1.012-2.546; *P*-for-trend=0.41). However, no association was further observed in the subgroup of participants aged 24 years or less at first full-term pregnancy (OR for Q5 *versus* Q1: 0.443, 95% CI: 0.185-1.064; *P*-for-trend=0.15) (data not shown).

Table 4. Odds ratios (OR) [a] and 95% confidence intervals (CI) for the association between invasive breast cancer and quintiles [b] of cumulative metric of airborne dioxin exposure, stratified analyses (N=1,145), E3N study, 1990-2008.

Populations		Cases, N (%)		Controls, N (%)		OR [a]	Lower 95%CI	Upper 95%CI	*P*-for-trend	*P* for interaction [f]
Menopausal status at index date										0.45
Premenopause									0.90	
	I	10	(20.8)	21	(18.6)	1.000				
	II	12	(25.0)	30	(26.5)	1.359	0.531	3.479		
	III	11	(22.9)	28	(24.8)	1.351	0.452	4.037		
	IV	9	(18.8)	26	(23.0)	0.878	0.286	2.698		
	V	6	(12.5)	8	(7.1)	1.407	0.407	4.865		
Postmenopause									0.57	
	I	44	(13.1)	111	(20.3)	1.000				
	II	83	(24.7)	100	(18.3)	1.594	1.078	2.356		
	III	65	(19.3)	108	(19.7)	1.354	0.895	2.047		
	IV	78	(23.2)	108	(19.7)	1.343	0.888	2.033		
	V	66	(19.6)	120	(21.9)	1.034	0.669	1.599		
Age at first full-term pregnancy [c]										0.01
<=24 years									0.03	
	I	32	(19.9)	53	(16.9)	1.000				
	II	38	(23.6)	72	(22.9)	0.888	0.534	1.474		

Populations		Cases, N (%)		Controls, N (%)		OR [a]	Lower 95%CI	Upper 95%CI	*P*-for-trend	*P* for interaction [f]
	III	37	(23.0)	59	(18.8)	1.037	0.610	1.763		
	IV	40	(24.8)	70	(22.3)	0.793	0.469	1.342		
	V	14	(8.7)	60	(19.1)	0.400	0.197	0.812		
>24 years									0.96	
	I	27	(13.0)	72	(23.0)	1.000				
	II	56	(26.9)	61	(19.5)	1.631	1.003	2.653		
	III	39	(18.8)	68	(21.7)	1.286	0.759	2.179		
	IV	48	(23.1)	49	(15.7)	1.581	0.922	2.711		
	V	38	(18.3)	63	(20.1)	1.158	0.657	2.039		
Breastfeeding										0.20
Ever									0.09	
	I	38	(15.6)	73	(16.9)	1.000				
	II	61	(25.1)	93	(21.5)	1.085	0.702	1.675		
	III	47	(19.3)	83	(19.2)	1.021	0.642	1.622		
	IV	59	(24.3)	86	(19.9)	1.037	0.656	1.641		
	V	38	(15.6)	98	(22.6)	0.638	0.384	1.061		
Never									0.60	
	I	27	(14.5)	69	(24.4)	1.000				
	II	40	(21.5)	50	(17.7)	1.542	0.918	2.588		
	III	40	(21.5)	62	(21.9)	1.342	0.776	2.322		
	IV	41	(22.0)	57	(20.1)	1.333	0.760	2.338		
	V	38	(20.4)	45	(15.9)	1.356	0.750	2.450		
Body mass index at baseline [d]										0.15
<=21.9 kg/m²									0.10	
	I	38	(16.6)	66	(18.0)	1.000				
	II	55	(24.0)	74	(20.2)	1.101	0.708	1.714		
	III	47	(20.5)	66	(18.0)	0.982	0.610	1.581		
	IV	54	(23.6)	80	(21.9)	0.902	0.562	1.450		
	V	35	(15.3)	80	(21.9)	0.688	0.405	1.168		
>21.9 kg/m²									0.49	
	I	27	(13.5)	76	(21.7)	1.00				
	II	46	(23.0)	69	(19.7)	1.570	0.944	2.610		
	III	40	(20.0)	79	(22.6)	1.477	0.863	2.528		
	IV	46	(23.0)	63	(18.0)	1.585	0.923	2.722		
	V	41	(20.5)	63	(18.0)	1.321	0.748	2.334		
Smoking status at baseline										0.92
Ever									0.22	
	I	24	(12.4)	50	(16.7)	1.000				
	II	41	(21.1)	47	(15.7)	1.409	0.818	2.427		
	III	44	(22.7)	70	(23.3)	1.238	0.722	2.123		
	IV	48	(24.7)	66	(22.0)	1.171	0.677	2.028		
	V	37	(19.1)	67	(22.3)	0.788	0.431	1.439		
Never									0.88	
	I	41	(17.4)	92	(22.1)	1.000				
	II	60	(25.5)	96	(23.1)	1.194	0.781	1.824		
	III	43	(18.3)	75	(18.0)	1.077	0.671	1.728		
	IV	52	(22.1)	77	(18.5)	1.173	0.730	1.884		
	V	39	(16.6)	76	(18.3)	0.979	0.582	1.647		

[a] adjusted for age, department of residence, menopausal status and date at blood collection or at baseline, existence of a biological sample (blood, saliva, none), index date, family history of breast cancer, age at first full-term pregnancy, recreational physical activity, status of birthplace and breastfeeding
[b] quintiles' cut offs: 1.7E-5, 2.2E-3, 1.9E-2 and 9.6E-2 µg-TEQ/m². The first quintile included all participants living ≥ 10 km for any dioxin source over the study period.
[c] median age at first full-term pregnancy based on the distribution among controls
[d] median value of body mass index based on the distribution among controls
[e] modal value of age at menarche based on the distribution among controls
[f] *P*-values derived from likelihood ratio test comparing the nested models with and without interaction terms.

Table 5 shows the resulting estimated ORs associated with an increase of 0.1 µg-TEQ/m² (which corresponds to one SD of the annual doses) in the intensity of airborne dioxin exposure in different years before the index date (2, 5, 10 and 15 years). Overall, ORs were all not statistically different from one, suggesting no effect of exposure intensity, whatever the timing of exposure.

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for the association between invasive breast cancer and time-weighted cumulative airborne dioxin exposure (for a 0.1 µg-TEQ/m² annual increase) according to time before diagnosis, E3N study, 1990-2008.

	Overall, N=1,145	
Time *t* prior to breast cancer diagnosis (years)	N cases / N controls	OR [a] (95%CI) [b]
2	401 / 661	1.0022 (0.9585-1.0069)
5	330 / 524	1.0040 (0.9434-1.0130)
10	183 / 306	1.0057 (0.9177-1.0173)
15	57 / 113	1.0040 (0.9290-1.0134)

[a] adjusted for age, department of residence, menopausal status and date at blood collection or at baseline, existence of a biological sample (blood, saliva, none), index date, family history of breast cancer, age at first full-term pregnancy, recreational physical activity, status of birthplace and breastfeeding
[b] 95% CI were obtained with 1000 bootstraps

4. Discussion

Among women from the French E3N cohort, no increased risk of breast cancer for higher dioxin exposure levels was observed overall, as well as when considering hormone-receptor status of breast cancers separately. Our results suggested an increased risk of overall breast cancer for the second *versus* the first quintile of exposure, which was also observed for ER-positive breast cancer and among postmenopausal women. A suggestive decrease in breast cancer risk associated with higher dioxin exposure levels was observed among women younger at first birth. An increase in annual airborne dioxin exposure was not associated with the risk of overall breast cancer at each year prior to diagnosis.

In line with our results, several studies showed no association between dioxin exposure and female breast cancer risk, although assessment of dioxin exposure was based on comparison of contaminated zones or serum concentration (Bertazzi et al., 1993; Pesatori et al., 2009; Warner et al., 2011). In a cohort involving the population exposed to dioxins following the Seveso industrial accident (1976, Italy), no association with breast cancer occurrence was found after 10- and 20-year follow-up comparing women living in one of the two contaminated zones with women living in a non-contaminated surrounding area (Bertazzi et al., 1993; Pesatori et al., 2009). In a specific retrospective cohort of women aged 0 to 40 years at the time of the accident and living in the two contaminated areas, an increase in TCDD serum concentration was not associated with increased breast cancer risk (Warner et al., 2011). In addition, the most recent meta-analysis, conducted on the association between external TCDD exposure and cancer incidence, reported no statistically significant risks for breast cancer (Xu et al., 2016). One ecological study, which was conducted in populations living in the vicinity of industrial facilities, although limited to MSWIs, reported a weak increase in breast cancer risk for higher exposure (18,824 cases, RR: 1.09, 95% CI: 1.01-1.18; (Fabre et al., 2008)). There has been a study that reported a decreased breast cancer risk among women aged 60 years and more and living in a highly exposed zone around a MSWI, although results of this study have to be interpreted with caution due to the lack of adjustment for individual breast cancer risk factors (434 cases, OR: 0.31, 95% CI: 0.08-0.89; (Viel et al., 2008)). Most of the above studies did not assess dioxin exposure at the individual address level (Fabre et al., 2008; Pesatori et al., 2009; Revich et al., 2001; Viel et al., 2008) and none considered dietary dioxin exposure in the statistical analysis. Our findings are in agreement with the results from our previous study conducted in the E3N cohort, in which we observed no association between estimated dietary dioxin exposure and overall breast cancer risk

(Danjou et al., 2015); although no information was available on the origin of the food consumed, which may be an important factor to consider in the exposure assessment, particularly for women consuming food produced in the vicinity of dioxin sources.

Differences in methods for assessing dioxin exposure, exposure levels and presence of study limitations may explain the inconsistent results from the literature and make comparison with our findings difficult (Xu et al., 2016). Dioxin exposure levels were higher in accidentally exposed populations than in our study population. Monitoring of soil contamination by dioxins after the Seveso accident led to mean soil levels of TCDD ranging from 15.5 to 580 µg/m² in the most contaminated zone (Bertazzi et al., 1998) whereas in our study, average cumulative airborne dioxin exposure was estimated at 0.14 and 0.12 µg-TEQ/m² among cases and controls respectively. Fabre et al. used an atmospheric dispersion model and estimated an average cumulative annual dioxin deposit of 7.9×10^{-3} µg/m²/year from 1972 to 1990 over four French departments (Fabre et al., 2008). In the study by Viel et al., dioxin exposure consisted in exposure zones (very low, low, intermediate and high exposure) based on predicted ground-level air concentrations and measurements in soil samples (Viel et al., 2008).

Our results suggested a modest increase in breast cancer risk when comparing participants of the second *versus* the first quintile of exposure, in particular for ER-positive tumors and among postmenopausal women at index date; however this was not consistently seen across quintiles. These observations may support the carcinogenic effect of dioxins. While currently the role in human breast cancer development remains controversial, TCDD has been shown to have a variety of carcinogenic effects in experimental animal and mechanistic studies. As a non-genotoxic agent, the primary mechanism of TCDD for carcinogenesis is the promotion of tumor development after activation of the AhR, including cell proliferation, hyperplasia and block of apoptosis (Bekki et al., 2015; Mandal, 2005; Schwarz and Appel, 2005). Ahn et al. (2015) observed an effect of TCDD on proliferation of human breast epithelial cells at low doses, but not at higher doses (Ahn et al., 2005). Dioxins may also cause an increase in reactive oxygen species (ROS) leading to DNA damage and mutations (Mandal, 2005). Studies have suggested that dioxins interfere with estrogen signaling through ER-AhR cross talk and have differential effects depending on hormone levels (Brunnberg et al., 2011; Rodgers et al., 2018). Dioxins may cause anti-estrogenic responses in rodent mammary gland and in human breast cancer cell lines in the presence of estrogen, including inhibition of 17β-estradiol-induced cell proliferation (Safe, 1995). On the contrary, in the absence of estrogen, the activated AhR directly associates with the unliganded

ER, leading to activation of transcription of estrogen-responsive gene promoters and estrogenic effects (Ohtake et al., 2003). There have been limited epidemiological studies on the effect of dioxin exposure on breast cancer risk according to hormone-receptor status (Rodgers et al., 2018). In line with our results, no difference in breast cancer risk according to estrogen- and progesterone-receptors was found among women from the Seveso cohort, although numbers were small (Warner et al., 2011). The increased odds ratio for ER-positive breast cancer observed in our study requires confirmation in future studies. While we observed an increased OR for the second *versus* the first quintile of exposure in post-menopause, no association between dioxin exposure and breast cancer risk was found among premenopausal women. Few studies have performed stratification by menopausal status. No difference in breast cancer risk was reported in the Seveso cohort for pre- and post-menopausal women (Pesatori et al., 2009; Warner et al., 2011). Because women from the E3N cohort were aged 45 to 60 years old at inclusion, the proportion of premenopausal women at index date, in our study, was small, and likely to result in unstable estimates of odds ratios.

In contrast with our overall results, we observed a statistically significant decrease in breast cancer odds ratios among women younger at first birth. This particular result may be consistent with the protective effect of early maternal age on breast cancer risk (Kobayashi et al., 2012; Sun et al., 2017). Inverse associations between organochlorine compounds and breast cancer risk have been suggested in some studies (Gammon et al., 2002; Itoh et al., 2009; Iwasaki et al., 2008; Raaschou-Nielsen et al., 2005; Rusiecki et al., 2004), although not in women exposed in young ages. Furthermore, our observation is interesting in view of the suggestion of a potential role of TCDD in the inhibition of mammary tumor formation in animal studies (Kociba et al., 1978) and observation of an anti-proliferative action of TCDD in breast cancer cell lines, through AhR-dependent and AhR-independent pathways (Wang et al., 1997; Yoshioka et al., 2012; Zhang et al., 2009). However, it is also important to note that our analyses may be limited by a small number of participants in some categories and underestimation of the variance due to categorization into quintiles, possibly yielding unstable measures of association. Although our statistical models were adjusted for confounders, we cannot exclude that residual confounding may have occurred. Also, given the elevated number of tests performed, we cannot exclude that some of the statistically significant findings may have occurred by chance.

Our results may indicate potential multiphasic dose-response effects of airborne dioxin exposure on breast cancer risk at low-dose, although not statistically significant (supplementary material figure 1). As for other endocrine disruptors, non-monotonic effects

of dioxins have been suggested on several human health outcomes (Birnbaum, 2012; Lagarde et al., 2015; Vandenberg et al., 2012). Non-monotonic dose-response curves have been defined as non-linear relationships between dose and effect, where the slope of the curve changes sign within the range of doses examined (Vandenberg et al., 2012). To our knowledge, this is the first epidemiological study showing potential multiphasic dose-response of dioxin exposure. A previous study has shown an inverted U-shaped relationship between TCDD serum levels and early onset of menopause (Eskenazi et al., 2005). A complex interplay of different mechanisms of action, such as ligand receptor-mediated events, has been proposed to explain non-monotonic dose-response curves in chemical carcinogenesis, including for dioxins (Ahn et al., 2005; Lutz, 1998; Tuomisto et al., 2006). The dose-response effect of low-dose dioxin exposure on breast cancer occurrence requires increased scrutiny in future studies.

Strengths of our study included the quality of the information prospectively collected and regularly updated; and the statistical models were adjusted for known individual breast cancer risk factors, minimizing residual confounding. Moreover, factors that may influence individual dioxin exposure were considered in the estimation on breast cancer risk, such as age, breastfeeding and pregnancy. We were also able to estimate breast cancer risk according to hormone-receptor subtypes. Although diet is quantitatively the main pathway for non-occupationally dioxin exposure, adjustment for dioxin intake in our models did not change our results (Danjou et al., 2015). Moreover, most of the E3N participants are teachers and from affiliated occupations, thus their occupational dioxin exposure was assumed to be negligible and homogenous among the study population; although, as occupational places might be located in the vicinity of dioxin sources, airborne dioxin exposure at the occupational place should also be assessed in future studies.

Our study has several limitations. First, in our study, dioxin exposure was not directly measured in blood samples or adipose tissues. Although the E3N women provided blood samples in 1995-1997, the volume in storage was insufficient to measure dioxin levels, and a new blood sampling would not be relevant regarding the etiology of breast cancer (Rodgers et al., 2018). GIS-based methods have been previously used as an alternative to assess exposure to air pollutants in absence of measured data and their use in epidemiological studies have grown in the last years (Cordioli et al., 2013; Rodgers et al., 2018). We assessed airborne dioxin exposure through a GIS-based metric that allowed the estimation of long-term exposure at the individual address level (Coudon et al., 2018). The GIS included parameters known to influence individual airborne dioxin exposure according to the literature: residence-

to-source proximity, dioxin emission intensity of 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, 2006). Exposure classification into quintiles using the GIS-based metric showed "substantial" to "almost perfect" agreement with dioxin dispersion modeling (SIRANE, (Soulhac et al., 2017, 2012, 2011)) across different settings (Coudon et al., 2018; Viera et al., 2005). We were able to consider the residential history of the participants over the study period and, in absence of dioxin monitoring data, we implemented a standardized method for the estimation of dioxin emissions using the UNEP Toolkit (UNEP, 2013). Geocoding of the participants' residential addresses and industrial facilities was achieved through an automatic method whose accuracy was assessed in a previous study (Faure et al., 2017).

Second, the cumulative index of exposure in our study may not reflect exposure over lifetime. Prevalent dioxin exposure was assessed from 1990 to index date (up to 2008) as the E3N participants were included in the cohort in 1990 and the residential history was not recorded before inclusion (except for place of residence at birth). Moreover, information on past emissions of dioxins from industrial sources was not available as far back in time, participants being born between 1925 and 1950, leading to left truncation of the exposure estimates and underestimation of cumulative exposure. Although we intended to encompass this limitation by adjusting all the models for the status urban or rural of the birthplace, participants might not be comparable regarding the dioxin exposure levels before 1990. Future studies should consider the impact of left-truncated exposure estimates on the association with breast cancer risk (Hazelbag et al., 2015; Vandenbroucke and Pearce, 2015).

Third, our study was based on a multi-source approach, considering major industrial dioxin sources (waste incineration, metal production, cement industry, etc.) and the evolution over time of the facilities' technical characteristics. Traffic-related exposure was not considered as its contribution to average dioxin concentration was estimated to be negligible in a previous study on dioxin modeling (<3%; (Coudon et al., 2017)) and stable over the study period (CITEPA, 2015). Emissions from domestic activities, including heating, chimney fire, cooking methods (*e.g.* stove, wood stove and barbecue) as well as backyard burning of domestic and green wastes, may contribute to the airborne dioxin exposure and have been positively associated with breast cancer risk (White et al., 2014). Dioxin release from illegal cable burning (*i.e.* the process in which copper and lead are recovered by burning the insulating material from electricity and electronics) may be a critical source of dioxin emissions and potentially relevant exposure sources nowadays (Stockholm Convention

Clearing House, n.d.). However, because of the lack of data over the French territory (geographical and monitoring data), these emissions could not be considered in the exposure assessment. These punctual and non-industrial sources, in addition to the lack of past residential history and historical dioxin exposure estimates before 1990, may have resulted in exposure misclassification likely to contribute to imprecise measures of association drawn toward unity (Basagaña et al., 2013). Information on domestic activities and lifetime residential history should be collected in future studies and additional methods should be employed to take into account these types of dioxin sources in the exposure assessment.

Finally, a number of observations have suggested that breast cancer may originate in early life and that women may experience multiple time-variable windows of susceptibility, including the prenatal period, puberty and pregnancy, when mammary cells rapidly proliferate and differentiate, in which dioxins could affect hormonal pathways and induce the development of breast cancer later in life (Cohn, 2011; Rodgers et al., 2018; Teitelbaum et al., 2015). Therefore, assessing dioxin exposure during these critical periods of breast development may be relevant. In our study, we were not able to estimate the risk of breast cancer at these specific time windows, because airborne dioxin exposure was not assessed over the lifetime. Future studies should investigate the impact of dioxin exposure during the windows of breast susceptibility on breast cancer later in life.

Focusing our analysis on the E3N women that had permanently lived in the Rhône-Alpes region over the study period lowered the number of participants and thus the statistical power of our study. Confirmation of our findings is required in further studies and larger populations. In particular, further enlargement to breast cancer cases and their matched controls of the entire E3N cohort and identification of dioxin sources at the national level is planned. Moreover, future studies should investigate of the joint effect of dietary and airborne dioxin exposure in statistical models. Finally, the GIS-based metric may be adapted for the exposure assessment of other environmental pollutants in relation to breast cancer risk or used in the investigation of other pathologies.

5. Conclusions

Among women from the E3N cohort, no increased odds ratio for breast cancer was observed for higher airborne dioxin exposure overall, as well as for hormone-receptor defined breast cancer. The increased odds ratios for low exposure levels observed overall and for ER-positive breast cancer might be compatible with non-monotonic dose-response effect of dioxins on breast cancer. These results require confirmation in larger populations. Our GIS-based metric, developed to assess long-term and low-dose airborne dioxin exposure at the individual address level, may provide an alternative in absence of measurements of ambient dioxin concentrations and may be used to assess exposure to other pollutants behaving similarly as dioxins.

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Declarations of interest

None

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Highlights

- No increased OR for breast cancer for higher levels of dioxin exposure were observed
- Increased OR for the second quintile of dioxin exposure were suggested
- This might be compatible with low-dose non-monotonic dose-response effect of dioxins on cancer