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Positive association between dietary exposure to polybrominated diphenyl ethers and breast cancer risk in the French E3N cohort: The role of vegetable oil consumption

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ABSTRACT

Exposure to endocrine-disrupting chemicals, like Polybrominated diphenyl ethers (PBDEs), is suspected of playing a role in the occurrence of breast cancer. Moreover, there is growing evidence that food chemical contaminants, especially lipophilic ones such as PBDEs, could interact with different components of the diet. The objective of the present study was to assess the association between dietary intake of PBDEs and breast cancer risk in the French E3N cohort study, and to investigate the potential modification of this association by vegetable oil consumption.

The study included 67 879 women. Intakes of eight PBDEs were estimated using food consumption data from a validated semi-quantitative food frequency questionnaire, and food contamination levels measured by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). Cox proportional hazards models were used to estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI) for the association between total PBDEs dietary intake and breast cancer risk. Interaction measures for vegetable oil consumption were estimated on both additive and multiplicative scales.

The women were followed for a maximum of 21.4 years, and 5 686 developed an incident breast cancer. A positive linear trend was highlighted between dietary intake of PBDEs in quintile groups and breast cancer risk, borderline with statistical significance (p-trend = 0.06, HR_{Q5vsQ1} and 95% CI: 1.09 [0.99;1.20]). Interaction measures for vegetable oil consumption were significant in both additive and multiplicative scales. Higher effect sizes of the association were highlighted in high consumers of vegetable oil, i.e. ≥4.6 g/day (HR_{Q5vsQ1} and 95% CI: 1.23 [1.08; 1.40]), and almost no effect were found in low consumers (HR_{Q5vsQ1} and 95% CI: 0.97 [0.86; 1.10]).

Highlighting such interactions between nutrients and chemicals is crucial to develop efficient dietary recommendations to limit the negative health effects associated with exposure to food chemical contaminants.

1. Introduction

The incidence of breast cancer has increased over the past decades, mostly from 1980 to the last 1990s in Western countries, and more recently in many low and middle income countries (Torre et al., 2017; Sung et al., 2021). In 2020, breast cancer was the most diagnosed of all cancers worldwide, with 2.3 million new cases (Sung et al., 2021). However, despite a large body of research, the risk factors known to date are not sufficient to explain this incidence increase (Ferlay et al., 2018; Kamińska et al., 2015; Brown et al., 2018). Exposures to chemical contaminants, particularly endocrine-disrupting chemicals, are suspected to be one of the factors responsible for this increase (Mouly and Toms, 2016).

Polybrominated diphenyl ethers (PBDEs) are brominated chemicals with flame retardant properties. They have been widely used since the 1970s for petroleum extraction and fireproofing of plastics and textiles.

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Due to their toxicity, their use has been progressively regulated since the 2000s. However, due to their volatile properties and resistance to degradation, PBDEs are widespread in the environment and have contaminated the food chain (Jinhui et al., 2017). Indeed, diet represents the main source of exposure to PBDEs for the general population (ESFA, 2011). Moreover, PBDEs are known to bioaccumulate in human and animal tissues. A serum-elimination halves life for five congeners of PBDEs, ranging from 0.94 to 4.12 years, has been estimated (Sjödin et al., 2020). PBDEs have been classified as Persistent Organic Pollutants (POPs) by the Stockholm Convention, so elucidating their long-term toxic effects seems to be of great importance (Linares et al., 2015; UNEP, 2019). Adverse health effects identified to date include neurological disorders, immunotoxicity, reproductive toxicity, and endocrine and metabolic disruption (Linares et al., 2015; Darnerud, 2008). Additionally, a growing number of studies have evaluated their effects on carcinogenesis. Actually, in 2019, the PBDEs were included in the high-priority list of agents not previously evaluated by the International Agency for Research on Cancer (IARC) Monographs (IARC Monographs Priorities Group, 2019).

The relation between exposure to PBDEs and breast cancer risk has not been completely elucidated. However, some linking molecular mechanisms have been proposed, including endocrine disruption, notably on oestrogen or androgen signalling pathways (Linares et al., 2015; Darnerud, 2008; Kanaya et al., 2019), potentially mediated by epigenetic modifications of DNA (Ding et al., 2021). In particular, PBDEs have been shown to stimulate the proliferation of human breast cancer cells in vitro and ex vivo (Kanaya et al., 2019; Li et al., 2012). In mice, PBDEs have been positively associated with breast cancer growth (Wei et al., 2020). Concerning human studies, internal levels of PBDEs, in blood or adipose tissues, have been previously analysed in relation to breast cancer risk, leading to contradictory results (Hurley et al., 2019; Hurley et al., 2011; Holmes et al., 2014; He et al., 2018; Mancini et al., 2020). Different sources of heterogeneity have been proposed to explain these divergences, including the possible co-exposure to other different environmental contaminants, the limited sample size for powered stratified analysis, or the constraints of single-spot biomarkers, generally measured at diagnosis time, to reflect the true long-term exposure patterns (Ding et al., 2021). To the best of our knowledge, no study has yet been conducted to investigate the relationship between dietary exposure to PBDEs and breast cancer risk.

There is growing evidence that food chemical contaminants could interact with different components of the diet. Nevertheless, these possible interactions are still insufficiently taken into account in toxicology and epidemiology studies, while this is an emerging concern (Wells et al., 2016; Park and Seo, 2016; Park and Seo, 2017). Indeed, due to their possible common source of exposure, shared mechanism of absorption, transport or storage, and their possible common molecular pathways, interactions between nutrients and chemicals may occur at different levels, i.e. co-exposition, toxicokinetic level and toxicodynamic level (Cano-Sancho and Casas, 2021). Lipophilic chemicals, such as PBDEs, are particularly likely to interact with nutrients at all the previously mentioned levels. For example, fish is a common source of both fatty acids and PBDEs (French agency for food, environment and occupational health & safety, 2011a). Dietary fatty acids and PBDEs also have similar intestinal absorption mechanisms through micelles and share the same structure of transport to peripheral tissues (i.e. chylomicrons and lipoproteins), so that interactions between fatty acids and PBDEs may occur at different levels (Cano-Sancho and Casas, 2021). More specifically, vegetable oil has been shown to increase the bioaccessibility of PBDEs after in vitro digestion, and increase their accumulation in Caco-2 cell model, but decreases their transepithelial transport (Li et al., 2021). Thus, interactions between dietary intake of PBDEs and lipid consumption, particularly vegetable oil, seem possible at different levels. The impact of these toxicological interactions in epidemiological studies remains to be elucidated.

The objective of the present study was to assess the association between dietary intake of PBDEs and breast cancer risk in the French E3N cohort study (*Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale*), and to investigate the potential modification of this association by vegetable oil consumption or lipid intake.

2. Materials and methods

2.1. The E3N cohort

The E3N study is a large ongoing prospective cohort of women set up in France in 1990. The detailed protocol has been described elsewhere (Clavel-Chapelon, 2015; Clavel-Chapelon et al., 1997). Briefly, 98 995 women born between 1925 and 1950 and insured by the French national health insurance plan for people working for the national education system, the *Mutuelle Générale de l'Education Nationale* (MGEN) were included. Women were followed every-two or three years by self-administered questionnaires. Over time, a good participation rate has been maintained (around 83%. The study was approved by the French National Commission for Data Protection and Privacy; all participants gave written informed consent.

2.2. Study population

The present study included all participants who had completed the dietary questionnaire sent in June 1993 (n = 74 522). Women who had prevalent cancer at baseline (n = 4 709), those who did not complete any questionnaire after the dietary questionnaire (n = 568), and those who had extreme energy intake values (i.e. below the 1st or above the 99th percentiles for the ratio between energy intake and energy requirement) (n = 1366) were excluded. Finally, this study included 67 879 women.

2.3. Assessment of food consumption

Dietary data were collected in 1993 using a previously validated semi-quantitative food frequency questionnaire including 208 food items (Van Liere et al., 1997). This questionnaire assessed the habitual diet of the previous year, collecting information concerning food and drink consumption for eight occasions (breakfast, morning snack, aperitif before lunch, lunch, afternoon snack, pre-dinner aperitif, dinner and after dinner snack). Information on vegetable oil consumption (in g/day) was derived from this questionnaire and included peanut, sunflower, olive, corn and unspecified vegetable oil consumption. Participants' mean daily nutrient intakes, such as lipids intake (in g/day), were then estimated using a food composition table derived from the French food composition table of the French Information Center on Food Quality (CIQUAL).

2.4. Assessment of dietary exposure to PBDEs

Food contamination data were obtained from the 2nd French Total Diet Study (TDS2) conducted by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) (French agency for food, environment and occupational health & safety, 2011a; French agency for food, environment and occupational health & safety, 2011b; Sirot et al., 2009). In short, a total of 20 280 different food products were collected between June 2007 and January 2009 in eight French regions of the metropolitan territory, reaching 1 352 composite samples of foods prepared as consumed. Eight PBDEs were measured in food corresponding to the main known or supposed sources of exposure. For the present study, PBDEs values below the limit of detection were replaced by 0 (lower-bound scenario) or by ½ of the limit of detection (middle-bound scenario).

The E3N databases on food consumption and the ANSES database on food contaminants concentrations have been merged, as described in

detail elsewhere (Mancini et al., 2020). For each participant, the daily mean dietary intake to each PBDE (ng/day) was obtained by multiplying the mean daily quantities consumed of each food component by the levels of contamination of the corresponding food components. Then, the total PBDEs dietary intake was obtained by summing the intake of each PBDE (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183 and BDE 209).

2.5. Identification of breast cancer cases and death

Breast cancer cases were identified mainly through self-administered questionnaires sent every-two or three years. Additional cases were identified from next-of-kin spontaneous reports or through information from the national cause of death registry. Pathology reports or medical records were obtained for 93% of cases, allowing diagnosis validation. Non-validated cases were also retained, because the proportion of false-positive self-reports was low in our study population (<5%). Cases were validated up to November 2014, which was therefore used as the date of end of follow-up in statistical analyses.

Information on death was available from the MGEN health insurance database, from reports by family members, and from the national cause of death registry.

2.6. Covariates

Adjustment variables included in the Cox models described below were selected using a Directed Acyclic Graph (DAG) (Supplementary figure 1a and Supplementary figure 1b) in order to estimate the total effect of total PBDEs dietary intake on breast cancer risk. In order to respect temporality, values of adjustment covariates were obtained from the second questionnaire (sent in January 1992) when available, so to precede the time of collection of the main exposure variable, i.e. the dietary questionnaire (sent in June 1993) informing food consumption over the previous year.

Information on birth generation (≤1930; (1930–1935]; (1935–1940]; (1940–1945]; >1945) and educational level (<12 years; 12 to 14 years; >14 years) were collected at the first questionnaire sent in 1991. Information on smoking status (non-smoker; former smoker; current smoker), body mass index (kg/m^2, obtained from height and weight), parity and age at first full-term pregnancy (FFTP) (nulliparous; one or two children and age at FFTP < 30; more than 3 children and age at FFTP < 30; age at FFTP ≥ 30), cumulated duration of previous breastfeeding (no breastfeeding: less than 6 months of breastfeeding; at least 6 months of breastfeeding), utilisation of contraceptive pill (ever/never), menopausal status and recent use of menopausal hormone therapy (MHT) (pre-menopaused, menopaused with recent use of MHT, i.e. less than a year ago; menopaused without recent use of MHT) were obtained from the second questionnaire sent in 1992. Finally, information on physical activity (continuous, in metabolic equivalents of task-hour/week), daily intake of alcohol (continuous, in g/day), daily intake of lipids (continuous, in g/day), daily total energy intake (continuous, in kcal/day), and food group consumptions (continuous, in g/day) were obtained from the dietary and non-dietary questionnaires sent in 1993. Adherences to western and prudent dietary patterns derived from Principal Component Analysis have also been obtained from the dietary questionnaire, as described elsewhere (Edefonti et al., 2008).

For covariates with < 5% of missing values, those were imputed by the mode (for categorical variables) or the median (for continuous variables). A missing category was created for covariates having ≥ 5% of missing values (only menopausal status and recent MHT use).

2.7. Statistical analyses

Baseline characteristics (median and standard deviation for continuous variables, numbers and proportions for categorical variables) of the study population were described in the overall population, separately among each quintile group of total PBDEs dietary intake (in ng/day, using the lower-bound scenario), and separately among cases and non-cases. Proportions of each PBDE congener (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183 and BDE 209) to total PBDEs dietary intake and correlations between each PBDE congeners were also described in the study population. Each food group's relative contributions (in percentages) to PBDEs dietary intake were estimated.

Cause-specific Cox proportional hazards models, with age as the time scale, were used to estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI) for association between PBDEs dietary intake in quintile groups (in ng/day, using the lower-bound scenario) and breast cancer risk. Time at entry was the age of return of the dietary questionnaire. Exit time was the age of breast cancer diagnosis (for cases), the age at the last completed questionnaire before death or lost to follow-up, the age of diagnosis of another cancer, or the age at the end of the follow-up period, whichever occurred first.

Three models were fitted separately. Model 1 was only adjusted for age as the time-scale. Model 2 was further adjusted on birth generation, educational level, smoking status, body mass index, parity and age at FFTP, cumulated duration of previous breastfeeding, utilisation of contraceptive pill, menopausal status and recent use of MHT (pre-menopaused, menopaused with recent use of MHT; menopaused without recent use of MHT, menopaused and missing data on recent use of MHT) and physical activity. Model 3, the main model including all the variables identified by the DAG (Supplementary figure 1a), was additionally adjusted on daily alcohol intake, daily lipids intake and daily total energy intake except from alcohol and lipid. For each model, linear trends were estimated by fitting a semi-continuous variable based on the median value of exposure of each quintile group. A model 4, corresponding to model 2 additionally adjusted on daily alcohol intake and daily total energy intake except from alcohol intake, was used to test the potential interactions with dietary compounds (Supplementary figure 1b).

In order to investigate a potential effect modification of the association between PBDEs dietary intake and breast cancer risk by vegetable oil consumption, we added interaction product terms between PBDEs dietary intake in quintile groups and vegetable oil consumption in two categories (<median; ≥median) in model 4. A likelihood-ratio test was used to test the global significance of all regression coefficients corresponding to interaction terms. Interactions measures were presented both on the multiplicative and additive scales, as recommended by Knol et al (Knol and VanderWeele, 2012). Reference categories were chosen such that the stratum with the lowest risk would become the reference category when both factors are considered jointly (Knol et al., 2011), i.e. the first quintile group for PBDEs dietary intake and the group of high-consumers (≥median) of vegetable oil were used as reference. For the additive scale, Relative Excess Risk due to Interaction (RERIs) between the second, third, fourth and fifth quintile group of PBDEs dietary intake and the low-consumption group of vegetable oil, and their 95% Confidence Intervals (CI) estimated with the delta method were presented (Hosmer and Lemeshow, 1992). For the multiplicative scale, exponentials of regression coefficients for each interaction terms and their 95% CI were reported. Finally, the HRs for the association between PBDEs dietary intake and breast cancer risk in two strata of the population defined according to the median of vegetable oil consumption (4.6 g/day) were presented.

In order to investigate a potential effect modification by lipid intake in general, rather than specifically vegetable oil, interaction products term between PBDEs dietary intake in quintile groups and lipid intake in two categories (<median; ≥median) were added in model 4. The p-value of the likelihood-ratio test and the interaction measures on both multiplicative and additive scales were reported. The third quintile group for PBDEs dietary intake and the low-intake group (<median) for lipid intake were used as reference.

All statistical tests were two-sided, and the threshold for statistical

significance was set at 5%. Statistical analyses were performed using the Statistical Analysis Systems software, version 9.4 (SAS Institute, Cary, NC) and the R software, version 4.0.3.

2.8. Sensitivity analyses

Separate Cox cause-specific hazard models according to ER status were fitted, in order to investigate a potential differential effect of PBDEs dietary intake on ER^+ and ER^- breast cancer risk. For these analyses, breast cancer cases having an unknown status of ER were excluded (N = 1162). For ER^+ models, participants having an ER^- breast cancer were censored at the age of diagnosis, and conversely, participants having an ER^+ breast cancer were censored at the age of diagnosis for ER^- models. Only the results for ER^+ breast cancer risk were presented in the two strata of the population defined according to the median of vegetable oil consumption, the number of ER^- breast cancer cases being too small (N = 797) to perform subgroup analyses and achieve sufficient statistical power.

In order to investigate potential residual confounding from the diet, model 3 was additionally adjusted separately on the following dietary covariates: adherence to a prudent dietary pattern (continuous), adherence to a western dietary pattern (continuous), fish consumption (continuous, g/day), fresh dairy consumption (continuous, g/day), and meat consumption (continuous, g/day), the three latter being the most important food groups contributing to total PBDEs dietary intake. In addition, the energy adjustment residual method was also carried out, using as the main exposure variable the residuals of a regression model in which PBDEs dietary intake is the dependent variable and total energy intake is the independent variable (Willett et al., 1997). In order to investigate a potential reverse causation bias, analyses excluding all cases diagnosed during the five first years of follow-up were performed. In order to account for the pharmacokinetic impact of dilution of chemicals in the body mass, analyses using the PBDEs dietary intake divided by the body weight (in ng/kg/day) were also performed. Considering that the lower-bound scenario implies an underestimation of the real exposure, models using total PBDEs dietary intake estimated with the middle-bound scenario were also fitted, in order to test the impact of uncertainty relative to undetected values on the estimated association with breast cancer risk. Finally, the main model was stratified on menopausal status: the pre-menopause stratum included only pre-menopaused women at baseline, and they were censored at the date of menopause if the latter occurred during the follow-up; the post-menopause stratum included only post-menopaused women at baseline.

3. Results

3.1. Characteristics of the study population

The study population was constituted of 67 897 women followed for a maximum of 21.4 years (from 1993 to 2014). The median duration of follow-up was 20.3 years, and the total duration of follow-up was 1 194 816 person-years. Among these women, 5 686 developed an incident breast cancer during the follow-up.

The baseline characteristics of the study population according to quintile groups of total PBDEs dietary intake are presented in Table 1. The participants had a median age of 52.5 years old at inclusion. They mostly received from 12 to 14 years of school education (52.8%) and never smoked (55.4%). They had a median body mass index of 22.2 kg/m^2, and a median energy intake of 2 158 kcal/day. A little more than half of them were pre-menopaused (52.9%) at baseline. The baseline characteristics of participants among cases and non-cases are presented in Supplementary table 1.

The median estimated dietary intake and exposure of total PBDEs using the lower-bound scenario were 39.9 ng/day and 0.67 ng/kg/day, respectively. The proportions of each congener to the total PBDEs dietary intake are presented in Supplementary table 2. The PBDE representing the largest part of the intake was PBDE-209 (61.6%), followed by BDE-47 (19.6%) and BDE-99 (7.4%). Food groups contributing the most to total PBDEs dietary intake were fish, fresh dairy and meat, which justified 23.0%, 19.8% and 14.7% of the total PBDEs intake, respectively (Supplementary figure 2).

Correlations between each PBDE are presented in Supplementary table 3. Overall, all congeners were strongly correlated with each other, except for PBDE-209 and PBDE-183 which were more weakly correlated with the other congeners.

3.2. Dietary intake of PBDEs and breast cancer risk

In models 1 and 2, a significant positive linear trend between total PBDEs dietary intake in quintile groups and breast cancer was highlighted. The fourth and fifth quintile groups were statistically significantly positively associated with breast cancer risk compared to the first quintile group in both models. In model 3, the main model adjusted on dietary variables, a positive linear trend borderline with statistical significance was highlighted (p-trend = 0.06). Higher breast cancer risk borderline with statistical significance was observed for the fourth and fifth quintile groups compared to the first quintile group (HR_{Q4vsQ1} and 95% CI: 1.08 [0.99;1.18]; HR_{Q5vsQ1} and 95% CI: 1.09 [0.99;1.20]) (Table 2).

3.3. Effect modification by vegetable oil consumption

A significant interaction was observed between total PBDEs dietary intake in quintile groups and vegetable oil consumption in two categories (p = 0.023). All interaction measures on the multiplicative scale were < 1, and the RERIs were < 0 (Table 3). When presenting results of model 4 in two strata of the population according to vegetable oil consumption, a significant positive linear trend between total PBDEs dietary intake in quintile groups and breast cancer risk was observed in high-consumers of vegetable oil (p-trend = 0.012). In this strata, statistically significant increased breast cancer risks were highlighted for the second, third, fourth and fifth quintile groups compared to the first quintile group (HR_{Q2vsQ1} and 95% CI: 1.19 [1.04; 1.36]; HR_{Q3vsQ1} and 95% CI: 1.16 [1.01; 1.32]; HR_{Q4vsQ1} and 95% CI: 1.18 [1.04; 1.34]; HR_{Q5vsQ1} and 95% CI: 1.23 [1.08; 1.40]). For low-consumers of vegetable oil, no significant linear trend was observed (p-trend = 0.97), and the HR were all non-significant and inferior or close to 1 (Table 4).

3.4. Effect modification by lipid intake

No significant interaction was found between total PBDEs dietary intake in quintiles and lipid intake in two categories (p = 0.27). Interaction measures on the multiplicative and additive scales were all non-significantly different of 1 and 0, respectively (Supplementary table 4).

3.5. Sensitivity analyses

When investigating these associations according to the subtype of ER breast cancer, a positive linear trend was observed for ER^- breast cancer risk (p-trend = 0.04). The HR for the third, fourth and fifth quintile groups were > 1 and higher than those observed for all breast cancer risk (HR_{Q3vsQ1} and 95% CI: 1.20 [0.95;1.51]; HR_{Q4vsQ1} and 95% CI: 1.24 [0.98;1.57]; HR_{Q5vsQ1} and 95% CI: 1.25 [0.97;1.62]). No significant linear trend was observed for ER^+ breast cancer risk (p-trend = 0.51) and the HR for all quintile groups were lower than those observed for all breast cancer risk (HR_{Q2vsQ1} and 95% CI: 1.02 [0.92;1.13]; HR_{Q3vsQ1} and 95% CI: 0.93 [0.84;1.04]; HR_{Q4vsQ1} and 95% CI: 1.05 [0.94;1.17]; HR_{Q5vsQ1} and 95% CI: 1.03 [0.91;1.16]) (Supplementary table 5). However, a limited number of ER^- breast cancer cases were included in the analyses (N = 797), which led to wide 95% CI.

When stratifying the analyses for ER^+ breast cancer on vegetable oil consumption, a similar difference of effect size between strata than in

Table 1
Baseline characteristics of the study population according to quintile groups of total PBDEs dietary intake (ng/day) (N = 67 879).

	Dietary intake of total PBDEs (ng/day) [3]					
	All (N = 67,879)	**Quintile 1 [0.56–28.40] (N = 13,575)**	**Quintile 2 [28.40–36.06] (N = 13,576)**	**Quintile 3 [36.06–43.91] (N = 13,576)**	**Quintile 4 [43.91–54.30] (N = 13,576)**	**Quintile 5 [53.30–220.21] (N = 13,576)**
Dietary intake of PBDEs (ng/day) [3]	39.86 (16.72)	23.25 (4.86)	32.40 (2.20)	39.86 (2.25)	48.50 (2.98)	63.29 (13.46)
Dietary exposure to PBDEs (ng/kg/day)	0.67 (0.29)	0.39 (0.10)	0.56 (0.08)	0.68 (0.10)	0.82 (0.12)	1.07 (0.27)
Age (years) [3]	51.53 (6.64)	53.52 (6.91)	51.88 (6.73)	51.27 (6.51)	50.77 (6.39)	50.57 (6.39)
Educational level (years) [1]						
<12	7,648 (11.27)	1,980 (14.59)	1,514 (11.15)	1,396 (10.28)	1,307 (9.63)	1,451 (10.69)
[12–14]	35,870 (52.84)	7,328 (53.98)	7,267 (53.53)	7,248 (53.39)	7,118 (52.43)	6,909 (50.89)
>14	24,361 (35.89)	4,267 (31.43)	4,795 (35.32)	4,932 (36.33)	5,151 (37.94)	5,216 (38.42)
Birth generation [1]						
<=1930	6,504 (9.58)	1,876 (13.82)	1,443 (10.63)	1,143 (8.42)	1,026 (7.56)	1,016 (7.48)
(1930; 1935]	9,098 (13.40)	2,274 (16.75)	1,927 (14.19)	1,751 (12.90)	1,604 (11.81)	1,542 (11.36)
(1935; 1940]	13,616 (20.06)	2,903 (21.38)	2,702 (19.90)	2,736 (20.15)	2,647 (19.50)	2,628 (19.36)
(1940; 1945]	16,767 (24.70)	3,088 (22.75)	3,377 (24.88)	3,393 (24.99)	3,456 (25.46)	3,453 (25.43)
>1945	21,894 (32.26)	3,434 (25.30)	4,127 (30.40)	4,553 (33.54)	4,843 (35.67)	4,937 (36.37)
Smoking status [2]						
Current	8,602 (12.67)	1,789 (13.17)	1,721 (12.68)	1,713 (12.62)	1,699 (12.52)	1,680 (12.37)
Former	21,682 (31.94)	3,947 (29.08)	4,213 (31.03)	4,423 (32.58)	4,490 (33.07)	4,609 (33.95)
Never	37,595 (55.39)	7,839 (57.75)	7,642 (56.29)	7,440 (54.80)	7,387 (54.41)	7,287 (53.68)
Menopausal status and recent MHT use [2]						
Premenopausal	35,931 (52.93)	6,040 (44.49)	6,956 (51.24)	7,421 (54.66)	7,731 (56.95)	7,783 (57.33)
Menopaused and recent MHT use (less than a year ago)	9,653 (14.22)	2,007 (14.79)	1,989 (14.65)	1,923 (14.17)	1,900 (14.00)	1,834 (13.51)
Menopaused and no recent MHT use	19,018 (28.02)	4,769 (35.13)	3,973 (29.26)	3,603 (26.54)	3,370 (24.81)	3,303 (24.33)
Menopaused and missing data on recent MHT use	3,277 (4.83)	759 (5.59)	658 (4.85)	629 (4.63)	575 (4.24)	656 (4.83)
Parity and age at first full-term pregnancy (FFTP) [2]						
Nulliparous	7,972 (11.74)	1,786 (13.16)	1,571 (11.57)	1,599 (11.78)	1,436 (10.58)	1,580 (11.64)
One or two child and age at FFTP < 30 years	33,442 (49.27)	6,560 (48.32)	6,592 (48.56)	6,673 (49.15)	6,846 (50.43)	6,771 (49.87)
More than two child and age at FFTP < 30 years	19,284 (28.41)	3,795 (27.96)	4,000 (29.46)	3,810 (28.06)	3,845 (28.32)	3,834 (28.24)
Age at FFTP>=30 years	7,181 (10.58)	1,434 (10.56)	1,413 (10.41)	1,494 (11.01)	1,449 (10.67)	1,391 (10.25)
Cumulative duration of previous breastfeeding [2]						
No breastfeeding	25,718 (37.89)	5,395 (39.74)	5,091 (37.50)	5,127 (37.77)	4,964 (36.56)	5,141 (37.87)
Cumulative duration of breastfeeding < 6 months	29,699 (43.75)	5,644 (41.58)	5,881 (43.32)	6,038 (44.48)	6,148 (45.29)	5,988 (44.11)
Cumulative duration of breastfeeding >=6 months	12,462 (18.36)	2,536 (18.68)	2,604 (19.18)	2,411 (17.75)	2,464 (18.15)	2,447 (18.02)
Contraceptive pill use (current or past) [2]						
Never	25,525 (37.60)	6,026 (44.39)	5,331 (39.27)	4,984 (36.71)	4,627 (34.08)	4,557 (33.57)
Ever	42,354 (62.40)	7,549 (55.61)	8,245 (60.73)	8,592 (63.29)	8,949 (65.92)	9,019 (66.43)
BMI (kg/m^2) [2]	22.21 (3.11)	22.07 (2.97)	22.21 (2.95)	22.21 (3.01)	22.21 (3.10)	22.38 (3.44)
Total physical activity (metabolic equivalents of task -hour/week) [3]	37.97 (49.71)	36.50 (54.91)	37.48 (47.11)	38.31 (48.98)	38.72 (47.72)	38.85 (49.41)

(*continued on next page*)

Table 1 (*continued*)

	Dietary intake of total PBDEs (ng/day) [3]					
	All (N = 67,879)	**Quintile 1 [0.56–28.40] (N = 13,575)**	**Quintile 2 [28.40–36.06] (N = 13,576)**	**Quintile 3 [36.06–43.91] (N = 13,576)**	**Quintile 4 [43.91–54.30] (N = 13,576)**	**Quintile 5 [53.30–220.21] (N = 13,576)**
Lipid consumption (g/day) [3]	85.79 (27.02)	66.73 (18.26)	78.90 (19.59)	86.97 (21.54)	94.78 (24.04)	107.59 (29.43)
Alcohol consumption (g/day) [3]	6.87 (13.91)	4.97 (13.39)	6.36 (13.30)	7.14 (13.88)	7.65 (13.95)	8.23 (14.81)
Total energy intake (kcal/day) [3]	2157.60 (560.40)	1776.75 (432.39)	2017.83 (434.86)	2175.50 (470.62)	2328.36 (503.86)	2590.39 (582.84)
Adherence to Western dietary pattern [3]	−0.12 (0.93)	−0.69 (0.63)	−0.34 (0.71)	−0.08 (0.77)	0.18 (0.86)	0.57 (1.06)
Adherence to Prudent dietary pattern [3]	−0.12 (0.98)	−0.50 (0.78)	−0.27 (0.81)	−0.11 (0.86)	0.07 (0.95)	0.35 (1.18)

Numbers (Percentages) are presented for categorical variables; Median (Standard deviation) are presented for continuous variables.
(1) Information collected at the first questionnaire sent in 1991.
(2) Information collected at the second questionnaire sent in 1992.
(3) Information collected at the third questionnaire sent in 1993

Table 2
Association between total PBDEs dietary intake (ng/day) and breast cancer risk in the E3N cohort (N = 67 879). Hazard ratios (HR) and 95% Confidence Interval (CI) are estimated by Cox multivariable regression models.

	Number (%) of non-cases	Number (%) of cases	**M1** HR [95% CI]	**M2** HR [95% CI]	**M3** HR [95% CI]
	N = 62193	N = 5686			
Dietary intake of PBDEs in quintiles (ng/day)					
Quintile 1	12,509 (20.11)	1066 (18.75)	Reference	Reference	Reference
Quintile 2	12,443 (20.01)	1133 (19.93)	1.05 [0.97; 1.15]	1.05 [0.97; 1.14]	1.04 [0.96; 1.14]
Quintile 3	12,471 (20.05)	1105 (19.43)	1.02 [0.94; 1.12]	1.02 [0.93; 1.11]	1.00 [0.92; 1.09]
Quintile 4	12,391 (19.92)	1185 (20.84)	**1.11 [1.02; 1.20]**	**1.10 [1.01; 1.19]**	1.08 [0.99; 1.18]
Quintile 5	12,379 (19.90)	1197 (21.05)	**1.13 [1.04; 1.23]**	**1.12 [1.03; 1.22]**	1.09 [0.99; 1.20]
P-trend			**0.002**	**0.004**	0.063

M1: Adjusted for age as the time-scale (years).
M2: Adjusted for M1 + birth generation (≤1930; (1930–1935]; (1935–1940]; (1940–1945]; >1945), educational level (<12 years; 12 to 14 years; >14 years), smoking status (non-smoker; former smoker; current smoker), body mass index (continuous, in kg/m2) parity and age at FFTP (nulliparous; one or two children and age at FFTP < 30; more than 3 children and age at FFTP < 30; age at FFTP ≥ 30), cumulated duration of previous breastfeeding (no breastfeeding: less than 6 months of breastfeeding; at least 6 months of breastfeeding), utilisation of contraceptive pill (ever; never), menopausal status and recent use of MHT (pre-menopaused, menopaused with recent use oh MHT; menopaused without recent use of MHT, menopaused and missing data on recent used of MHT), and physical activity (continuous, in metabolic equivalents of task-hour/week).
M3: Adjusted for M2 + daily alcohol intake (continuous, in g of ethanol/day), daily lipids intake (continuous in g/day), and daily total energy intake except from alcohol and lipid (continuous in kcal/day).
P-trend: P-value for linear trend estimated by fitting a semi-continuous variable based on the median value of exposure of each quintile group.

Table 3
Interactions measures between total PBDEs dietary intake in quintiles (ng/day) and vegetable oil consumption in two categories (<median; ≥median), on breast cancer risk in the E3N cohort (N = 67 879).

		Interaction measures in M4	
Dietary intake of PBDEs (ref: Quintile 1)	Vegetable oil consumption (ref: ≥Median)	**Multiplicative scale [95% CI]**	**Additive scale RERIs [95% CI]**
Quintile 2	<Median	**0.80 [0.57;0.95]**	**−0.25 [-0.46;-0.04]**
Quintile 3	<Median	**0.77 [0.65;0.92]**	**−0.28 [-0.49;-0.08]**
Quintile 4	<Median	0.86 [0.73;1.03]	−0.16 [-0.36;0.04]
Quintile 5	<Median	**0.79 [0.67;0.94]**	**−0.26 [-0.47;-0.05]**
P-value for global interaction		**0.023**	

M4: Adjusted for age as the time-scale (years), birth generation (≤1930; (1930–1935]; (1935–1940]; (1940–1945]; >1945), educational level (<12 years; 12 to 14 years; >14 years), smoking status (non-smoker; former smoker; current smoker), body mass index (continuous, in kg/m2) parity and age at FFTP (nulliparous; one or two children and age at FFTP < 30; more than 3 children and age at FFTP < 30; age at FFTP ≥ 30), cumulated duration of previous breastfeeding (no breastfeeding: less than 6 months of breastfeeding; at least 6 months of breastfeeding), utilisation of contraceptive pill (ever; never), menopausal status and recent use of MHT (pre-menopaused, menopaused with recent use oh MHT; menopaused without recent use of MHT, menopaused and missing data on recent used of MHT), physical activity (continuous, in metabolic equivalents of task-hour/week) + daily alcohol intake (continuous, in g of ethanol/day), and daily total energy intake except from alcohol (continuous in kcal/day).
P-value for global interaction was obtained with the likelihood-ratio test on all interaction terms.
HR: Hazard Ratio, CI: Confidence Interval, RERIs: Relative Excess Risks due to Interactions.

principal analyses were observed, with higher HR for high-consumers of vegetable oil (p-trend = 0.04) than for low-consumers (p-trend = 0.26) (Supplementary table 6).

When additionally adjusting the main model on dietary variables, results remained globally similar, although a slight increase of HR was observed when adjusting for "healthy" dietary factors, i.e. adherence to prudent dietary pattern and fish consumption compared to the main analyses (Supplementary table 7). Conversely, a slight decrease in HR was observed when adjusting for "unhealthy" dietary factors, i.e. adherence to western dietary pattern and meat consumption (Supplementary table 7). In addition, when using the energy adjustment

Table 4
Association between total PBDEs dietary intake in quintiles (ng/day) and breast cancer risk in the E3N cohort, stratified on median of vegetable oil consumption (N = 67 879). Hazard Ratios (HR) and 95% Confidence Interval (CI) are estimated by Cox multivariable regression models.

	Vegetable oil consumption < median [0–4.6) g/d			**Vegetable oil consumption ≥ median [4.6–33.1] g/d**		
	Number (%) of non-cases	Number (%) of cases	**M4** HR [95% CI]	Number (%) of non-cases	Number (%) of cases	**M4** HR [95% CI]
	N = 31110	N = 2829		N = 31083	N = 2857	
Dietary intake of PBDEs in quintiles (ng/day)						
Quintile 1	7395 (23.77)	676 (23.90)	Reference	5114 (16.45)	390 (13.65)	Reference
Quintile 2	6663 (21.42)	593 (20.96)	0.95 [0.85; 1.06]	5780 (18.60)	540 (18.90)	**1.19 [1.04; 1.36]**
Quintile 3	6242 (20.06)	529 (18.70)	0.89 [0.80; 1.00]	6229 (20.04)	576 (20.16)	**1.16 [1.01; 1.32]**
Quintile 4	5714 (18.37)	556 (19.65)	1.02 [0.90; 1.14]	6677 (21.48)	629 (22.02)	**1.18 [1.04; 1.34]**
Quintile 5	5096 (16.38)	475 (16.79)	0.97 [0.86; 1.10]	7283 (23.43)	722 (25.27)	**1.23 [1.08; 1.40]**
P-trend			0.969			**0.012**

M4: Adjusted for age as the time-scale (years), birth generation (≤1930; (1930–1935]; (1935–1940]; (1940–1945]; >1945), educational level (<12 years; 12 to 14 years; >14 years), smoking status (non-smoker; former smoker; current smoker), body mass index (continuous, in kg/m2) parity and age at FFTP (nulliparous; one or two children and age at FFTP < 30; more than 3 children and age at FFTP < 30; age at FFTP ≥ 30), cumulated duration of previous breastfeeding (no breastfeeding: less than 6 months of breastfeeding; at least 6 months of breastfeeding), utilisation of contraceptive pill (ever; never), menopausal status and recent use of MHT (pre-menopaused, menopaused with recent use oh MHT; menopaused without recent use of MHT, menopaused and missing data on recent used of MHT), physical activity (continuous, in metabolic equivalents of task-hour/week) + daily alcohol intake (continuous, in g of ethanol/day), and daily total energy intake except from alcohol (continuous in kcal/day).
P-trend: P-value for linear trend estimated by fitting a semi-continuous variable based on the median value of exposure of each quintile group.

residual method, the results were globally similar to those obtained with the main model (Supplementary table 8).

When excluding cases diagnosed during the five first years of follow-up, the association was more pronounced with higher HR than in the main analyses (HR_{Q4vsQ1} and 95% CI: 1.11 [1.01;1.23; HR_{Q5vsQ1} and 95% CI: 1.12 [1.01;1.25]) (Supplementary table 9). When using total PBDEs dietary intake estimated with the middle-bound scenario, the results remained virtually unchanged (Supplementary table 10). When using total PBDEs dietary exposure in ng/kg/day, the association was attenuated with lower HR than in the main analyses (HR_{Q4vsQ1} and 95% CI: 1.03 [0.94;1.13; HR_{Q5vsQ1} and 95% CI: 1.04 [0.94;1.14]) (Supplementary table 11). Finally, when stratifying on menopausal status, the HR were higher for pre-menopaused women, while similar for post-menopaused women, compared to results obtained for the entire population (Supplementary table 12).

4. Discussion

This study has highlighted a positive linear trend, borderline with statistical significance, between dietary intake of PBDEs and all breast cancer risk. A significant interaction between PBDEs dietary intake and vegetable oil consumption on breast cancer risk has been observed both in additive and multiplicative scale, with a larger effect size of PBDEs intake for high consumers of vegetable oil, and almost no effect in low consumers.

The median exposure to PBDEs estimated in the present study (0.67 ng/kg/day) was slightly higher than that reported by ANSES in the French TDS2 using to the lower-bound scenario (0.54 ng/kg/day) (French agency for food, environment and occupational health & safety, 2011b). This latter study was based on the same food contamination levels as those used in the present study, but on consumption data derived from the second Individual and National Study on Food Consumption (INCA2), including 1918 adults from 18 to 79 years between 2005 and 2007. Consequently, the differences of PBDEs dietary exposure estimates are likely due to differences in dietary consumptions, which are probably attributable to the different characteristics of the two study populations in terms of age, sex and socio-economic status.

To the best of our knowledge, no other epidemiological study has previously investigated the association between dietary intake of PBDEs and breast cancer risk. Few studies investigating the association between internal levels of PBDEs and breast cancer have been conducted. Two studies have been performed on serum levels of PBDEs congeners, one case-control study and one nested case-control study, supporting no association with breast cancer risk (Hurley et al., 2019; Holmes et al., 2014). Two case-control studies have been conducted on adipose level of PBDEs congeners, identifying no association (Hurley et al., 2011) or positive associations with certain congeners (He et al., 2018). Finally, a case-control study nested in the E3N cohort has been carried out, highlighting no association between plasma levels of PBDEs and breast cancer (Mancini et al., 2020). Among the previously mentioned studies, two have investigated this association according to the breast cancer ER status. One study did not highlight any differences (Mancini et al., 2020), while the second observed that some congeners were associated with ER + breast cancer risk only (He et al., 2018). PBDEs congeners have been shown to disrupt ER signalling pathways in human breast cancer cells and in embryos and larvae of zebrafish, acting as agonists or antagonists of ER (Kanaya et al., 2019; Liu et al., 2015), suggesting that the effect of PBDEs on breast cancer might depend on the ER status. Nevertheless, a study has shown that BDE-209 could stimulate both ER^+ and ER^- breast cancer cells proliferation (Li et al., 2012). This could be explained by the phosphorylation of PKCα and ERK1/2 induced by PBDE-209, these proteins being involved in cell proliferation and apoptosis (Li et al., 2012). Although our study suggests a differential association according to the ER status, the mechanisms which could explain this phenomenon are not completely elucidated. In addition, our results for ER^- breast cancer should be interpreted carefully, due to the relatively small number of cases.

Previous toxicological studies have been interested in interaction between nutrients and chemical food contaminants, especially lipophilic chemicals and fat compounds (Cano-Sancho and Casas, 2021). For instance, a previous in-vitro study have shown a substantial increase in bioaccessibility of PBDEs after corn oil addition to raw fish (Mi et al., 2017). Moreover, as mentioned in the introduction, Li et al.'s study has highlighted that the addition of vegetable oil increases bioaccessibility of PBDEs from fish samples after an in vitro digestion (Li et al., 2021). The same study has also shown that the addition of vegetable oil increases the accumulation of most congeners of PBDEs in Caco-2 cells models, although it seems to decreases their transport from the apical to

the basolateral pole of Caco-2 cells models (Li et al., 2021). Similarly, in Caco-2 cells models, fatty acids have been shown to increase uptake and transport of PCBs, which are lipophilic contaminants like PBDEs (Dulfer et al., 1996). In turn, a study on pregnant mice has observed an increasing mammary tumour incidence by 2,3,7,8-tetrachlorodibenzo-p-dioxin, another lipophilic contaminant, only in mice fed with high-fat diet (La et al., 2010). The increased bioaccesibility of PBDEs by co-ingestion of oil may be due to the promotion of formation of mixed micelles containing lipid and bile salts, enhancing the solubility of hydrophobic compounds (Li et al., 2021; Mi et al., 2017). The increased accumulation of PBDEs in Caco-2 cell models could be explained by the presence of fatty acids in oil, which have been shown to promote absorption of lipophilic compounds by stimulation of secretion of chylomicrons by enterocytes (Failla et al., 2014). In conclusion, the more pronounced effect of PBDEs among high consumers of vegetable oil observed in the present study might be explained by an augmentation of the bioaccessibility of PBDEs during the digestion, as well as a promotion of their absorption by the enterocytes, due to the co-ingestion of vegetable oil.

Some limitations need to be taken into account when interpreting the results of the present study. First, the dietary consumptions of the study population were assessed in 1993, whereas the contamination levels of PBDEs congeners in food samples were measured between 2007 and 2009. Between 1993 and 2009, food contamination levels may have changed, resulting in imperfect estimates of dietary intake of PBDEs at baseline. However, since the PBDEs have long half-lives and are persistent in the environment, the decrease of food contamination levels potentially occurring between these two periods is expected to be negligible. Moreover, the latter is probably uniform among food groups, as the presence of PBDEs is ubiquitous in the environment. Consequently, we can hypothesise that the resulting error in the estimation of exposure may be homogeneous among participants, resulting in a correct classification of subjects between them regarding the quantiles of exposure. Another potential source of error in the exposure estimation is related to the use of food frequency questionnaires to estimate dietary consumptions. Indeed, this tool may be subject to bias due to difficulties in recalling and estimating average food consumptions over a long period of time, and to social desirability bias in self-reporting consumptions. However, in our prospective study, the dietary questionnaire has been filed in at baseline, before any breast cancer diagnosis. Consequently, the resulting errors are likely to be non-differential, i.e., non-linked to the breast cancer status. It has been shown that non-differential sources of errors due to food frequency questionnaires in prospective studies generally leads to attenuation of the estimated association (Kipnis, 2011; Thiébaut et al., 2007; Kipnis et al., 2003). In addition, the estimated effect of PBDEs probably includes a part of residual confounding with the overall diet, despite adjustments on dietary variables, due to imperfect estimation of these latter by the food frequency questionnaires. Moreover, due to their strong correlations, only the sum of all the PBDEs congeners was used in the analyses, not allowing taking into account some possible non-additive effects on breast cancer risk. Finally, the E3N cohort is composed only of middle-aged women, with a higher level of education than the general population, so the generalizability of the results should be done carefully.

This study also presents several strengths. This is the first epidemiological study investing the association between dietary intake of PBDEs and breast cancer, and attempting to take into account potential interactions between PBDEs congeners and dietary components. While the estimation of the dietary exposition may be imperfect as discussed in the limitations, studying specifically dietary exposure to PBDEs, in contrast with other studies focusing on internal levels, is of interest because it allows to formulate dietary recommendations aiming to reduce consumers' exposure. In addition, studies based on human biomonitoring are still very expensive and invasive for participants, which represents a limitation in terms of number of individuals included in the studies. On the contrary, due to the fact that our study is based on indirect estimates of dietary exposure, we could include a very large study population reaching good statistical power, and having the possibility of performing several stratified and sensitivity analyses. Moreover, the long follow-up time (17.6 years on average) has enabled to investigate long term health effects of PBDEs. In addition, prevalent breast cancer cases at baseline have been excluded, so that dietary consumptions have been assessed before any breast cancer diagnosis, preventing reverse causation bias. Furthermore, good quality data were used, the food frequency questionnaire being previously validated, and the breast cancer diagnosis being validated for 93% of cases. Finally, the richness of data of the E3N cohort has enabled to adjust for many covariates, which were selected using a DAG.

The present study has highlighted for the first time a positive association between dietary exposure to PBDEs and breast cancer risk. Moreover, the results suggest an enhancer role played by vegetable oil consumption with regard to this association. From a public health perspective, highlighting such interactions between nutrients and chemicals is crucial to develop specific dietary recommendations that could allow reducing the bioavailability of food contaminants, thus limiting their toxic effects. Indeed, food composition, both in nutrients and chemical contaminants, and interactions between them, should be considered when developing dietary guidelines. These preventive strategies become particularly relevant for ubiquitous POPs whose production and emissions have been already strongly regulated or banned but have widely contaminated the food chain. Further studies are needed to explore the association between PBDEs and breast cancer as well as the potential interactions between PBDEs and different food components, especially lipophilic ones.

Ethics approval and consent to participate

The study was approved by the French National Commission for Data Protection and Privacy (ClinicalTrials.gov identifier: NCT03285230). All participants gave written informed consent.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Pauline Frenoy: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Chloé Marques:** Writing – review & editing. **Thibault Fiolet:** Writing – review & editing. **German Cano-Sancho:** Writing – review & editing. **Gianluca Severi:** Writing – review & editing. **Francesca Romana Mancini:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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