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Risk of breast cancer associated with long-term exposure to benzo[a]pyrene (BaP) air pollution: Evidence from the French E3N cohort study

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ABSTRACT

Background: Benzo[a]pyrene (BaP) is an endocrine-disrupting pollutant formed during incomplete combustion of organic materials. It has been recognized as a reproductive and developmental toxicant, however epidemiological evidence of the long-term effect of ambient air BaP on breast cancer (BC) is limited. Thus we evaluated associations between ambient air BaP exposure and risk of BC, overall and according to menopausal status and molecular subtypes (estrogen receptor negative/positive (ER−/ER+) and progesterone receptor negative/positive (PR−/PR+)), stage and grade of differentiation of BC in the French E3N cohort study.

Methods: Within a nested case-control study of 5222 incident BC cases and 5222 matched controls, annual BaP exposure was estimated using a chemistry-transport model (CHIMERE) and was assigned to the geocoded residential addresses of participants for each year during the 1990–2011 follow-up period. Multivariable conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Overall, cumulative airborne BaP exposure was significantly associated with the overall risk of BC, for each 1 interquartile range (IQR) increase in the concentration levels of BaP (1.42 ng/m^3), the OR = 1.15 (95% CI: 1.04–1.27). However, by menopausal status, the significant positive association remained only in women who underwent menopausal transition (i.e. premenopausal women at inclusion who became postmenopausal at diagnosis), OR per 1 IQR = 1.20 (95% CI: 1.03–1.40). By hormone receptor status, positive associations were observed for ER+, PR + and ER + PR + BC, with ORs = 1.17 (95% CI: 1.04–1.32), 1.16 (95% CI: 1.01–1.33), and 1.17 (95% CI: 1.01–1.36) per 1 IQR, respectively. There was also a borderline positive association between BaP and grade 3 BC (OR per 1 IQR = 1.15 (95% CI: 0.99–1.34).

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

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Conclusions: We provide evidence of increased risk of BC associated with cumulative BaP exposure, which varied according to menopausal status, hormone receptor status, and grade of differentiation of BC. Our results add further epidemiological evidence to the previous experimental studies suggesting the adverse effects of BaP.

1. Background

Benzo[a]pyrene (BaP) is a common environmental pollutant formed during incomplete combustion or pyrolysis of organic materials, and is one of the best known and most characterized components of the polycyclic aromatic hydrocarbons (PAHs) family (Gianelle et al., 2013). BaP is used as a surrogate for the estimation of total PAHs exposure since its fraction is relatively stable in the PAHs complex (Beyea et al., 2006). The general population can be exposed to BaP through ambient air, tobacco smoke, water, and food. Major sources of PAHs in ambient air (both outdoors and indoors) include residential and commercial heating with wood, coal, or other biomasses (oil and gas), other indoor sources such as cooking and tobacco smoke, and outdoor sources like motor-vehicle exhaust (especially from diesel engines), industrial emissions and forest fires. Average concentrations of PAHs in the ambient air in urban areas generally range from 1 to 30 ng/m^3 (Baan et al., 2009). BaP air pollution is a major public health problem in areas where domestic coal and wood-burning is frequent. In these areas, BaP emissions have increased in the last decade due to increased emissions from household combustion of biomass (Guerreiro et al., 2014). On average, around 20% of the European population was exposed to BaP concentrations exceeding the EU annual target value (1 ng/m^3), and only 7% live in areas where the concentrations were under the estimated tolerable risk level of 0.12 ng/m^3 (Guerreiro et al., 2016; Smith, 2006). Occupational exposure to PAHs occurs primarily through inhalation and skin contact (IARC Working Groups, 2012). Industrial sources of BaP include coal liquefaction, coal gasification, coke production, coke ovens, coal-tar distillation, roofing and paving, wood impregnation/preservation with creosote, aluminum production, carbon-electrode manufacture, chimney sweeping, and power plants, with the highest levels of exposure to PAHs (up to 100 μg/m^3) observed in aluminum production (IARC Working Groups, 2012).

BaP has been recognized as a reproductive and developmental toxicant; its carcinogenicity has been well demonstrated in many experimental animal models (Li et al., 2017; Archibong et al., 2012) and has been shown to increase the incidence of breast cancer (BC), as well as of sarcomas, liver and lung tumours (Balansky et al., 2007; Malik et al., 2018). Based on the strong experimental evidence of carcinogenicity in animals, reinforced by the consistent mechanistic evidence, BaP has been classified as a group 1 carcinogen in humans by the International Agency for Research on Cancer (IARC) (IARC Working Groups, 2012). However, epidemiological studies concerning the association between exposure to ambient air BaP and BC remain sparse. The Long Island BC Study Project (LIBCSP) using BaP as a surrogate for PAHs exposure found positive associations between vehicular traffic-related BaP exposure and BC incidence (Mordukhovich et al., 2016). The study by Nie et al. using BaP as a surrogate for total PAHs exposure related to traffic emissions found an increased risk of BC among pre-menopausal women exposed to increased traffic emissions at menarche (OR = 2.05; 95% CI: 0.92–4.54, P trend = 0.03) and among post-menopausal women exposed at first birth (OR = 2.57; 95% CI: 1.16–5.69, P trend = 0.19) (Nie et al., 2007). Also, White et al. reported a 30 to 50% increase in BC incidence associated with PAH indoor sources in population-based case-control study conducted on Long Island, New York (White et al., 2016).

Furthermore, several studies suggested that tobacco smoking may influence individual BC risk associated with BaP exposure (Jones et al., 2019; Gray et al., 2016; Terry et al., 2002). Also, higher dietary exposure of BaP has been reported to play a role in the etiology of BC and the joint effect of BaP and alcohol consumption showed an elevated risk of BC (Ronco et al., 2011). Therefore further analyses are needed to clarify if the associations between BaP exposure and BC risk are modified by tobacco and alcohol. BaP has also been reported to induce BC metastasis in both in vitro and in vivo studies (Guo et al., 2015). Recently, Malik et al. have demonstrated that BaP promoted an inflammatory microenvironment able to drive the metastatic potential of human breast cells through enabling migration and invasion of breast epithelial cells (Malik et al., 2018). The relationships between BaP and BC risk may also vary according to grade of differentiation of BC. Yet, previous studies have not specifically considered associations accordingly. A number of studies have suggested that the impact of environmental exposures on BC risk might be greater during specific windows of susceptibility in a woman's life, including prenatal development, puberty, and pregnancy, when mammary cells rapidly proliferate and differentiate (Cohn, 2011; Rodgers et al., 2018; Teitelbaum et al., 2015; Rudel et al., 2011). Also, the « menopausal transition » defined as the period preceding menopause (i.e. absence of menstrual periods for at least 12 months) (Sherman, 2005; Harlow et al., 2012; Freeman, 2015) may be a relevant window of susceptibility to BaP exposure due to important structural and functional changes in the breast gland.

Based on its inflammatory, genotoxic, and estrogenic properties, we hypothesized that long-term exposure to ambient air BaP might play a role in the etiology of BC. Using data from the French E3N cohort study (Clavel-Chapelon, 2015), we investigated associations between cumulative exposure of ambient air BaP and BC risk. We assessed the associations for BC overall and according to menopausal status at inclusion and diagnosis, molecular subtypes, stage, and grade of differentiation of BC, and further investigated whether any of the observed associations were modified by alcohol and tobacco smoking.

2. Material and methods

2.1. The E3N study

E3N (Etude Epidémiologique après de femmes de l'Education Nationale) is an ongoing French prospective cohort study established in 1990 to investigate the main risk factors for cancer and severe chronic conditions in women (Clavel-Chapelon, 2015). Participants were recruited between June 1990 and November 1991 among women aged 40–65 years, living in France and insured by national health insurance covering workers from the French National Education System (Mutuelle Générale de l'Education Nationale, MGEN). E3N is the French part of the European Prospective Investigation on Cancer (EPIC), a vast European cohort study coordinated by IARC and involving nearly 500,000 Europeans in 10 countries (Riboli et al., 2002). At baseline of the E3N cohort, 98,995 participants filled in a self-administered questionnaire, including data on socio-demographic characteristics, lifestyle (smoking and physical activity), reproductive factors (ages at menarche and menopause, use of exogenous hormones, number of children, age at first full-term pregnancy, and breastfeeding), anthropometry (height, weight, waist and hip circumference), past medical history (benign breast disease and gynecological screening), and familial history of cancer. Follow-up questionnaires were sent every 2–3 years thereafter, with a total of twelve questionnaires sent to the participants to date (participation rate at each questionnaire ~83%). Education level was used as a proxy for socioeconomic status (SES). Daily alcohol intake (g/day) was estimated from the first diet history questionnaire in 1993 (Leblanc et al., 2005; Sirot et al., 2012).

Between 1994 and 1999, E3N participants were invited to give a blood specimen. Blood samples were collected from 25,000 women, and

saliva samples were later collected from an additional 47,000 women. The occurrence of cancer was self-reported in each questionnaire, and a small number of cancers were further identified from the insurance files or information on causes of death obtained from the National Service on Causes of Deaths (CépiDC-Inserm). BC cases were identified through self-reports in the questionnaires, from the MGEN files or through information from death certificates. The pathology reports, were obtained for 93% of self-declared cases, and the proportion of false-positive self-reports was low (<5%). The addresses of the subjects selected for the study have been reported in the baseline (1990) and in the 5th to the 10th follow-up questionnaires (years 1997, 2000, 2002, 2005, 2008, and 2011). In the 3rd and the 4th follow-up questionnaires (years 1993 and 1995), only postal codes of participants were reported. In addition, participants' place of birth (postal code and municipality) was obtained from the first questionnaire and assigned an urban/rural status based on data from the closest national census (Binachon et al., 2014). Informed consent was obtained from each participant, and the study was approved by the French National Commission for Data Protection and Privacy (CNIL).

2.2. Nested case control study design

The present analysis was based on a nested case-control subset of the E3N cohort (Amadou et al., 2020a). We included women without any cancer, with completed home address at baseline, and living in the metropolitan French territory (except Corsica) during the 1990–2011 follow-up period. A total of 6298 histologically confirmed invasive BC incident cases were diagnosed during the 1990–2011 follow-up period. Among them, 19 women with phyllodes tumors and 3 women with missing data on matching variables were excluded. For each BC case, one control was randomly selected by incidence density sampling (Amadou et al., 2020b). Two complementary groups of cases according to availability of biological samples (blood or saliva) were used, to best select appropriate controls and to allow ancillary objectives based on biological samples (to study the impact of BaP exposure on DNA methylation and interactions with genetic polymorphisms) (Amadou et al., 2020a). For the first group of cases (with a blood sample), controls were matched to cases on the department of residence, age (±1 year), date (±3 months), and menopausal status at blood collection. Controls for the second group (without a blood sample) were matched on the same criteria, but at baseline, and additionally matched on availability of a saliva sample. The matched case-control design was used to control for confounding and to have individuals with the same duration of follow-up in each pair in the statistical analyses. Women with more than one missing address, as well as those living abroad during the follow-up time were further excluded (N = 1054 cases and 1054 controls). Finally, the analyses were carried out in a subsample of 5222 women diagnosed with a primary invasive BC and 5222 matched controls with complete information on home addresses. Data on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) status were obtained from pathology reports. ER and PR status were available for 79.8% (ER− = 760; ER+ = 3405; and unknown = 1057) and 77.4% (PR− = 1439; PR+ = 2602; and unknown = 1181) of cases, respectively. Information on the tumor-node-metastasis (TNM) stage was extracted from pathological reports. A total of 4733 (90.6%) BC cases had the TNM stage information. Information on grade of BC differentiation at diagnosis was also obtained based on pathological reports and available for 4164 (79.7%) BC cases. For women with more than one tumor diagnosed at the same time, the more advanced-stage tumor was considered, or if the stages were the same, the higher-grade tumor.

2.3. Estimation of long term exposure to airborne BaP

Using residential histories of the study subjects from their enrolment in the cohort until the index date at BC diagnosis for cases and at the selection for controls, atmospheric exposure to BaP was estimated using a chemistry-transport model (CHIMERE).

Airborne BaP concentrations (ng/m^3) have been simulated using the CHIMERE by the National Institute for Industrial Environment and Risks (INERIS) for the period 1990 to 2010 (Guerreiro et al., 2016; Menut et al., 2013) and detailed methods have been described elsewhere (Guerreiro et al., 2016). Briefly, the CHIMERE model is a chemistry-transport model (CTM) used to simulate pollutant transport from local to continental scales, with a spatial resolution of 0.125° × 0.0625° (around 7 × 7 km) (Bessagnet et al., 2010; Hodzic et al., 2010; Kiesewetter et al., 2014; Couvidat et al., 2018). This model uses emission data, meteorological fields, and boundary conditions as inputs and solves the system of equations representing the physical and chemical processes involved in the evolution of concentrations. Since we lacked the BaP concentration for the year 2011, the latter was estimated using the mean slope of the concentration of the 2005–2010 period for each address.

The ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute – ESRI, Redlands, CA, USA) and its reference street network database, BD Adresse® from the National Geographic Institute (IGN) were used to geocode the residential history of the study subjects (X and Y coordinates, addresses) (Faure et al., 2017). Overall, 60,354 residential addresses in metropolitan France collected from the follow-up questionnaires (1990–2011) were geocoded. A total of 83% of the subject's residences were automatically geocoded to the address whereas 17% were manually checked.

Based on their geocoded residential addresses, BaP exposure was estimated for each woman and for each calendar year (from 1990 to 2011). The cumulative level of BaP exposure for each woman was then estimated by summing the annual concentration from their entry into the E3N cohort to their index date.

2.4. Statistical methods

BaP exposure was estimated on a continuous scale and further categorized into quartiles to compare the distributions of subject characteristics according to quartiles of the cumulative levels of BaP exposure. We used ANOVA tests for continuous variables and Chi-square tests for categorical variables. Quartile categories were based on the cumulative BaP exposure in all controls. Associations with BC risk were modelled using conditional logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (95% CI) (Kuo et al., 2018). The models were performed by considering the cumulative BaP exposure as both continuous (an increment of 1 interquartile range (IQR) in levels of BaP in controls, 1.42 ng/m^3)) and categorical (based on the quartiles) variables. Crude models were conditioned on the matching factors including age, date, department of residence, menopausal status, at blood collection or at baseline as explained above, and the existence of biological samples (blood, saliva, none) (model 1). We considered two adjusted models to account for known BC risk factors and other factors that could potentially confound the association between BaP exposure and BC. Using a directed acyclic graph to identify potential confounding variables (selected on the basis of literature review), the first model was adjusted for physical activity (<25.3, 25.3–35.5, 35.6–51.8, and ≥51.8 METs-h/week), level of education (secondary, 1 to 2-year university degree, ≥ 3-year university degree), reproductive factors (including: age at menarche (<12, 12–13, and ≥14 years), parity and age at first full-term pregnancy (AFP) (0, 1–2 children & AFP < 30 years, 1–2 children & AFP ≥ 30 years, and ≥3 children), breastfeeding (ever, never), oral contraceptive use (ever, never), menopausal hormone treatment (MHT) (ever, never)) (Thun et al., 2017), status of birthplace (rural, urban) (Binachon et al., 2014) and smoking status (never, current, and former) (Sobinoff et al., 2012). In the second multivariable model, we further adjusted for a *priori* risk factors including alcohol intake (0, 1–6.7, > 6.7 g/day), BMI (<25, 25-<30, and ≥30 kg/m^2), family history of breast cancer (FHBC) (yes, no) and history of personal benign breast

disease (yes, no) (Ronco et al., 2011; Thun et al., 2017). We finally reported the results of the second fully adjusted models in the manuscript as there was no change in the estimated ORs between these two adjusted models.

While all other adjustment variables were taken from the E3N baseline questionnaire, contraceptive and MHT variables were collected from the last questionnaire before the date of diagnosis in cases, and the alcohol intake was collected from the year 1993 questionnaire

Covariates with less than 5% of missing data, were replaced by their modal or median value of cases and controls separately; and those with more than 5% of missing data (alcohol intake and status of birthplace) were included with a separate category for missing data (Garcia-Acosta and Clavel-Chapelon, 1999).

Analyses were conducted for all subjects and according to menopausal status at inclusion and at the index date (premenopausal women, postmenopausal women, and women premenopausal at inclusion who transitioned to postmenopausal at the index date categorized as undergoing « menopausal transition ») in order to assess the heterogeneity. ». To test a potential monotonous relationships between BaP exposure and BC risk, we performed test for trends by using the median value of each category as continuous term in the multivariable models (Brownstein and Cai, 2019).

Additional subgroup analyses were conducted according to BC hormone receptor (ER, PR) status, stage and grade of BC differentiation. Heterogeneity through these subgroups was assessed using multinomial logistic regression and *P* values for heterogeneity were derived from Wald tests (Wang et al., 2016).

Effect modification analyses by tobacco smoking status, alcohol consumption, birthplace status, exposure duration, and reproductive factors were conducted using unconditional logistic regression models, in order to avoid excluding incomplete case-control pairs with missing data and to have enough cases/controls for statistical power. These models were additionally adjusted for all matched variables (department of residence, age (±1 year), date (±3 months), and menopausal status at blood collection or at baseline. Test for interaction for each potential effect modifier was computed by the likelihood ratio test.

We used restricted cubic splines (Durrleman and Simon, 1989), with four knots placed at 5th, 35th, 65th, and 95th percentiles of the BaP distribution (Harrell, 2001) to check graphically the non-linearity of the relationship between BaP and BC risk.

In a sensitivity analysis, we excluded subjects with short follow-up time (<2 years), that could impact BC risk estimates (Hazelbag et al., 2015). Specific sensitivity analyses were done using the mean annual concentration (from entry into the cohort to the index date) instead of the cumulative dose at the index date. Random mixed-effect models were applied to control spatial correlations between subjects within the same geographical square (modelled as a random effect) of the CHIMERE method. This allowed the estimation of variance, which represented the random variability across the geographical square, and the significance of the random effect was examined using a likelihood ratio test (Harrison et al., 2018; Bm et al., 2009). Furthermore, supplementary quartiles analyses, with cutoff points of the exposure distribution based on each subgroup (according to menopausal status) were performed. All statistical tests were two-sided and *P* values < 0.05 were considered statistically significant. All analyses were performed using STATA software version 14 (College Station, Texas, USA).

3. Results

3.1. Characteristics of the study population

Table 1 shows the distributions of characteristics of the study subjects, overall and according to the quartiles of cumulative airborne BaP levels. The mean age of the study subjects at inclusion into the cohort was 49.6 ± 6.3 years. As compared to women in the lower quartiles, those in the upper quartiles of cumulative BaP exposure were more likely to have a higher level of alcohol intake ($P < 0.001$), to be born in an urban area ($P < 0.001$), to be less physically active ($P = 0.009$), to have a higher education level ($P < 0.001$), to be nulliparous ($P = 0.026$), and to have a higher age at first pregnancy ($P = 0.007$). Also, breastfeeding was more frequent among women of the upper quartiles as compared to those from the lower quartiles ($P < 0.001$). In contrast, a history of personal benign breast disease was less common among women of the upper quartiles as compared to those from the lower quartiles ($P < 0.001$). For other factors, there were no substantial differences across quartiles. The overall cumulative airborne BaP exposure was on average 1.94 ± 1.37 ng/m^3, with the minimum and the maximum ranging from 0.0017 to 15.1 ng/m^3. The average mean annual airborne BaP exposure was 0.19 ± 0.11 ng/m^3, ranging from 0.037 to 1.84 ng/m^3. Fig. 1 showed the distribution of the cumulative airborne BaP levels during follow-up (from entry into the cohort to the index date) in cases and controls. For other factors, there were no substantial differences across quartiles.

3.2. Ambient air BaP exposure and BC risk

The results of the associations between cumulative airborne BaP exposure and BC risk overall and by menopausal status at inclusion into the cohort and at case-control index date are shown in Table 2. Overall, the cumulative BaP exposure was associated with an increased risk of BC. For each 1 IQR increase in the levels of BaP (1.42 ng/m^3), the ORs were 1.19 (95% CI: 1.08–1.31) in the crude model and 1.15 (95% CI: 1.04–1.27) in the multivariable-adjusted model. In the subgroup analyses by menopausal status at inclusion and at the index date, the positive association appeared statistically significant only among women who underwent menopausal transition (i.e. premenopausal women at inclusion who became postmenopausal at index date. For each 1 IQR increase in BaP levels, the OR was 1.20 (95% CI: 1.03–1.40) in the adjusted model. There was no association among neither premenopausal nor postmenopausal women during the whole follow-up period. No statistically significant association was observed by quartiles of BaP levels in all women and by menopausal status (Table 2). Results of the cubic spline modelling using four knots with the 25th percentile value as the reference category, showed linearity of the relationship between cumulative airborne BaP exposure and overall BC risk (Supplementary Fig. 1).

When considering the hormone receptor status of BC, we found positive associations for ER+, PR+ and ER+ PR+ breast tumors in the multivariable-adjusted models, with ORs of 1.17 (95% CI: 1.04–1.32), 1.16 (95% CI: 1.01–1.33), and 1.17 (95% CI: 1.01–1.36) per 1 IQR increase in BaP levels, respectively, while no associations were observed for ER-, PR- and ER-PR breast tumors. By quartile analyses, no significant associations were obtained in both unadjusted and multivariable models (Table 3).

In subgroup analyses by grade of tumor differentiation, there was a borderline positive association between BaP exposure and grade 3 BC (P heterogeneity < 0.001). The ORs associated with 1 IQR increase in BaP were 1.18 (95% CI: 1.02–1.37) and 1.15 (95% CI: 0.99–1.34) in the unadjusted and adjusted models, respectively (Table 4). No further statistically significant association appeared between BaP and stage of BC (Table 4).

3.3. Effect modification and sensitivity analyses

The association between BaP exposure and the risk of BC was not modified by alcohol intake, urban/rural status of the birthplace, or reproductive hormone factors (P interaction > 0.05). In contrast, significant effect modification was observed for tobacco smoking status at inclusion (P interaction $= 0.033$) wherein the association remained significant only among current smokers (adjusted OR was 1.21; 95% CI: 1.07–1.36 for 1 IQR increase in BaP) (Supplementary Table 1).

As a sensitivity analysis, the exclusion of women with a follow-up

Table 1
Demographic and lifestyle characteristics of the study participants overall, and according to the quartiles distribution of the cumulative airborne BaP exposure in the case-control study nested within the E3N cohort, France, 1990–2011.

		Quartile of cumulative BaP exposure (ng/m^3)				
Characteristics	Overall	≤ 1.06	> 1.06–1.68	> 1.68–2.49	> 2.49	P value
Cases, n (%)	5222 (50.0)	1284 (49.6)	1279 (49.5)	1351 (50.9)	1308 (50.0)	
Controls, n (%)	5222 (50.0)	1306 (50.4)	1304 (50.5)	1306 (49.1)	1306 (50.0)	0.755
Age (years), mean ± SD	49.6 ± 6.3	50.3 ± 6.5	49.8 ± 6.2	49.2 ± 6.2	49.0 ± 6.3	0.123
Alcohol drinking (g/day), n (%)						
0	875 (8.4)	147 (5.7)	240 (9.3)	257 (9.7)	231 (8.8)	
1–6.7	2682 (25.7)	381 (14.7)	733 (28.4)	769 (28.9)	799 (30.6)	
> 6.7	3867 (37.0)	568 (21.9)	1042 (40.3)	1123 (42.3)	1134 (43.4)	
Missing	3020 (28.9)	1494 (57.7)	568 (22.0)	508 (19.1)	451 (17.2)	<0.001
Body Mass Index (kg/m^2), n (%)						
<25	874 (83.0)	2141 (82.6)	2150 (83.3)	2214 (83.3)	2169 (83.0)	
25-<30	1459 (14.0)	378 (14.6)	365 (14.1)	360 (13.6)	356 (13.6)	
≥ 30	311 (3.0)	71 (2.7)	68 (2.6)	84 (3.1)	89 (3.4)	0.579
Smoking status, n (%)						
Never	5691 (54.5)	1459 (56.3)	1412 (54.7)	1441 (54.2)	1379 (52.8)	
Current	1524 (14.6)	357 (13.8)	357 (13.8)	409 (15.4)	401 (15.3)	
Former	3229 (30.9)	774 (29.9)	814 (31.5)	807 (30.4)	834 (31.9)	0.135
Status of birthplace, n (%)						
Rural	2798 (26.8)	836 (32.3)	801 (31.0)	678 (25.5)	483 (18.5)	
Urban	6489 (62.1)	1497 (57.8)	1528 (59.2)	1684 (63.4)	1780 (68.1)	
Missing	1157 (11.1)	257 (9.9)	254 (9.8)	295 (11.1)	351 (13.4)	<0.001
Physical activity (METs-h/week), n (%)						
< 25.3	2533 (24.2)	597 (23.0)	637 (24.7)	607 (22.9)	692 (26.5)	
25.3–35.5	2749 (26.3)	683 (26.4)	661 (25.6)	732 (27.5)	673 (25.7)	
35.6–51.8	2676 (25.6)	642 (24.8)	657 (25.4)	714 (26.9)	663 (25.4)	
≥ 51.8	2486 (23.8)	668 (25.8)	628 (24.3)	604 (22.8)	586 (22.4)	0.009
Education, n (%)						
Secondary	1676 (16.0)	445 (17.2)	439 (17.0)	403 (15.2)	389 (14.9)	
1- to 2-year university degree	5118 (49.0)	1317 (50.8)	1322 (51.2)	1254 (47.2)	1225 (46.9)	
≥ 3 year university degree	3650 (35.0)	828 (32.0)	822 (31.8)	1000 (37.6)	1000 (38.3)	<0.001
Menopausal at inclusion, n (%)						
Premenopausal	6275 (60.1)	1501 (57.9)	1482 (57.4)	1649 (62.1)	1643 (62.9)	
Postmenopausal	4169 (39.9)	1089 (42.1)	1101 (42.6)	1008 (37.9)	971 (37.1)	<0.001
Menopausal at index date, n (%)						
Premenopausal	1680 (16.1)	955 (36.9)	368 (14.2)	221 (8.3)	136 (5.2)	
Postmenopausal	8764 (83.9)	1635 (63.1)	2215 (85.8)	2436 (91.7)	2478 (94.8)	<0.001
Use of oral contraceptives, n (%)						
No	4305 (41.2)	1085 (41.9)	1099 (42.5)	1059 (39.9)	1062 (40.6)	
Yes	6139 (58.8)	1505 (58.1)	1485 (57.5)	1598 (60.1)	1552 (59.4)	0.189
Use of menopausal hormone therapy, n (%)						
No	4244 (40.6)	1633 (63.0)	1003 (38.8)	875 (32.9)	733 (28.0)	
Yes	5977 (57.2)	901 (34.8)	1523 (59.0)	1722 (64.8)	1831 (70.1)	
Missing	223 (2.1)	56 (2.2)	57 (2.2)	60 (2.3)	50 (1.9)	<0.001
Parity, n (%)						
Nulliparous	1236 (11.8)	289 (11.1)	288 (11.1)	310 (11.7)	349 (13.4)	
1–2	6299 (60.3)	1543 (59.6)	1551 (60.1)	1647 (61.9)	1558 (59.6)	
≥ 3	2909 (27.9)	758 (29.3)	744 (28.8)	700 (26.4)	707 (27.0)	0.026
Age at First Pregnancy (years), n (%)						
Nulliparous	1236 (11.8)	289 (11.2)	288 (11.1)	310 (11.7)	349 (13.3)	
< 30	7968 (76.3)	1990 (76.8)	2027 (78.5)	2004 (75.4)	1947 (74.5)	
≥ 30	1240 (11.9)	311 (12.0)	268 (10.4)	343 (12.9)	318 (12.2)	0.007
Age at menarche (years), n (%)						
< 12	2148 (20.6)	543 (21.0)	523 (20.2)	549 (20.7)	533 (20.4)	
12–13	5406 (51.7)	1328 (51.3)	1365 (52.9)	1381 (52.0)	1332 (51.0)	
≥ 14	2890 (27.7)	719 (27.7)	695 (26.9)	727 (27.3)	749 (28.6)	0.810
Breastfeeding, n (%)						
Nulliparous	1236 (11.8)	289 (11.1)	288 (11.1)	310 (11.7)	349 (13.4)	
No	3520 (33.7)	1015 (39.2)	886 (34.3)	862 (32.4)	757 (28.9)	
Yes	5688 (54.5)	1286 (49.7)	1409 (54.6)	1485 (55.9)	1508 (57.7)	<0.001
Family history of breast cancer, n (%)						
No	9003 (86.2)	2229 (86.1)	2222 (86.0)	2299 (86.5)	2253 (86.2)	
Yes	1441 (13.8)	361 (13.9)	361 (14.0)	358 (13.5)	361 (13.8)	0.951
History of personal benign breast disease, n (%)						

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Overall	Quartile of cumulative BaP exposure (ng/m^3)				
		≤ 1.06	> 1.06–1.68	> 1.68–2.49	> 2.49	P value
No	7733 (74.0)	1855 (71.6)	1887 (73.1)	1988 (74.8)	2003 (76.6)	
Yes	2711 (26.0)	735 (28.4)	696 (26.9)	669 (25.2)	611 (23.4)	<0.001
Mammography, n (%)						
No	2623 (25.1)	684 (26.4)	634 (24.5)	664 (25.0)	641 (24.5)	
Yes	7821 (74.9)	1906 (73.6)	1949 (75.5)	1993 (75.0)	1973 (75.5)	0.353

P value comparing the distribution of the baseline characteristics of the study subjects according to the quartiles of cumulative airborne BaP exposure: Anova test for continuous variables and chi-square test for categorical variables.
SD, standard deviation; MET, Metabolic Equivalent of Task, BaP: benzo[a]pyrene.
Menopausal status at index date: date of diagnosis of the case in the case-control pair.

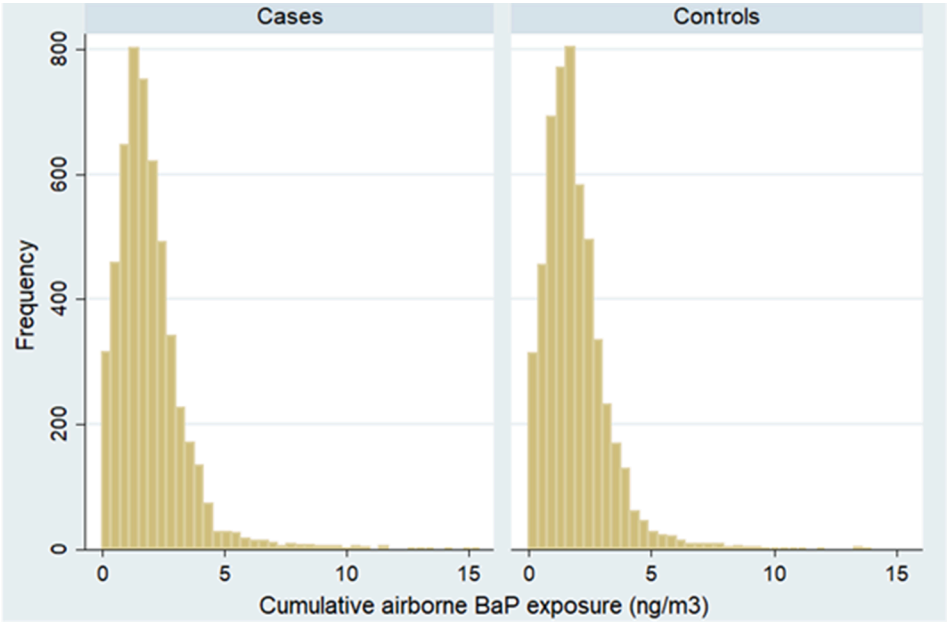


Fig. 1. Distribution of the cumulative airborne BaP exposure during the follow-up (from inclusion into the cohort to the index date) by case/control status: the case-control study nested within the E3N cohort, France, 1990–2011 BaP: benzo[a]pyrene.

period of ≤2 years before the diagnosis of BC did not significantly change the findings in both continuous and quartiles categories analyses (Supplementary Table 2). Random mixed-effect model analysis to control the spatial correlation between subjects within the same geographical square showed a random effect variance of 0.014; the significance of the random effect, which was tested with and without the geographical square using a likelihood ratio test comparing, was negligible (p-value = 0.085) (Harrison et al., 2018; Bm et al., 2009). In further sensitivity analyses using the mean of BaP during the follow-up period (1990–2011), the OR estimates were slightly decreased in all women, whereas it remained comparable for women during the menopausal transition (Supplementary Table 3). Additional analyses stratified by the median of the exposure duration (11 years) showed a positive association in women exposed for more than 11.2 years (OR = 1.16; 95% CI: 1.03–1.30), while no statistically significant association was seen among women exposed for less than 11.2 years (OR = 1.14; 95% CI: 0.93–1.40) (Table 5). Furthermore, results of specific quartiles analyses according to menopausal status remained no statistically significant (data not shown).

4. Discussion

In this study, using a validated transport chemistry model to estimate exposure to BaP based on residential history addresses, long-term exposure to BaP was associated with an increased risk of developing BC overall. Furthermore, positive associations with risk of BC were observed among premenopausal women at inclusion who became postmenopausal during the follow-up. In the subgroup analyses by hormone receptor status, we provided evidence of a positive association between BaP exposure and risk of ER+, PR+, and ER+ PR+ BC. When considering the grade of tumour differentiation, a significant association was found between BaP and increased risk of grade 3 differentiated BC. In the analyses testing effect modification by smoking, we observed a stronger positive association among current smoking women.

In the last years, the possible role of BaP in the etiology of BC has been widely investigated in experimental studies, which have strongly demonstrated an increased risk of BC (Malik et al., 2018; Guo et al., 2015; Rathore and Cekanova, 2015). Nevertheless, very few epidemiological studies have investigated the association between BaP exposure and BC risk. The study by Ronco et al. exploring the association between dietary BaP and BC risk in a case-control study in Uruguay, reported that high consumption of BaP was strongly associated with the risk of BC (Ronco et al., 2011). Other two previous studies showed that BaP exposure, used as a surrogate of PAHs exposure related to vehicular traffic, increased the risk of BC (Mordukhovich et al., 2016; Nie et al., 2007). Overall, our results support these previous laboratory findings in animal models and human cells/ tissues and the few epidemiological studies reporting the impact of BaP exposure on the risk of developing BC. To be noted, in the present study only 0.2% of the study population were exposed to levels exceeding the European Union annual target

Table 2
Association for BC risk with airborne BaP exposure in continuous and quartiles: Overall and by menopausal status in the case-control study nested within the E3N cohort, France, 1990–2011.

Cumulative airborne BaP exposure (ng/m^3)	Matched cases/ controls (n)	Crude OR (95% CI)	Multivariable OR (95% CI)
Overall			
Continuous	5222/5222	1.19 (1.08–1.31)	1.15 (1.04–1.27)
≤ 1.06	1284/1306	Ref	Ref
> 1.06–1.68	1279/1304	1.15 (0.91–1.44)	1.12 (0.89–1.41)
> 1.68–2.49	1351/1306	1.34 (1.02–1.75)	1.24 (0.94–1.64)
> 2.49	1308/1306	1.32 (0.97–1.81)	1.21 (0.88–1.67)
P trend		0.150	0.373
P likelihood		0.164	0.475
Premenopausal at inclusion and at index date			
Continuous	591/591	1.53 (0.88–2.66)	1.44 (0.79–2.64)
≤ 1.06	399/399	Ref	Ref
> 1.06–1.68	111/111	1.43 (0.84–2.43)	1.33 (0.75–2.36)
> 1.68–2.49	55/55	1.30 (0.55–3.05)	1.29 (0.52–3.19)
> 2.49	26/26	2.18 (0.64–7.38)	1.84 (0.51–6.62)
P trend		0.217	0.364
P likelihood		0.424	0.706
Premenopausal at inclusion and postmenopausal at index date*			
Continuous	1958/1958	1.24 (1.06–1.44)	1.20 (1.03–1.40)
≤ 1.06	195/190	Ref	Ref
> 1.06–1.68	456/481	0.87 (0.56–1.36)	0.90 (0.57–1.44)
> 1.68–2.49	642/608	1.03 (0.62–1.71)	1.02 (0.60–1.71)
> 2.49	665/679	0.91 (0.53–1.59)	0.90 (0.51–1.60)
P trend		0.131	0.293
P likelihood		0.410	0.630
Postmenopausal at inclusion and index date			
Continuous	1991/1991	1.08 (0.92–1.27)	1.07 (0.90–1.26)
≤ 1.06	532/552	Ref	Ref
> 1.06–1.68	526/536	1.34 (0.94–1.89)	1.25 (0.87–1.79)
> 1.68–2.49	481/461	1.71 (1.12–2.61)	1.51 (0.97–2.35)
> 2.49	452/442	1.86 (1.13–3.06)	1.57 (0.93–2.64)
P trend		0.923	0.800
P likelihood		0.073	0.306

Crude OR were conditioned on the matching factors.
Multivariable models were adjusted for physical activity, smoking status, alcohol intake, level of education, body mass index, previous family history of breast cancer, personal history of benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone therapy use and status of birthplace.
The OR (95% CI) in the continuous model corresponds to an increment of 1 IQR level of BaP in controls (1.42 ng/m^3).
* Menopausal transition.

value of 1 ng/m^3 (Smith, 2006), while 77% were exposed to levels over the estimated tolerable risk level of 0.12 ng/m^3 (Guerreiro et al., 2016).

PAHs have been found to exhibit both estrogenic and antiestrogenic responses, which have been consistently associated with the development of BC (Santodonato, 1997). Stratified analyses to better understand the effect of BaP exposure according to menopausal status, showed higher BC risk among women premenopausal at inclusion who transitioned to postmenopausal status at the index date, whereas no

Table 3
Association for BC risk with airborne BaP exposure in continuous and quartiles, according to hormone receptor status in the case-control study nested within the E3N cohort, France, 1990–2011.

Cumulative airborne BaP exposure (ng/m^3)	Matched cases/ controls (n)	Crude OR (95% CI)	Multivariable OR (95% CI)
ER-			
Continuous	760/760	1.14 (0.91–1.44)	1.08 (0.85–1.38)
≤ 1.06	227/225	Ref	Ref
> 1.06–1.68	193/198	0.91 (0.50–1.64)	0.84 (0.45–1.55)
> 1.68–2.49	175/169	0.99 (0.48–2.02)	0.83 (0.39–1.78)
> 2.49	165/168	0.89 (0.38–2.07)	0.76 (0.31–1.85)
P trend		0.888	0.688
P likelihood		0.944	0.931
ER+			
Continuous	3,405/3,405	1.23 (1.09–1.38)	1.17 (1.04–1.32)
≤ 1.06	637/654	Ref	Ref
> 1.06–1.68	849/862	1.16 (0.89–1.51)	1.14 (0.86–1.50)
> 1.68–2.49	966/949	1.32 (0.96–1.82)	1.22 (0.88–1.70)
> 2.49	953/940	1.40 (0.97–2.02)	1.25 (0.85–1.83)
P trend		0.096	0.315
P likelihood		0.308	0.687
P heterogeneity			0.010
PR-			
Continuous	1439/1439	1.18 (0.99–1.39)	1.13 (0.95–1.35)
≤ 1.06	298/299	Ref	Ref
> 1.06–1.68	368/377	1.02 (0.65–1.62)	1.00 (0.61–1.62)
> 1.68–2.49	383/377	1.15 (0.67–1.97)	1.12 (0.63–1.99)
> 2.49	390/386	1.20 (0.65–2.22)	1.16 (0.60–2.22)
P trend		0.514	0.555
P likelihood		0.880	0.899
PR+			
Continuous	2602/2602	1.22 (1.06–1.40)	1.16 (1.01–1.33)
≤ 1.06	555/568	Ref	Ref
> 1.06–1.68	657/664	1.14 (0.85–1.52)	1.11 (0.83–1.49)
> 1.68–2.49	712/695	1.28 (0.90–1.82)	1.19 (0.83–1.71)
> 2.49	678/675	1.29 (0.85–1.96)	1.15 (0.75–1.75)
P trend		0.275	0.625
P likelihood		0.565	0.809
P heterogeneity			0.548
ER-PR-			
Continuous	612/612	1.16 (0.91–1.50)	1.11 (0.85–1.45)
≤ 1.06	168/167	Ref	Ref
> 1.06–1.68	164/167	0.94 (0.48–1.83)	0.83 (0.41–1.66)
> 1.68–2.49	143/136	1.02 (0.46–2.25)	0.80 (0.34–1.88)
> 2.49	137/141	0.83 (0.32–2.13)	0.69 (0.25–1.87)
P trend		0.643	0.504
P likelihood		0.892	0.901
ER + PR+			
Continuous	2459/2459	1.24 (1.07–1.43)	1.17 (1.01–1.36)
≤ 1.06	495/509	Ref	Ref
> 1.06–1.68	630/634	1.16 (0.86–1.56)	1.14 (0.84–1.54)

(continued on next page)

Table 3 (*continued*)

Cumulative airborne BaP exposure (ng/m^3)	Matched cases/ controls (n)	Crude OR (95% CI)	Multivariable OR (95% CI)
> 1.68–2.49	683/666	1.30 (0.90–1.86)	1.21 (0.84–1.75)
> 2.49	651/650	1.29 (0.84–1.97)	1.15 (0.74–1.78)
P trend		0.338	0.675
P likelihood		0.565	0.774
P heterogeneity			0.193

Crude OR were conditioned on the matching factors.
Unconditional multivariable models were adjusted for physical activity, smoking status, alcohol intake, level of education, body mass index, previous family history of breast cancer, personal history of benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone therapy use and status of birthplace.
The OR (95% CI) in the continuous model corresponds to an increment of 1 IQR level of BaP in controls (1.42 ng/m^3).
ER, estrogen receptor; PR, progesterone receptor; BaP: benzo[a]pyrene.

Table 4
Association for BC risk with airborne BaP exposure in continuous, by grade of differentiation and stage in the case-control study nested within the E3N cohort, France, 1990–2011.

Cumulative airborne BaP exposure (ng/m^3)	Matched cases/controls (n)	Crude OR (95% CI)	Multivariable OR (95% CI)
Grade of differentiation			
Grade 1	614/614	1.19 (0.85–1.68)	1.13 (0.80–1.61)
Grade 2	1483/1483	1.18 (0.97–1.43)	1.08 (0.88–1.32)
Grade 3	2066/2066	1.18 (1.02–1.37)	1.15 (0.99–1.34)
P heterogeneity			<0.001
Stage			
Stage I	2919/2919	1.15 (1.02–1.31)	1.10 (0.96–1.25)
Stage II	1412/1412	1.32 (1.07–1.62)	1.31 (1.05–1.63)
Stage III-V	402/402	1.28 (0.89–1.85)	1.29 (0.88–1.89)
P heterogeneity			0.632

Crude OR were conditioned on the matching factors.
Multivariable models were adjusted for physical activity, smoking status, alcohol intake, level of education, body mass index, previous family history of breast cancer, personal history of benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone therapy use and status of birthplace.
The OR (95% CI) in the continuous model corresponds to an increment of 1 IQR level of BaP in controls (1.42 ng/m^3). Staging analyses were done on the four stages after excluding cases with missing stage information (489 cases) and their matched controls (489). Grading analyses were based on the three main type of grade after excluding cases with missing grade information (1058 cases) and their matching controls (1058).
BaP: benzo[a]pyrene.

associations were observed among women only in premenopausal or postmenopausal status during the whole follow-up period. Previous studies were conducted mainly without distinctions in menopausal status, except for a study by Steck et al, suggesting a positive association between BaP exposure from meat intake and risk of postmenopausal ER+ and PR + BC (OR = 1.47; CI = 0.99–2.19) (Steck et al., 2007). Our results suggested that the effect of BaP exposure on BC risk may be stronger during the menopausal transition. BaP is well known to cause adverse effects on the female reproductive system (Li et al., 2017; Yi et al., 2019; Zhao et al., 2014), and these effects could be stronger among women with long term exposure, in particular, those exposed

Table 5
Association for BC risk with cumulative airborne BaP exposure in continuous models, stratified by the median of the exposure duration in the case-control study nested within the E3N cohort, France, 1990–2011.

Cumulative airborne BaP exposure duration (ng/m^3)	Matched cases/controls (n)	Crude OR (95% CI)	Multivariable OR (95% CI)
Median duration, years			
< 11.2	2602/2602	1.20 (0.99–1.47)	1.14 (0.93–1.40)
≥ 11.2	2602/2602	1.19 (1.06–1.33)	1.16 (1.03–1.30)
P interaction			0.829

Crude OR were conditioned on the matching factors.
Multivariable models were adjusted for physical activity, smoking status, alcohol intake, level of education, body mass index, previous family history of breast cancer, personal history of benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone therapy use and status of birthplace. The OR (95% CI) in the continuous model corresponds to an increment of 1 IQR level of BaP in controls (1.42 ng/m^3).
BaP: benzo[a]pyrene.

during the menopausal transition. Exposures during specific windows of susceptibility in a woman's life, including prenatal development, puberty, pregnancy, and menopausal transition, may be associated with greater BC risk (Rudel et al., 2011; Rodgers et al., 2018). Menopausal transition defined as the period preceding menopause with durations varying among individuals and populations from 4 to over 8 years in the literature (Sherman, 2005; Harlow et al., 2012; Freeman, 2015); is considered as a specific period of susceptibility for BC risk because important structural and functional changes occur in the breast gland, as well as alterations in the breast micro-environment and hormone signaling that may influence BC development (Terry et al., 2019; Giles et al., 2018). This increased sensitivity during the menopausal transition has been reported by previous studies on the BC risk associated with different risk factors (Bacon, 2017). For example, Emaus et al. (2014) reported that weight gain shortly before or around menopause was associated with increased risk of BC, the HRs per kg per year were 1.38 (95% CI: 1.09–1.75) and 1.69 (95% CI 1.32–2.16), respectively (Emaus et al., 2014). Similarly, BMI change from age 40 to 50 was found to be related to increased BC risk, with an adjusted OR of 1.32 (95%CI: 1.05–1.65) per 5 kg/m^2 increase, and 1.45 (95%CI: 1.06–1.98) comparing the highest (≥35 kg/m^2) vs lowest category (<1 kg/m^2) (Cordina-Duverger et al., 2016). Also during the menopausal transition, mammary tissue may be more responsive to lowered levels of estrogens, as well as to endocrine-disrupting chemicals, through enhanced hormone receptor sensitivity. Similar to what has been suggested for hormone therapy, it has been hypothesized that endocrine-disrupting chemicals including BaP may promote the growth of pre-existing occult lesions to clinically detectable tumors during the menopausal transition (Terry et al., 2019). These observations stress the importance to specifically consider analyses of the cumulative dose of airborne BaP exposure on BC risk during the menopausal transition.

Another striking observation of our analyses is that the positive associations are more pronounced for ER+, PR+ and ER+ PR+ breast tumors. These findings are in concordance with the function of BaP to act as an endocrine disruptor that interferes with the balance of the endocrine system by mimicking or antagonizing the effects of endogenous hormones, altering the synthesis and metabolism of natural hormones, and/ or modifying hormone receptor levels (Stiborova et al., 2018). In line with our study, Petralia et al. (Petralia et al., 1999), found an increased risk of BC in association with occupational PAHs exposure only among women with ER + breast tumors (Petralia et al., 1999). Similarly, the large sister study reported an increased risk of overall and ER + BC associated with multiple air toxics, including acrylamide, polycyclic organic matter, propylene dichloride, and styrene (Niehoff

et al., 2019).

With regard to the BC grade of differentiation, we found a positive association between BaP and BC risk only for grade 3, suggesting that BaP may play a possible role in the differentiation, increased migration and invasive potential of human mammary cancer cells and tissues (Malik et al., 2018). The grade is a consistent indicator of BC aggressiveness. Several studies have suggested a potential role of exposure to endocrine disrupting chemicals in promoting tumor aggressiveness (Koual et al., 2019; Ochieng et al., 2015; Dairkee et al., 2008). However, whether BaP exposure results in more aggressive forms of BC remains insufficiently known.

In our study, in addition to the principal analyses using the BaP continuous exposure variable (increment of 1 IQR of the level of BaP in all controls, 1.42 ng/m^3), quartiles categorical analyses were performed. Statistical efficiency is usually greater using a continuous analysis that provided whether the model fit (e.g. linearity assumption) is good (Royston et al., 2006; Turner et al., 2010). Our restricted cubic splines analyses suggest that a linear relationship between BaP and BC is reasonable. However, for the sake of completeness and of comparison, as well as to estimate exposure dose effect, we performed categories analyses, even though from a statistical viewpoint, categorization of a continuous variable can often result in a loss of statistical efficiency (Turner et al., 2010; Lagakos, 1988). Overall, in quartiles categorical analyses, we did not observe any statistically significant associations in the multivariable-adjusted models. This lack of associations could highlight the absence of dose effects of BaP exposure on the risk of breast cancer. Also, it should be noticed that the quartiles categories were based on the cumulative BaP exposure in all controls, and the BaP exposure distribution may vary by menopausal status. This heterogeneity could also explain some variations between continuous and quartiles analysis results, in particular for women who underwent menopausal transition. Nonetheless, in order to check this issue, we have performed supplementary analyses, with cutoff points of the exposure distribution based on each subgroup (according to menopausal status), however the quartiles analyses remained no statistically significant (data not shown).

Several biological mechanisms may underline the association between BaP exposure and the risk of BC. The main mechanism of BaP action is recognized to be through direct damage to DNA by inducing DNA adduct formations that cause DNA lesions and mutations (Cavalieri and Rogan, 2014; Kennedy et al., 2005). BaP requires metabolic activation prior to reaction with DNA; cytochrome P450 (CYP) enzymes, mainly CYP1A1 and 1B1, are the most important enzymes involved in this process (Spink et al., 2009; Matsunawa et al., 2009). Besides this well-established genotoxic function, BaP could act through several other mechanisms. BaP itself can bind to and activate Aryl hydrocarbon-receptor (AhR) and ER pathways. The AhR plays a role in the response to oxidative stress in cell-cycle regulation and apoptosis, by regulating the transcription of a series of genes that contributes to breast carcinogenesis (Zhao et al., 2014; Clement et al., 2017). There is also evidence that breast cells exposed to BaP result in perturbation of inflammation mediators (and dysregulation of tumorigenic miRNAs, leading to an inflammation microenvironment (via TNF-α and NFκB leading to IL-6 upregulation) that facilitates migration and invasion of breast epithelial cells (Malik et al., 2018). Overall, BaP can cause cytotoxic, genotoxic, mutagenic, epigenetic, and inflammatory effects in various tissues and cell types (animals and human) that can induce proliferation, apoptosis, oxidative stress, inhibition of DNA repair, tumor growth, and invasion.

To our knowledge, this investigation is the first epidemiological study that assesses the relation between long-term exposure to airborne BaP and the risk of BC. The main strengths of our study include a prospective design of the E3N cohort, a large sample size, and the availability of information on a wide range of potential confounders. Moreover, in contrast to characterizing exposure at a single point in time, we considered the residential history to reconstruct annual exposure and estimate cumulative exposure over the study period of up to 22 years. In addition, exposure was assigned in a standardized blind way according to the case-control status of the subjects. However, our findings should be interpreted with consideration of some limitations. One of the most important limitations is the absence of BaP historical measures at a fine spatial scale (Beyea et al., 2008) requiring the use of the CHIMERE model to estimate the BaP exposure. While its resolution is 7 km by 7 km, this method has been validated by comparisons with pollutant measurements (Couvidat et al., 2018; Clement et al., 2017) and has been used to estimate BaP exposure and other air pollutants in Europe (Guerreiro et al., 2016). However, we could not exclude a limitation of this resolution in its ability to capture the variability within the squares, specifically in areas with potential fine-scale emission heterogeneity. Yet, sensitivity analyses controlling for inter-individual correlation within the same square showed no significant effect. Any misclassification of exposure was unlikely to be differential. Another main limitation of our study was the lack of earlier residential history and historical BaP exposure concentration before inclusion into the cohort in 1990 , which may lead to a loss of accuracy of exposure estimates. However, it has been suggested that BaP acts as an initiator and promoter, and that long-term exposure may not be required for initiated cells to become tumors (Assessment UENC, 2019). Finally, despite the extensive adjustments of potential confounding and known BC risk factors, we cannot entirely rule out the existence of some residual confounders.

In conclusion, our findings support an association between airborne BaP exposure and an increased risk of BC. The risk significantly varies according to menopausal status, with a significant risk in women in women who transitioned from pre to postmenopausal status during the study period. Variations were also observed by tumor hormone receptor status, grade of differentiation, and smoking status. Our results add further epidemiological evidence to the previous experimental studies suggesting the carcinogenicity and the adverse effects of BaP on BC. Study designs allowing to investigate time-varying exposures, such as case-cohort analyses, might be of interest in future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

Our research is based on the existing French national cohort E3N. Informed consent was obtained from all participants and the study was approved by the French National Commission for Data Protection and

Privacy (CNIL).

Consent for publication

All authors have read the manuscript and have agreed to the submission.

Authors' contributions

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106399.

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