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ABSTRACT

Background: Although the genetic and hormonal risk factors of breast cancer are well identified, they cannot fully explain the occurrence of all cases. Epidemiological and experimental studies have suggested that exposure to environmental pollutants, especially those with potential estrogenic properties, as polychlorinated biphenyls (PCBs) may have a role in breast cancer development. Being the most abundantly detected in human tissues and in the environment, congener 153 (PCB153) is widely used in epidemiological studies as indicator for total PCBs exposure.

Objectives: We aimed to estimate the association between cumulative atmospheric exposure to PCB153 and breast cancer risk.

Methods: We conducted a case-control study of 5,222 cases and 5,222 matched controls nested within the French E3N cohort from 1990 to 2011. Annual atmospheric PCB153 concentrations were simulated with the deterministic chemistry-transport model (CHIMERE) and were assigned to women using their geocoded residential history. Their cumulative PCB153 exposure was calculated for each woman from their cohort inclusion to their index date. Breast cancer odds ratios (ORs) associated with cumulative PCB153 exposure and their 95% confidence intervals (95% CI) were estimated using multivariate conditional logistic regression models.

Results: Overall, our results showed a statistically significant linear increase in breast cancer risk related to cumulative atmospheric exposure to PCB153 as a continuous variable (adjusted OR=1.19; 95% CI: 1.08-1.31 for an increment of one standard deviation among controls (55 pg/m^3)). Among women who became postmenopausal during follow-up, the association remained statistically significant (adjusted OR=1.23; 95% CI: 1.09-1.39). In analyses by hormone receptors status, the positive association remained significant only for ER-positive breast cancer (adjusted OR=1.18; 95% CI: 1.05-1.33).

Discussion: This study is the first to have estimated the impact of atmospheric exposure to PCB153 on breast cancer risk. Our results showed a statistically significant increase in breast cancer risk, which may be limited to ER-positive breast cancer. These results warrant confirmation in further independent studies but raise the possibility that exposure to PCB153 increase breast cancer risk.

Keywords: polychlorinated biphenyls, air pollution, breast cancer, residential history, nested case control

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Abbreviations

AFP: age at first full-term pregnancy; BMI: body mass index; CIs: confidence intervals; CNIL: Commission for Computerized Data and Individual Freedom; CYP1A: cytochrome P4501A; CYP2B: cytochrome P4502B; DAG: directed acyclic graph; E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; EMEP: European Monitoring and Evaluation Program; EFSA: European Food Safety Authority; EPIC: European Prospective Investigation into Cancer and Nutrition; ER: estrogen receptors; HT: menopausal hormone replacement therapy; IARC: International Agency for Research on Cancer; INERIS: National Institute for Industrial Environment and Risks; MET: metabolic equivalent task; ORs: odds ratios; PCBs: Polychlorinated biphenyls; PCB-DL: dioxin-like polychlorinated biphenyls; PR: progesterone receptors; SD: standard deviation; TNM: tumor-node-metastasis.

1. Introduction

Breast cancer is the most common cancer among women, with an estimated 2.09 million new cases in 2018, and the leading cause of death from females cancer worldwide (Bray et al., 2018). Although hormonal and genetic risk factors are well identified, they do not explain all cases of breast cancer. Air pollution is the leading environmental cause of premature death in the world (OECD, 2014) with 6.4 million attributable deaths in 2015 (Cohen et al., 2017). In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as carcinogenic to humans (Loomis et al., 2013). Epidemiological and laboratory studies have suggested that exposure to environmental pollutants, particularly those with endocrine disrupting and estrogenic properties, may have a role in the carcinogenesis of breast cancer (Calaf et al., 2020; Rodgers et al., 2018).

Polychlorinated biphenyls (PCBs) are synthetic chemical molecules, constituted by 209 congeners involving one to ten chlorines attached to a biphenyl nucleus. They are classified as endocrine disrupters, with different properties depending on their composition and chemical structure. PCBs were widely used by industries in the years 1930 to 1970, but their production was only prohibited in the 1980s in many countries, including France (Arnich et al., 2009; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). While their main uses were as dielectric fluid in capacitors and transformers, they have also been used in construction materials (including paints, adhesives, lighting ballasts or rubber products). They are released into the environment by leakage, volatilization or erosion. As persistent organic pollutants, PCBs are stable in various environmental matrices, i.e., biota, air, water, soil or sediment, and have been shown to bioaccumulate in the human body (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). Depending on the route of exposure, humans are exposed to different mixtures of PCBs. Although in the Europe population, around 90% of total PCB exposure comes from food contamination (European Food Safety Authority (EFSA), 2005), PCB inhalation leads to relatively higher exposure to more volatile and less chlorinated congeners compared to ingestion (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016) and experimental data suggest a higher absorption by inhalation than by ingestion (Casey et al., 1999).

In addition, the different congeners do not necessarily have the same mechanisms of action (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). For epidemiological studies, Wolff *et al.* have proposed a classification of PCBs into three main groups according to their effects, related to structural activity (Wolff et al., 1997). Group I includes PCBs with potential estrogenic effects, while Group II includes those with potential anti-estrogenic and immunotoxic effects, including dioxin-like PCBs (PCB-DL), i.e., with the same toxic properties as dioxins. Group III includes PCBs with phenobarbital-like effects, inducing cytochromes P4501A (CYP1A) and P4502B (CYP2B), and being biologically persistent (Wolff et al., 1997). Furthermore, in the environment, food and human tissue, PCB congeners 28, 52, 101, 138, 153 and 180 are those with the highest concentrations and are commonly used in the literature as indicators of PCBs exposure (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). In epidemiological studies, PCB153 (group III of the Wolff's classification) is widely used as indicator for total PCBs exposure because it is often the most abundantly detected in human tissues and in the environment (Bachelet et al., 2011; Demers et al., 2000; Ferrante et al., 2014; Wielsøe et al., 2017; World Health Organization et al., 2016), and the World Health Organization considered PCB153 as the main contributor to estimate PCBs body burden (World Health Organization et al., 2016). Also, several studies have suggested a positive correlation between PCB153 and total PCBs (Bachelet et al., 2011; Demers et al., 2000).

In 2013, PCBs were classified as carcinogenic to humans by IARC with limited indications for breast cancer (Lauby-Secretan et al., 2013). Several case-control and nested case-control in a cohort studies have investigated associations between exposure to PCBs considered all together ("all PCBs") and breast cancer risk, with heterogeneous results. All studies estimated exposure to PCBs from blood or adipose tissue samples, especially breast tissue, but none estimated airborne exposure to PCBs. Four studies found statistically significant positive associations between all PCBs and breast cancer risk (Wielsøe et al., 2017; Huang et al., 2019; Recio-Vega et al., 2011; Millikan et al., 2000), one showed an inverse association (Itoh et al., 2009), while the majority of the studies reported no association (Bonefeld-Jorgensen et al., 2011; Raaschou-Nielsen et al., 2005; Moysich et al., 2002;

Laden et al., 2001; Høyer et al., 2000; Ward et al., 2000; Stellman et al., 2000; Holford et al., 2000; Helzlsouer et al., 1999; Dorgan et al., 1999; Høyer et al., 1998; Hunter et al., 1997). However, associations differed according to the congeners investigated. A meta-analysis published in 2015 found statistically significant positive associations only for PCBs in groups II and III (according to Wolff's classification (Wolff et al., 1997)) with pooled odds ratios (OR) of 1.23 (95% confidence intervals (CI), 1.08-1.40) and 1.25 (95% CI: 1.09-1.43), respectively (Zhang et al., 2015). In contrast, the analysis of PCBs as a whole did not show a statistically significant association with breast cancer. The effects of PCBs on breast cancer risk therefore remain controversial.

The objective of our study was to estimate the association between chronic atmospheric exposure to PCB153 and breast cancer risk in a case-control study nested in the French E3N (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale, epidemiological study on women member of the MGEN health insurance) prospective cohort, from 1990 to 2011 in the continental mainland France.

2. Methods

2.1. The E3N cohort study

The E3N study is a national closed prospective cohort study aiming to investigate risk factors for cancer and other chronic diseases in women (Clavel-Chapelon and E3N Study Group, 2015). This cohort is a component of the EPIC study (European Prospective Investigation into Cancer and Nutrition), involving 10 European countries (Riboli et al., 2002). Women were recruited between June 1990 and November 1991. The eligibility criteria were: being born between 1925 and 1950, residing in the continental mainland France and being members of the MGEN (a national health insurance plan covering mostly teachers) at inclusion. Among the 500,000 women contacted, nearly 100,000 were included (n=98,995) after returning a self-questionnaire about lifestyle, reproductive factors, anthropometry, medical history, familial history of cancer and after signing an informed consent, in compliance with the French National Commission for Computerized Data and Individual Freedom (CNIL). Follow-up self-questionnaires were sent every two or three years by post and to date, 12

questionnaires have been sent with a participation rate of about 80%. All the questionnaires are available on the cohort's website (www.e3n.fr). Between 1994 and 1999, blood samples were gathered from 25,000 volunteers in a biological material bank. Between 2009 and 2011, saliva samples were collected from an additional 47,000 women (Clavel-Chapelon and E3N Study Group, 2015). The addresses of the participants were obtained at inclusion and at the 5th to the 10th follow-up questionnaires. Questionnaires 3 and 4 recorded only postal codes and no address data were kept for questionnaire 2 (Amadou et al., 2020). An urban / rural status was assigned to each participants' place of birth (zip code and commune) obtained at the first questionnaire (Binachon et al., 2014).

Breast cancer occurrence was collected mainly by self-reporting in follow-up questionnaires and a few additional cases were retrieved from insurance data or information on causes of death obtained from the National Services on Causes of Deaths (Amadou et al., 2020). Ninety-three percent of breast cancer cases were validated after reviewing pathology reports or other medical reports obtained from medical practitioners. Tumor characteristics, including histological type and hormone receptor status, were extracted from the pathological reports. When a woman was diagnosed with more than one tumor at the same time, we considered the characteristics of the more advanced breast cancer in terms of tumor-node-metastasis (TNM) stage, or grade of differentiation if the TNM stages were the same.

2.2. The nested case-control study

The protocol of this study has been described previously (Amadou et al., 2020). Briefly, the present XENAIR case-control study, nested in the E3N cohort, involved 6,298 incident cases of primary invasive breast cancers diagnosed from inclusion to the 10th questionnaire (2011), excluding breast Paget's disease and phyllodes tumors (N = 19). We considered also cases whose pathology reports have not been obtained, since the proportion of false-positive self-reports was lower than 5% in the E3N cohort study population. Cases must not have been previously diagnosed with other cancers. Each case was individually matched to one control, randomly selected by incidence density, at the time of the case diagnosis (index date), with delay since inclusion as a time scale. At the index date of the case, the controls had to be followed and had no previous diagnosis of any cancer. The matching

variables were specific to presence or absence of a blood sample: cases with blood sampling (before diagnosis) were matched with controls who also had a blood sample (before the index date of the matching case). They were matched on age (± 1 year), residential area (French Departments), date (± 3 months) and menopausal status at the time of blood collection. Cases without a blood sample were matched to controls on the same criteria at inclusion and additionally on whether or not there was a saliva sample. Women with missing data on matching variables, and their paired were excluded (N = 6).

2.3. Assessment of long-term exposure to airborne PCB153

2.3.1. Estimation of atmospheric PCB153 concentrations

Atmospheric PCB153 concentrations were estimated annually from 1990 to 2010 in the mainland France by the National Institute for Industrial Environment and Risks (INERIS), with the air quality model CHIMERE (Couvidat et al., 2018). The model set-up has been described previously (Amadou et al., 2020). Briefly, CHIMERE is an atmospheric chemistry-transport model simulating pollutant atmospheric dispersion and other physical and chemical processes (for example chemical degradation, deposition, particle formation and evolution) at the national scale, based on meteorological and emission inventory with a 1 km resolution (based on pollutant emission estimated per activity sector from the European Monitoring and Evaluation Program (EMEP MSC-east) in this study), and provides hourly averaged concentrations. The model was run at a spatial resolution of 0.125° x 0.0625° (approximately 7x7 km). These concentrations were expressed in pg/m^3. The lack of PCB153 measurement data over the whole period did not allow a detailed evaluation of the concentration estimated. As PCB153 concentrations were not available for 2011, average change rates over the last 5 years (2005 to 2010) were calculated for each address and then used to extrapolate the 2011 concentrations. To illustrate the spatial and temporal evolution of CHIMERE PCB153 concentrations at ground level, we produced maps for 5 years (1990, 1995, 2000, 2005 and 2010) in Lambert 93 projection.

2.3.2. Geocoding of the residential history

The residential history of the participants was geocoded by trained technicians, blinded to the case or control status women, 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 (Faure et al., 2017). Addresses were geocoded automatically and 16.85% were manually relocated to improve their accuracy. Overall, 80.6% of addresses were geocoded to the exact address, 8.9% were located to the street segment and 10.5% were geocoded with an accuracy level lower than street segment, i.e., town hall, postal code or city. The addresses were geocoded in Lambert 93 projection, in order to be compatible with the projection used for the assessment of CHIMERE PCB153 concentrations.

2.3.4. Management of addresses

For missing addresses during follow-up (until index date), we systematically applied decision rules to assign addresses. For the 3rd (Q3) and 4th (Q4) questionnaires, only postal codes were recorded. We recovered the complete addresses (number, street, postal code and town) from questionnaires Q1 and Q5. If the complete address of Q1 and Q5 were identical and the postal codes of Q3 and Q4 corresponded to the postal code of Q1 and Q5, we assumed that the woman had not moved between Q1 and Q5 and we assigned to Q3 and Q4 the address of Q1. When the addresses of Q1 and Q5 were different, the postal codes of Q3 and Q4 were compared to the postal codes of Q1 and Q5 ones. If there were equal to Q1, we assigned the address of Q1. If there were equal to Q5, we assigned the address of Q5. When it was not possible to impute a complete address, we conserved only the postal code if available. Using these same decision rules, imputations were also made for missing addresses after Q5. If the address at Q5 was identical to the address at Q7 then the address at Q5 was assigned to Q6. However, when addresses were different, we considered that the relocation took place in the middle of the period Q5-Q7. If Q6 was in the first half of the period, we assigned it the address of Q5, otherwise Q7. Women for which the addresses at inclusion or one address during follow-up (up to index date) was missing and could not be imputed, despite decision rules, as well as women with addresses outside the continental mainland France (N = 586 cases and 542 controls) and corresponding matched women (N = 468 cases and 512 controls), were excluded.

2.3.5. Exposure assessment

Based on hourly concentrations, annual averaged PCB153 concentration values (in pg/m^3) were assigned to each woman, for each year from the cohort inclusion to the index date, using addresses or postal codes. If a woman moved within a year, the PCB153 concentration was weighted by the time spent at each address. For each woman, a cumulative exposure to PCB153 was then calculated, by adding the concentrations of each year from inclusion in the cohort to the index date.

2.4. Statistical analyses

Atmospheric exposure to PCB153, socio-demographic characteristics and other covariates were described for cases and controls, using mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. The woman characteristics were collected by self-questionnaires, mainly at baseline. Alcohol consumption was collected at Q3 and for hormonal treatments, we used the information available in the last questionnaire before the index date. Menopausal status at index date was determined from self-reported data during follow-up on menopausal status and age at menopause (see the data dictionary in Supplementary Material (Table S2)). A histogram was plotted to represent the variability of cumulative exposures among women. The distribution of the woman characteristics was also described according to PCB153 exposure quintiles based on the distribution of controls. Furthermore, the evolution of PCB153 concentrations between 1990 and 2011 corresponding to the different addresses of the women included in our analysis, have been described (1^{st} quartile, median, 3^{rd} quartile).

OR and corresponding 95% CI for invasive breast cancer were estimated using conditional logistic regression models, with PCB153 exposure as a continuous variable, for an increase of one SD in controls and by PCB153 exposure quintiles based on the distribution of controls with the first quintile as the reference group. The models were conditioned on the matching variables. Adjustment and interaction variables were selected from a literature review (Rojas and Stuckey, 2016; Sun et al., 2017; Dong and Qin, 2020; Binachon et al., 2014) and using a directed acyclic graph (DAG) (Supplementary Material, Fig. S1). Two models emerged from the DAG. A first model was performed

by adjusting only on the level of education (secondary, 1 to 2 year university degree, and ≥ 3 year university degree; used as a proxy for socio-economic status). A second model was performed using the following adjustment variables: total physical activity (< 25.3, 25.3-35.5, 35.6-51.8, and ≥ 51.8, in metabolic equivalent task-our per week (MET-h/week)), smoking status (never, current, former), alcohol drinking (never, ≤ 6.7 g/day, and > 6.7 g/day), body mass index (BMI) (< 25, 25-30, and ≥ 30 kg/m²), age at first full-term pregnancy (AFP) and parity (0, 0-2 children & AFP < 30 years, 0-2 children & AFP ≥ 30 years, and ≥ 3 children), breastfeeding (ever, never), oral contraceptive use (ever, never), menopausal hormone replacement therapy use (HT) (ever, never), and mammography before inclusion (yes, no). Additionally, a third model was conducted by adding other adjustment variables widely found in the literature: level of education (secondary, 1 to 2 year university degree, and ≥ 3 year university degree ; used as a proxy for socio-economic status), age at menarche (< 12, 12-14, and ≥ 14 years), menopausal status at index date (premenopausal, postmenopausal), previous family history of breast cancer (yes, no), previous history of personal benign breast disease (yes, no) and urban / rural status of the birthplace (see the data dictionary in Supplementary Material for a better specification of covariates (Table S2)). The effect modification by age at index date, physical activity, BMI, menopausal status over the study period, parity, breastfeeding and age at menarche were tested by including interaction terms between these variables and exposure of PCB153 in the models. Menopausal status over the study period was analyzed in three categories: premenopausal (women who self-reported premenopausal on the last returned questionnaire or an age at menopause greater than their age at the index date), postmenopausal (women who self-reported postmenopausal on the last returned questionnaire before the index date or an age at menopause younger than their age at the index date); and women premenopausal at study inclusion who transitioned to postmenopausal status before the index date.

A sensitivity analysis was performed considering only the women (in pairs) followed for at least 2 years to consider only women with a relatively long follow-up time since breast cancer is known to have a long period of latency. A model taking into account the correlation between women in the same geographical square of the CHIMERE model was further considered using a robust

variance derived from a generalized estimating equation approach. Furthermore, subgroup analyses were conducted according to the hormone receptors status (estrogen receptors (ER) and progesterone receptors (PR)) of breast tumor, only with continuous PCB153 exposure. Other models have also been estimated using the average annual PCB153 concentration, instead of cumulative concentration.

Simple imputations were used for variables with less than 5% missing data (Garcia-Acosta and Clavel-Chapelon, 1999). More specifically, continuous variables were replaced by the median while categorical variables were replaced by the modal class of cases for cases and of controls for controls, except for oral contraceptive use at index date. All women with missing data on this variable, had reported never used it at baseline. Accordingly, we assumed that they had not started using oral contraceptive later since the age at the inclusion in the cohort was between 40 and 65 years of age. For variables with more than 5% missing data, a category "missing data" was created. For HT, although less than 5% of the data were missing, no imputation was performed because this variable is largely dependent on age and time. For each model, the linearity of the logit of the effect of the quantitative variables (PCB153 exposure, considered in a continuous variable) was investigated using fractional polynomials.

All analyses were performed with R software version 3.6.1 and with a first-species risk of 5%. The p-values were estimated using the likelihood ratio test.

3. Results

3.1. Characteristics of the study participants

The selection of the 10,444 women involved in our nested case-control study is presented in a flow chart in Supplementary Material (Fig. S2). The characteristics of the 5,222 primary incident breast cancer cases (including 4941 histologically confirmed cases) and 5,222 matched controls are shown in Table 1. Cases were included on average at age 49.6 years (± 6.3) and were diagnosed on average at 60.6 years old (± 8.1). The delay between inclusion and diagnosis of breast cancer (i.e., the duration for which exposure was considered) was on average 11 years (± 5.7). Cases were more likely to be older than controls at first birth, to have had a mammography before inclusion, to have a family

history of breast cancer and to have a personal history of benign breast disease. The average annual concentration of atmospheric exposure to PCB153 was 9.9 pg/m^3 (± 4.2) for cases and 9.7 pg/m^3 (± 4.0) for controls. Average cumulative atmospheric exposure to PCB153 was 99.9 pg/m^3 (± 58.0) for cases and 98.1 pg/m^3 (± 55.2) for controls. The distribution of cumulative exposures showed a high variability between women (Fig. 1). The characteristics of women by quintiles of exposure are reported in Supplementary Material (Table S1). Compared to those in the lower quintile, women in the higher quintile were more likely to be non-smokers (50.3% vs 56.4%), to have higher levels of education (42.9% vs 31.7%), to have been born in urban areas (69.9% vs 59.5%), to have had a mammogram before inclusion (77.2% vs 73.4%) and to have used oral contraceptives (60.5% vs 55.9%). Conversely, high intensity physical activity and a personal history of benign breast disease appeared to be less represented in the highest quintile than in the lowest one (respectively 19.8% vs 25.7% and 22.2% vs 29.9%) (Supplementary Material, Table S1).

3.2. Evolution of PCB153 exposure

The spatial and temporal evolution of PCB153 concentrations is presented in Supplementary Material (Fig. S3). In 1990, the highest concentrations were found in the north and the northeast region, the Rhone Valley (southeast, from Lyon to Marseille) and in the Paris urban agglomeration. In 2010, despite the important decrease of pollutant concentration levels in the whole of France, these regions and urban areas remained the most polluted. Related to these numerical results, PCB153 concentrations at the addresses of the women in our study gradually decreased over time before stabilizing in the mid-2000s (Fig. 2). Annual average, median, and maximum PCB153 concentrations were respectively 12.2 pg/m^3 (± 4.3), 11.7 pg/m^3 and 37.6 pg/m^3 in 1990 and 2.9 pg/m^3 (± 2.0), 2.6 pg/m^3 and 12.9 pg/m^3 in 2011. The annual average PCB153 concentration decreased by an average of 6.6% per year between 1990 and 2011.

3.3. Associations between atmospheric PCB153 with breast cancer risk

Considering exposure as a continuous variable (for an increase of one SD in controls; 55 pg/m^3), there was a statistically significant association between cumulative atmospheric exposure to

PCB153 and breast cancer risk for the three models with ORs of 1.20 (95% CI: 1.09-1.32), 1.19 (95% CI: 1.08-1.31) and 1.17 (95% CI: 1.06-1.29) for Model 1, 2 and 3 respectively (Table 2). There was no statistically significant association for exposure considered in quintiles but an increase in risk was suggested for the fifth quintile versus the first one (OR=1.30; 95% CI: 0.90-1.87). Since the results did not materially change by the different adjustments, we chose to use the Model 2, the most complete DAG model, for the further analyses.

After stratification by menopausal status during follow-up, the association remained positively significant among women who were premenopausal at inclusion and were postmenopausal at index date, with exposure as a continuous variable (OR = 1.23; 95% CI: 1.09-1.39 for an increase of 55pg/m^3). An increase in risk was also suggested in postmenopausal women (OR = 1.15; 95% CI: 1.00-1.33 for an increase of 55pg/m^3). No statistically significant interaction with menopausal status was shown (P for interaction > 0.05) (Table 3). Moreover, there was no evidence of effect modification by age at index date, total physical activity, BMI, parity, breastfeeding and age at menarche (P for interaction > 0.05, data not shown).

An increase of breast cancer risk was observed for ER-positive (ER+) breast cancer (OR=1.18; 95% CI:1.05-1.33 for an increase of 55pg/m^3) and was suggested for PR-negative (PR-) and ER+PR- breast cancer (OR=1.18 (1.05-1.33) and OR=1.19 (0.94-1.50) respectively) (Table 4).

3.4. Additional and sensitivity analyses

After excluding women followed for less than two years and their matched controls (n = 716), the OR for cumulative exposure to PCB153 as continuous variable was similar to that found for the overall population (OR = 1.19; 95% CI: 1.08-1.31 for an increase of 55 pg/m^3, adjusted for Model 2 variables). Similar results were found when we accounted for the correlation between women living in the same geographical CHIMERE mesh (OR = 1.19; 95% CI: 1.08-1.31 for an increase of 55pg/m^3). Furthermore, an increase in risk was observed when using the yearly mean PCB153 exposure (OR = 1.16; 95% CI: 1.07-1.25; for an increase of one SD in controls; 4 pg/m^3).

4. Discussion

In this nested case-control study, we found a statistically significant positive association between cumulative atmospheric exposure to PCB153 as a continuous variable and breast cancer risk, overall and among women who transitioned from premenopause at study inclusion to postmenopause before their index date, and an increase in risk was suggested among postmenopausal women at inclusion. Further analyses, using exposure as continuous variable, according to hormone receptor status showed an increase in risk for ER+ breast cancer, but not for ER-negative (ER-) breast cancer.

To our knowledge, this is the first study evaluating the impact of cumulative atmospheric exposure to PCB153 on breast cancer risk. Previous studies were based mainly on PCBs measures in blood or breast adipose tissue samples (Leng et al., 2016; Zhang et al., 2015), considered to represent all pathways of exposure (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). However, most of the studies were based on a single measurement, assuming it was representative of past exposure, but only one measurement may not accurately reflect the exposure over 20 years, particularly for blood concentrations that tend to reflect more recent exposures (World Health Organization et al., 2016).

Among studies that investigated the relation between PCB153 exposure and breast cancer, three case-control studies using biological samples found a statistically significant positive association. A study from Greenland on blood samples of 77 breast cancer cases and 84 controls, found an OR of 2.69 (95% CI: 1.18-6.14), comparing the highest to the lowest tertile (Wielsøe et al., 2017). A Belgian study involving 60 cases and 60 controls, also using blood samples, reported an OR of 1.8 (95% CI: 1.4-2.5, for an increase of one unit of log-transform exposure) (Charlier et al., 2004). Moreover, a Chinese study, based on adipose tissue samples from 209 cases and 165 controls, reported an OR of 7.88 (95% CI: 4.13-15.02) for the third tertile compared to the first one (Huang et al., 2019). In contrast, the French CECILE study, on 695 cases and 1055 controls, using blood samples, found a significant inverse association with an OR of 0.75 (95% CI: 0.57-0.97) when comparing the last quartile (≥ 162.6 ng/g lipid) to the first one (< 36.6 ng/g lipid) (Bachelet et al., 2019). Furthermore, an American case-control study including 304 cases and 186 controls, using adipose tissue samples, found a statistically significant inverse association (OR = 0.93; 95% CI: 0.86-0. 99, for an increase of

10 ppb) (Holford et al., 2000). In addition, 14 studies using biological samples (11 on blood and three on adipose tissue) failed to highlight any statistically significant associations between PCB153 and breast cancer overall (Aronson et al., 2000; Arrebola et al., 2016; Cohn et al., 2012; Demers et al., 2002, 2000; Gammon et al., 2002; Holmes et al., 2014; Høyer et al., 2000; Laden et al., 2001; Morgan et al., 2017; Raaschou-Nielsen et al., 2005; Recio-Vega et al., 2011; Zheng et al., 2000). A meta-analysis studying the effect of plasma and adipose tissue levels of PCB congeners, found no statistically significant association for PCB153 based on the pooling of data from 11 studies including 2,881 cases from six countries (pooled OR = 1.04 ; 95% CI: 0.81-1.34, for the highest versus the lowest group of exposure) (Leng et al., 2016). A second meta-analysis, including 25 studies, and grouping PCBs according to their structural and biological properties, found a statistically significant association for CYP1A and CYP2B inducer congeners (Group III PCBs), including PCB153 (pooled OR = 1.25 ; 95% CI: 1.09-1.43, for the highest versus the lowest group of exposure) (Zhang et al., 2015).

The instability of the observed associations in our study and in previous reports could be explained by an important collinearity between PCB congeners. PCB153 exposure is likely to be correlated with other congeners with divergent biological mechanisms and the effects on breast cancer risk could be cancel out or altered (Bonefeld-Jørgensen et al., 2001; Holford et al., 2000; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016; Leng et al., 2016; Rodgers et al., 2018). This is difficult to take into account when PCBs are considered individually.

In the present study, analyses by menopausal status during follow-up, suggested an effect of PCB153 on breast cancer mainly on women who transitioned from premenopause at study inclusion to postmenopause before their index date. Menopausal transition is one of the specific periods of susceptibility for the mammary gland to breast cancer, as well as during prenatal development, puberty and pregnancy (Rodgers et al., 2018; Terry et al., 2019). This heightened susceptibility is due to structural and functional changes in breast tissue, as well as alterations in the microenvironment and hormone signaling. During the menopausal transition, the sensitivity of hormone receptors increases, making the breast tissue more sensitive to lower levels of estrogens but also to endocrine disruptors

(Terry et al., 2019). In previous studies on PCBs, the biological samples were generally taken at inclusion but could correspond to different times of exposure during women's life. This could explain the instability of the associations found in the literature. Further epidemiological studies on the menopausal transition are needed to better understand the effect of PCBs, and more generally endocrine disruptors, during this critical window of susceptibility.

Only a few studies have investigated breast cancer risk associated with PCBs exposure according to hormone receptor status and results have been divergent. An inverse association with ER- breast cancer was observed for PCB153 and overall PCBs (Raaschou-Nielsen et al., 2005) and one study showed a statistically significant inverse association for the ER+PR- tumor for overall PCBs (Itoh et al., 2009). Other articles did not find a statistically significant association by hormone receptor status (Gatto et al., 2007; Helzlsouer et al., 1999; Høyer et al., 2001; Rusiecki et al., 2004). In contrast to these previous studies, we found an increased risk of ER+ breast cancer associated with PCB153 exposure.

The molecular mechanisms underlying the observed association of PCB exposure with breast cancer risk remain not fully understood. PCBs act through various mechanisms of action associated with carcinogenesis and induce up to seven of the ten key characteristics in producing carcinogenicity (Smith et al., 2016), including the formation of reactive oxygen species and oxidative stress (Oakley et al., 1996; Smith et al., 2016), immunosuppressive effects and chronic inflammation (Lauby-Secretan et al., 2013; Smith et al., 2016). Highly chlorinated PCBs, such as PCB153, are associated primarily with receptor mediated activities and act as ligands for the aryl hydrocarbon receptor (AhR) and thus activating a large number of genes in a tissue- and cell-specific manner that can lead to cell proliferation, apoptosis and other carcinogenic effects (Smith et al., 2016).

Several reports have shown that PCB congeners, including PCB153, modulate ER signaling pathways with both estrogenic and/or anti-estrogenic effects (Andersson et al., 1999; Bonefeld-Jørgensen et al., 2001; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016; Smith et al., 2016). Mechanistic effects in vitro involve competition with 17b-estradiol (E2) for binding to ERa and ERb, promotion of proliferation of the human breast cancer cell line MCF-7,

and induction of gene expression (Bonefeld-Jørgensen et al., 2001). In addition to the pleiotropic effects of numerous congeners, contradictory findings in epidemiology studies might be further explained by experimental evidence suggesting a dose dependent role in promotion or inhibition of cell proliferation. Thus, Bonefeld-Jørgensen *et al.* observed a slightly increased cell proliferation in MCF-7 cells at low concentrations (1–10 nM) in cells co-treated with 0.01 nM 17b-Estradiol, whereas the compounds inhibited cell growth significantly at 1 and 10 mM (Bonefeld-Jørgensen et al., 2001). Moreover, PCB153 among other congeners, act as CYP1A and CYP1B1 enzyme inducers leading to enhanced estradiol metabolism into more toxic metabolites (Wolff et al., 1997).

Consistent with other observational studies (Gatto et al., 2007; Zheng et al., 2000), stratified analyses on BMI and breastfeeding did not show statistically significant interactions in the present study. Although the effect tends to disappear with age, breastfeeding history and duration have been associated with a decrease of PCBs levels (Agudo et al., 2009; Bachelet et al., 2011), reflecting PCBs excretion in breast milk (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans et al., 2016). Furthermore, significant associations, both, inverse (Agudo et al., 2009; Bachelet et al., 2011) and positive (Wolff et al., 2005) have been observed between BMI and serum concentrations of PCBs. In the former, this could be explained by a dilution of the PCBs in fat, whereas in the latter, slower excretion of PCBs in overweight people has been suggested (Wolff et al., 2007; Wood et al., 2016).

Our study has several strengths, partly due to the nested case-control design within the large E3N cohort. This design resulted in a large number of breast cancer cases and a sufficient statistical power to permit subgroup analyses. We were able to adjust for potential confounding factors or effect modifiers, and also perform subgroup analyses thanks to the availability of individual characteristics of women and breast tumors. Furthermore, the percentages of missing data were low, reflecting the high quality of the data collected in the E3N cohort. Another strong point of the E3N cohort was the high participation rate, and absence of major differences of respondents and non-respondents at inclusion regarding the region of residence and year of birth (Clavel-Chapelon and E3N Study Group, 2015). Moreover, in our nested case-control study, the comparison of included and excluded cases,

due to missing address, did not reveal relevant differences in the distribution of socio-demographic data and other covariates. Another strength of our study was the use of the residential history to reconstruct exposure over time taking into account residential mobility of study women and temporal changes in PCBs emissions over the study period. Although some cases had a shorter follow-up time, a sensitivity analysis conducted on women followed at least two years did not show any difference in the observed association. Furthermore, although data on workplace exposures or during commuting were not available, most women from the E3N cohort were teachers or worked in affiliated occupations, thus it can be assumed that the occupational PCBs exposure was homogeneous among study participants.

Our study has several limitations. The first limitation was the spatial resolution of the CHIMERE simulations (0.125° x 0.0625°, approximately 7km x 7km) used for the estimation of PCB153 exposure that may have led to exposure misclassification. While the CHIMERE model has been validated by comparison with measurement data for numerous atmospheric pollutants like particles, NO_2 or Ozone (Couvidat et al., 2018), it was not possible to evaluate the CHIMERE simulations for PCB153 due to the lack of measurement data for PCBs in France in time and space during the study period. The estimation of emissions by EMEP may also be uncertain, especially in the early 90's and may directly affect the quality of the CHIMERE simulations. The lack of measurements also limits the use of land use regression (LUR) and fine scale deterministic models to assess atmospheric PCB153 exposure over the French territory for the study period (1990-2011). Then, there is a lack of residential history of women before entering the cohort in 1990 (except at birth). It would have been interesting to consider lifetime exposures, but the life-course residential history of women were not available and data on pollution exposure are scarce before 1990. This left truncation of exposure information may have led to a potential underestimation of exposure that have been higher in the past, as well as the incapacity to identify effects during relevant windows of susceptibility of the mammary gland to carcinogens (puberty, first-term pregnancy, etc.) having occurred before inclusion (Rodgers et al., 2018; Terry et al., 2019). Nonetheless, in the third model, we adjusted for urban / rural status of the birthplace (Binachon et al., 2014), as a surrogate of air pollution exposure, and results did

not change. Moreover, our study only considered atmospheric PCB153 exposure and did not take into account dietary exposure. However, a study conducted in Sweden, on a large cohort of 36,777 women, on dietary exposure to PCB153 did not show a statistically significant association with breast cancer risk (Donat-Vargas et al., 2016). Also, our study did not take into account HER2 receptors status for subgroup analyses because the HER2 status was collected only from the year 2000 in the E3N cohort, consequently this information was not available for the overall study population. Furthermore, we could not exclude a potential limitation due to a lack of a single adjudication committee to ensure that tumor characteristics were identified and categorized in the same manner across hospitals. However, the potential misclassification regarding invasive / in situ status of tumor was very low (Collins et al., 2004) to result in substantial bias of the ORs estimated. Finally, our study focused only on airborne exposure to PCB153, and it cannot be excluded that other air pollutants or congeners may be confounders of the relationship between atmospheric exposure to PCB153 and breast cancer risk (Leng et al., 2016; White et al., 2018). Likewise, interactions cannot be excluded since additive, antagonistic or synergistic effects have been observed in several experimental studies between PCBs and other pollutants (including polybrominated diphenyl ethers, dioxins or cadmium) (Aubé et al., 2011; Buha et al., 2013; O'Kane et al., 2014; Pellacani et al., 2014) or between congeners themselves (Ferrante et al., 2011; Oh et al., 2007). Further epidemiological studies taking into account multi-exposure would be interesting, as well as studies on multiple congeners.

In conclusion, our study showed an increased risk of breast cancer associated with an increased cumulative atmospheric exposure to PCB153 overall and on women who transitioned from premenopause at study inclusion to postmenopause before their index date, supported by biological hypotheses. However, it is not excluded that biases may have been introduced, particularly through the absence of exposure data prior to cohort entry. Furthermore, to our knowledge, our study is the first to have estimated PCB153 atmospheric exposure and the results of previous studies using biological samples have not been consistent. Further epidemiological studies are needed to confirm our results, and to refine the effects of exposure during critical windows of susceptibility but also considering multipollutant, multi PCB-congeners and multi sources of exposure.

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Authors' contributions

All authors contributed to the study conception and design. FD analysed the data, interpreted the results and drafted the manuscript under the supervision of DP. AA, GS, FRM, KL, BF and DP helped with the data collection, data analysis and results interpretation. TC, LG, FC, BB, EF, PS, JG, and JC participated to the data collection, exposure assessment and analysis of spatial data (geocoding and spatial analyses). All authors critically reviewed the manuscript. BF was responsible for the conception and design and supervising the project. All authors read and approved the final manuscript.

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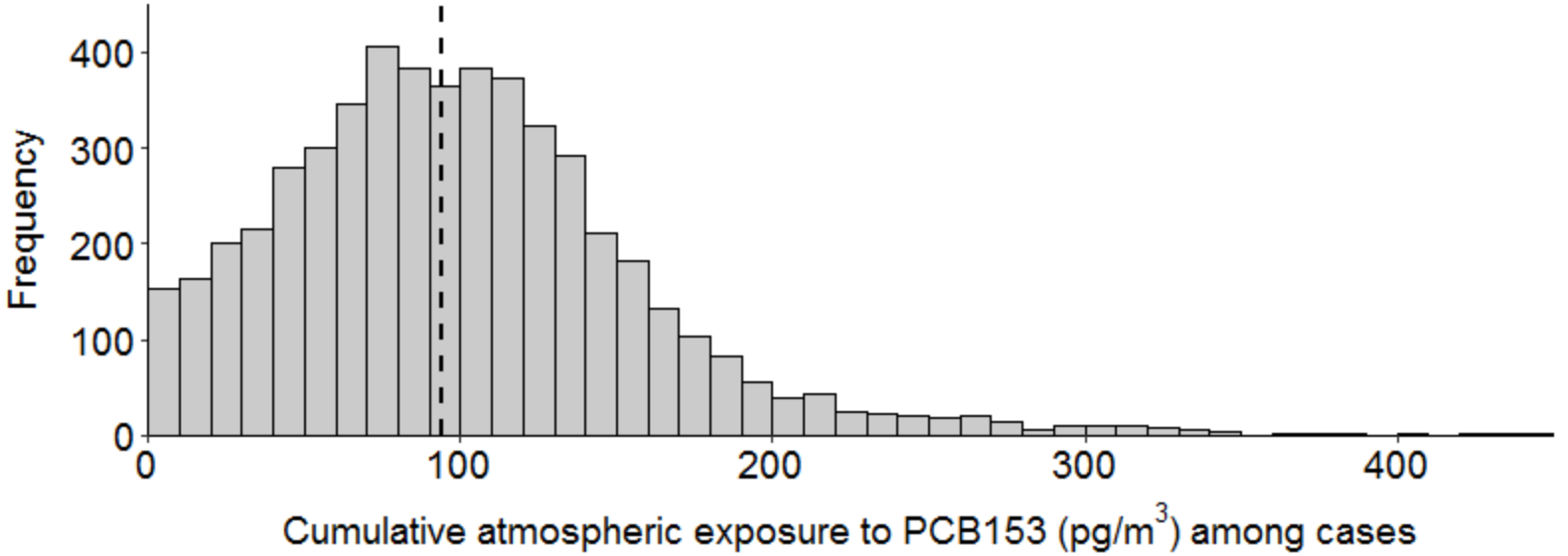
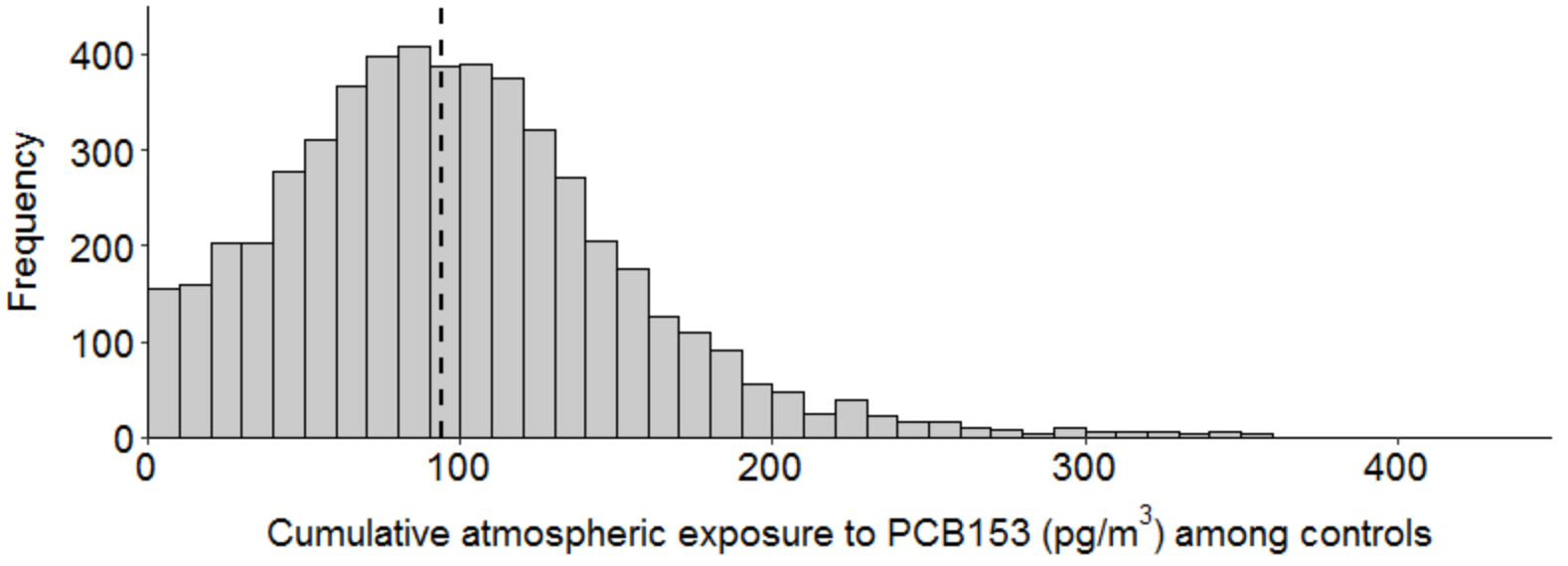
Figures

Fig. 1. Distribution of cumulative atmospheric exposure during follow-up (inclusion to index date) and the median (vertical dashed line) for cases and controls. XENAIR case-control study nested in the E3N cohort, France, 1990-2011

Fig. 2. Average annual evolution of hourly PCB153 atmospheric concentrations (median, 1st and 3rd quartiles) at the addresses of the study subjects by year, from 1990 to 2011. XENAIR case-control study nested in the E3N cohort, France, 1990-2011


Frequency
400
300
200
100
0
0
100
200
300
400
Cumulative atmospheric exposure to PCB153 (pg/m3) among cases


Frequency
400
300
200
100
0
0
100
200
300
400
Cumulative atmospheric exposure to PCB153 (pg/m3) among controls

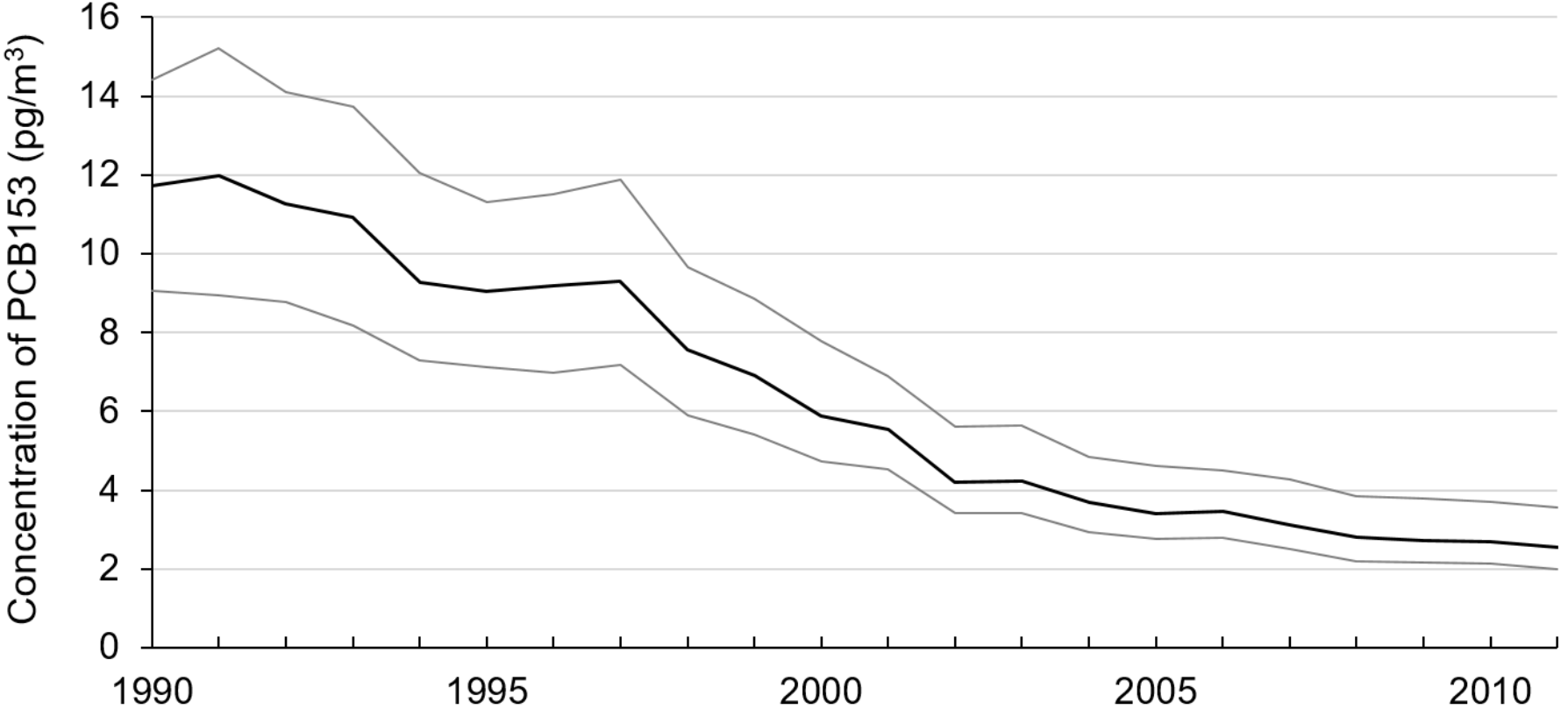

Concentration of PCB153 (pg/m3)
16
14
12
10
8
6
4
2
0
1990
1995
2000
2005
2010

Table 1. Characteristics of 5,222 cases and 5,222 controls in the XENAIR case-control study nested in the E3N cohort, France, 1990-2011

Characteristics	Cases (n = 5,222) Mean ± SD or n (%)	Controls (n = 5,222) Mean ± SD or n (%)
Age at baseline (years)	49.6 ± 6.3	49.5 ± 6.3
Age at diagnosis (years), among breast cancer cases	60.6 ± 8.1	
Time to diagnosis (years), among breast cancer cases	11.0 ± 5.7	
Annual average atmospheric exposure to PCB153 (pg/m^3)	9.9 ± 4.2	9.7 ± 4.0
Cumulative atmospheric exposure to PCB153 (pg/m^3)	99.9 ± 58.0	98.1 ± 55.2
Body Mass Index (kg/m^2)		
< 25	4,236 (81.1)	4,239 (81.2)
25-29	744 (14.2)	715 (13.7)
≥ 30	149 (2.9)	162 (3.1)
Missing	93 (1.8)	106 (2.0)
Alcohol drinking		
Never drinker	402 (7.7)	473 (9.1)
≤ 6.7 (g/day)	1,291 (24.7)	1,391 (26.6)
> 6.7 (g/day)	2,002 (38.3)	1,865 (35.7)
Missing	1,527 (29.2)	1,493 (28.6)
Smoking status		
Never smoker	2,800 (53.6)	2,861 (54.8)
Current smoker	781 (15.0)	743 (14.2)
Former smoker	1,626 (31.1)	1,603 (30.7)
Missing	15 (0.3)	15 (0.3)
Status of the birthplace		
Rural	1,369 (26.2)	1,429 (27.4)
Urban	3,299 (63.2)	3,190 (61.1)
Missing	554 (10.6)	603 (11.5)
Total physical activity (METs-h/week)		
< 25.3	1,304 (25.0)	1,229 (23.5)
25.3-35.5	1,388 (26.6)	1,359 (26.0)
35.6-51.8	1,341 (25.7)	1,322 (25.3)
≥ 51.8	1,187 (22.7)	1,299 (24.9)
Missing	2 (0.0)	13 (0.2)
Education		
Secondary	802 (15.4)	874 (16.7)
1- to 2-year university degree	2,460 (47.1)	2,584 (49.5)
≥ 3 year university degree	1,923 (36.8)	1,727 (33.1)
Missing	37 (0.7)	37 (0.7)
Age at menarche (years)		
< 12	1,098 (21.0)	1,050 (20.1)
12-13	2,604 (49.9)	2,588 (49.6)
≥ 14	1,420 (27.2)	1,470 (28.2)
Missing	100 (1.9)	114 (2.2)

Previous use of oral contraceptives		
Yes	3,075 (58.9)	3,064 (58.7)
No	2,086 (39.9)	2,127 (40.7)
Missing	61 (1.2)	31 (0.6)
Menopausal status at inclusion		
Premenopausal	3,107 (59.5)	3,127 (59.9)
Postmenopausal	2,072 (39.7)	2,069 (39.6)
Missing	43 (0.8)	26 (0.5)
Menopausal status at index date		
Premenopausal	873 (16.7)	804 (15.4)
Postmenopausal	4,306 (82.5)	4,392 (84.1)
Missing	43 (0.8)	26 (0.5)
Use of menopausal hormone replacement therapy		
Yes	3,064 (58.7)	2,913 (55.8)
No	2,029 (38.9)	2,187 (41.9)
Missing	129 (2.5)	122 (2.3)
Mammography during the previous follow-up period		
Yes	4,026 (77.1)	3,795 (72.7)
No	1,196 (22.9)	1,427 (27.3)
Parity		
0	674 (12.9)	562 (10.8)
1-2	3,163 (60.5)	3,075 (58.9)
≥ 3	1,350 (25.9)	1,559 (29.9)
Missing	35 (0.7)	26 (0.5)
Age at first full-term pregnancy (years)		
No child	674 (12.9)	562 (10.8)
< 30	3,795 (72.7)	4,034 (77.3)
≥ 30	681 (13.0)	558 (10.7)
Missing	72 (1.4)	68 (1.3)
Breastfeeding		
Yes	2,755 (52.8)	2,786 (53.4)
No	2,383 (45.6)	2,373 (45.4)
Missing	84 (1.6)	63 (1.2)
Previous family history of breast cancer		
Yes	886 (17.0)	555 (10.6)
No	4,248 (81.3)	4,584 (87.8)
Missing	88 (1.7)	83 (1.6)
Previous history of personal benign breast disease		
Yes	1,534 (29.4)	1,177 (22.6)
No	3,688 (70.6)	4,045 (77.4)

SD, standard deviation; MET, metabolic equivalent of task

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between invasive breast cancer and cumulative atmospheric exposure to PCB153 overall. XENAIR case-control study nested in the E3N cohort, France, 1990-2011

Cumulative atmospheric PCB153 exposure (pg/m^3)	**n cases/controls**	**Model 1**[a]		**Model 2**[b]		**Model 3**[c]	
		OR (95% CI)	**p-value**[d]	**OR (95% CI)**	**p-value**[d]	**OR (95% CI)**	**p-value**[d]
Continuous (for an increment of 55 pg/m$^{3)}$	5,222 / 5,222	1.20 (1.09-1.32)	< 0.001	1.19 (1.08-1.31)	< 0.001	1.17 (1.06-1.29)	0.002
Quintiles			0.14		0.16		0.25
I[e]	1,045 / 1,045	1		1		1	
II	1,029 / 1,044	0.97 (0.75-1.26)		0.98 (0.76-1.28)		0.99 (0.76-1.30)	
III	998 / 1,044	0.99 (0.73-1.35)		0.99 (0.73-1.36)		0.99 (0.72-1.36)	
IV	1,065 / 1,044	1.18 (0.84-1.66)		1.19 (0.84-1.67)		1.16 (0.82-1.65)	
V	1,085 / 1,045	1.30 (0.90-1.87)		1.30 (0.90-1.87)		1.27 (0.88-1.85)	

OR, odds ratio; CI, confidence interval;

[a] Adjusted for level of education

[b] Adjusted for total physical activity, smoking status, alcohol drinking, body mass index, age at first full-term pregnancy and parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, and mammography before inclusion

[c] Adjusted for level of education, total physical activity, smoking status, alcohol drinking, body mass index, age at first full-term pregnancy and parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, mammography before inclusion, previous family history of breast cancer, personal history of benign breast disease, age at menarche, menopausal status at index date and urban / rural status of the birthplace

[d] P-values derived from likelihood ratio test

[e] Quintiles values based on the distribution of controls (pg/m^3): 51.33; 80.27; 106.69; 137.93

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between invasive breast cancer and cumulative atmospheric exposure to PCB153 according to menopausal status during follow-up. XENAIR case-control study nested in the E3N cohort, France, 1990-2011

Cumulative atmospheric PCB153 exposure (pg/m^3)	**n cases/controls**	**OR[a] (95% CI)**	**p-value[b]**
Premenopausal			
Continuous (for an increment of 55 pg/m^3)	591 / 591	1.16 (0.93-1.44)	0.18
Quintiles			0.61
I[c]	361 / 361	1	
II	130 / 138	1.00 (0.65-1.52)	
III	55 / 45	1.32 (0.77-2.27)	
IV	35 / 35	1.09 (0.61-1.96)	
V	10 / 12	1.44 (0.74-2.79)	
Postmenopausal			
Continuous (for an increment of 55 pg/m^3)	1,991 / 1,991	1.15 (1.00-1.33)	0.05
Quintiles			0.25
I[c]	450 / 445	1	
II	425 / 431	0.87 (0.59-1.28)	
III	377 / 416	0.86 (0.54-1.35)	
IV	355 / 342	1.06 (0.64-1.75)	
V	384 / 357	1.23 (0.72-2.09)	
Change in menopausal status[d]			
Continuous (for an increment of 55 pg/m^3)	1,958 /1,958	1.23 (1.09-1.39)	< 0.001
Quintiles			0.31
I[c]	106 / 108	1	
II	326 / 328	1.26 (0.83-1.92)	
III	427 / 441	1.26 (0.79-1.99)	
IV	542 / 524	1.52 (0.93-2.49)	
V	557 / 557	1.56 (0.94-2.61)	

OR, odds ratio; CI, confidence interval;

P for interaction equal to 0.64 in continuous and 0.73 in quintiles

[a] Adjusted for total physical activity, smoking status, alcohol drinking, body mass index, age at first full-term pregnancy and parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, and mammography before inclusion (Model 2)

[b] P-values derived from likelihood ratio test

[c] Quintiles values based on the distribution of controls (pg/m^3): 51.33; 80.27; 106.69; 137.93

[d] Women who were premenopausal at inclusion and were postmenopausal at index date

Table 4. Odds ratios (ORs) and 95% confidence intervals (CI) for the association between invasive breast cancer and cumulative atmospheric exposure to PCB153 by hormone receptor status. XENAIR case-control study nested in the E3N cohort, France, 1990-2011

Cumulative atmospheric PCB153 exposure (pg/m^3)	**n cases/controls**	**OR[a] (95% CI)**	**p-value[b]**
ER -	760 / 760	1.04 (0.80-1.36)	0.75
ER +	3,405 / 3,405	1.18 (1.05-1.33)	0.01
PR -	1,439 / 1,439	1.14 (0.96-1.37)	0.14
PR +	2,602 / 2,602	1.08 (0.94-1.24)	0.30
ER- PR-	612 / 612	1.01 (0.75-1.35)	0.95
ER+ PR+	2,459 / 2,459	1.08 (0.94-1.25)	0.27
ER+ PR-	825 / 825	1.19 (0.94-1.50)	0.15
ER- PR+	140 / 140	0.90 (0.42-1.97)	0.80

OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor

[a] Adjusted for total physical activity, smoking status, alcohol drinking, body mass index, age at first full-term pregnancy and parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, and mammography before inclusion (Model 2); for an increment of 55 pg/m^3

[b] P-value derived from likelihood ratio test