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Dietary intakes of dioxins and polychlorobiphenyls (PCBs) and breast cancer risk in 9 European countries

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ABSTRACT

Background: Dioxins and polychlorobiphenyls (PCBs) are persistent organic pollutants that have demonstrated endocrine disrupting properties. Several of these chemicals are carcinogenic and positive associations have been suggested with breast cancer risk. In general population, diet represents the main source of exposure.

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Methods: Associations between dietary intake of 17 dioxins and 35 PCBs and breast cancer were evaluated in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort from nine European countries using multivariable Cox regressions. The present study included 318,607 women (mean ± SD age: 50.7 ± 9.7) with 13,241 incident invasive breast cancers and a median follow-up of 14.9 years (IQR = 13.5–16.4). Dietary intake of dioxins and PCBs was assessed combining EPIC food consumption data with food contamination data provided by the European Food Safety Authority.

Results: Exposure to dioxins, dioxins + Dioxin-Like-PCBs, Dioxin-Like-PCBs (DL-PCBs), and Non-Dioxin-Like-PCBs (NDL-PCBs) estimated from reported dietary intakes were not associated with breast cancer incidence, with the following hazard ratios (HRs) and 95% confidence intervals for an increment of 1 SD: $HR_{dioxins} = 1.00$ (0.98 to 1.02), $HR_{dioxins+DL\text{-}PCB} = 1.01$ (0.98 to 1.03), $HR_{DL\text{-}PCB} = 1.01$ (0.98 to 1.03), and $HR_{NDL\text{-}PCB} = 1.01$ (0.99 to 1.03). Results remained unchanged when analyzing intakes as quintile groups, as well as when analyses were run separately per country, or separating breast cancer cases based on estrogen receptor status or after further adjustments on main contributing food groups to PCBs and dioxins intake and nutritional factors.

Conclusions: This large European prospective study does not support the hypothesis of an association between dietary intake of dioxins and PCBs and breast cancer risk.

Abbreviation

AhR	aryl hydrocarbon cell receptor
BMI	body mass index
CI	confidence interval
DL-PCBs	dioxin-like polychlorinated biphenyls
EFSA	European food safety authority
EPIC	European prospective investigation into cancer and nutrition
GC-HRMS	Gas chromatography/high-resolution mass spectrometry
GC–MS/MS	Gas chromatography - tandem mass spectrometry
HRGC-HRMS	High-resolution gas chromatography/high-resolution mass spectrometry
GC-QqQ-MS/MS	Gas chromatography coupled to triple-quadrupole tandem mass spectrometry
HR	hazard ratio
IARC	international agency for research on cancer
IQR	interquartile range
LOD	limit of detection
LOQ	limit of quantification
NDL PCBs	non-dioxin like polychlorinated biphenyls
NHS	nurses' health study
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-para-dioxins
PCDFs	polychlorinated dibenzofurans
POPs	persistent organic pollutants
TCDD	2,3,7,8-tetrachlorodibenzo-para-dioxin
TDI	tolerable daily intake
TDS2	second French total diet study
TEF	toxic equivalency factor
TEQ	toxic equivalence quotient
WHO	world health organization

1. Introduction

Breast cancer is the most frequent of all cancers worldwide with 2.3 million new cases in 2020 (Sung et al., 2021). Known risk factors for breast cancer include age, exposure to estrogen through precocious puberty, late menopause and/or hormone treatments, as well as not breastfeeding, alcohol and tobacco use, overweight and lack of physical activity, family history of cancer and genetic predisposition to breast cancer (mutations of several genes including *BRCA1* and *BRCA2* genes) (World Cancer Research Fund International/American Institute for Cancer Research, 2017). Nevertheless, in the United Kingdom, it has been estimated that only 23.1% of breast cancers are attributable to overweight, alcohol, radiation, not breastfeeding, postmenopausal hormones, oral contraceptives (Brown et al., 2018). Despite advances in research, there are still knowledge gaps in the etiology of breast cancer that cannot be fully explained by the previously identified risk factors.

Recently, special attention has been paid to exposure to environmental contaminants, such as persistent organic pollutants (POPs), including dioxins and polychlorobiphenyls (PCBs), which are characterized by their toxicity, persistence, bioaccumulation and mobility (Kelly et al., 2007).

Dioxins include over 200 different compounds that come from industrial processes as by-products, smoking or discharges, but also from natural sources such as forest fires or eruptions. This collective term includes 75 polychlorinated dibenzo-para-dioxins (PCDDs) and 135 polychlorinated dibenzofurans (PCDFs). 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) is the most toxic dioxin and is considered as carcinogenic to humans, mainly through the activation of the aryl hydrocarbon receptor (AhR, a regulator of xenobiotic metabolism) (IARC Working Group on the Evaluation of Carcinogenic Risks to Rumans, 1997; Mandal, 2005).

PCBs include 209 congeners. These man-made contaminants were used in transformers, capacitors, paints and in some industrial applications produced between the 1930s and 1980s (Erickson and Kaley, 2011). PCBs can also be released from hazardous waste sites and incinerators. PCBs have been classified as "carcinogenic to humans" (group 1) by IARC based on evidence of carcinogenicity for malignant melanoma, non-Hodgkin lymphoma, and breast cancer (IARC, 2013). PCBs can be divided into two groups based on their toxic mode of action: 12 PCBs are classified as dioxin-like PCBs (DL-PCBs) based on their electronic and spatial structure similar to PCDD/Fs and their ability to activate the AhR. The remaining 197 congeners are classified as non-dioxin like PCBs (NDL-PCBs) and mainly induce other toxicity mechanisms (Kafafi et al., 1993). Dioxins, several DL-PCBs and NDL-PCBs also exhibit endocrine disruptor properties such as activating human thyroid hormone receptor-β-mediated transcription or estrogen receptors (Gore et al., 2015; La Merrill et al., 2020).

Dioxins and PCBs are ubiquitously present in the environment worldwide (Kelly et al., 2007; Meijer et al., 2003). Due to their strong affinity for fats and their half-life of several years (Milbrath Meghan O'Grady et al., 2009), PCBs and dioxins tend to accumulate in the food chain, especially in foods of animal origin such as fish products, dairy products or milk; hence, diet represents the main route of exposure for the general population (>90% of total exposure) (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2013; Knutsen et al., 2018).

Epidemiological studies mainly focused on accidental and

occupational exposure situations, with studies suggesting either an increased risk of breast cancer (Silver et al., 2009; VoPham et al., 2020) or no association with breast cancer (Warner et al., 2011). Notably, occupational and mass poisoning events have resulted in 3–5 times higher exposure in affected persons as compared to the general population (Guo et al., 1997; World Health Organization, 1998). To the best of our knowledge, only three longitudinal studies have investigated the association between dioxins exposure and breast cancer risk in the general population: the Nurses' Health Study II prospective cohort, which found a positive association between proximity with industrial dioxin-emitting facilities (indirect exposure) and invasive breast cancer incidence (VoPham et al., 2020); the French E3N prospective cohort, which found no relationship between dietary exposure to dioxins and invasive breast cancer risk (Danjou et al., 2015); and the Swedish Mammography cohort which found no relationship between dietary intake of PCB-153 and breast cancer risk (Donat-Vargas et al., 2016).

The aim of the present study was to evaluate the association between dietary intake of 17 dioxins and 35 PCBs and incidence of invasive breast cancer, based on the large-scale European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

2. Methods

2.1. Study population

The EPIC cohort consists of approximately 370,000 women and 150,000 men, aged 35–69, recruited between 1992 and 2000 in 23 research centers across 10 European countries: Denmark (Aarhus and Copenhagen), all over France and Greece, Germany (Heidelberg and Potsdam), Italy (Florence, Varese, Ragusa, Turin, and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, and Guipuzcoa), Sweden (Malmö and Umeå), the Netherlands (Bilthoven and Utrecht), and the United Kingdom (Cambridge and Oxford). Dietary and lifestyle data have been collected at baseline through validated questionnaires. Study design, recruitment and data collection have been previously described in detail elsewhere (Riboli et al., 2002; Riboli and Kaaks, 1997).

From the initial pool of 521,324 participants, the present analysis excluded 25,184 participants with prevalent tumors at baseline, 4,148 participants with no follow-up, and 148,007 men, leading to a sample of 343,985 women (Supplementary Fig. 1). Among them, we excluded the top or bottom 1% of the ratio of energy intake to energy requirement (n = 6,425), women with missing dietary and/or lifestyle information (n = 3,217), and Greek participants (n = 15,637) due to data access issues, and in situ incident breast cancer cases (n = 79), leading to a final population of 318,607 women with 13,241 incident invasive breast cancer cases.

Breast cancer cases have been reported using a combination of methods including health insurance records, cancer registries and active follow-up through study participants (Riboli et al., 2002).

All participants provided written informed consent to participate in the EPIC study. This study was approved by the ethics committee of IARC and all study centers.

2.2. Usual food consumption data in EPIC

Usual dietary intakes of participants were assessed by country-specific and validated dietary questionnaires at recruitment between year 1992 and 2000 depending from each study, as described in Supplementary Table 1. Semi-quantitative food frequency questionnaires covering one year of dietary habits were used in the Netherlands and Germany (both self-reported). Questionnaires similar to the quantitative dietary questionnaires, although structured by meals, were used in Spain, Northern Italy, France, and Ragusa (Southern Italy). Semi-quantitative food-frequency questionnaires with the same standard portions assigned to all participants were used in Denmark, Norway, Naples in Italy, and Umeå in Sweden. A dietary method combining a short semi-quantitative food-frequency questionnaire with a 7-day record on hot meals (lunches and dinners) was used in Malmö. The recipes included in the questionnaires were split into ingredients in a standardized way. The complete list of foods and ingredients consists of 43,954 items, ranging from 146 items in Umeå to 23,655 in Malmö. This comprehensive list was then aggregated into a simplified list (to harmonize the level of detail available for the different countries) containing 11,858 items. Food and ingredient items derived from each EPIC dietary questionnaire were thereafter classified using the EPIC-SOFT food classification system (Voss et al., 1998) leading to a harmonized list of 11,858 food items.

2.3. Treatment and compilation of EFSA food contaminant database

The EFSA launches each year a call for collection of chemical contaminant occurrence data in food including dioxins and PCBs. European national authorities and similar bodies, research institutions, academia, food business operators and other stakeholders are invited to submit analytical data through a standardized format, called SSD1 Standard Sample Description (European Food Safety Authority, 2010). The database from National and European monitoring program was provided by EFSA for the present study and included food samples collected between year 1995 and 2018. EFSA developed a precise and harmonized description system of the food matrix analyzed or consumed called FoodEx (EFSA (European Food Safety Authority), 2011). A first version FoodEx was developed in 2008 and was composed of 1,700 food groups organized in a hierarchical system based on 20 main food categories that were further divided into subgroups up to a maximum of 4 levels. Each food group was identified by a unique code. The analysed sample can be further described in terms of treatment (raw, cooked, dehydrated, canned…), packaging… (European Food Safety Authority, 2010) The database provided the following information for individual congeners: description of the analyzed food sample according to the FoodEx classification system, food processing, percentage of fat, analytical method used, limits of detection and of quantification, mode of expression, analytical results expressed for an individual congener or in some cases for the sum of multiple congeners, and unit of measurement. Results were expressed in whole weight or fat weight. Thus, all values were converted in the same mode of expression, whole weight, using the percentage of fat reported in the database directly from the data provider. If the percentage of fat was missing, it was imputed by the median value of the FoodEx level 4 groups.

Details concerning the exclusion rules applied to the database of PCB/dioxins in food are reported in the flow chart in Supplementary Fig. 2. Analytical results reported as a sum of multiple congeners were excluded since it was not possible to know which congeners were included in the sum. Reliable analytical methods considered were gas chromatography/high-resolution mass spectrometry (GC-HRMS), gas chromatography-tandem mass spectrometry (GC–MS/MS), high-resolution gas chromatography/high-resolution mass spectrometry (HRGC-HRMS), gas chromatography coupled to triple-quadrupole tandem mass spectrometry (GC-QqQ-MS/MS); values obtained using other analytical methods were excluded. Analytical results expressed in binary values (related to health-based guidance values) were excluded since it is not possible to calculate a median contamination level with qualitative values. Inclusion of samples suspected for non-conformity (e.g. European Rapid Alert System for Food and Feed (RASFF) is not a random sampling) and samples from targeted monitoring can lead to an overestimation of the contamination and consequently the intake, thus they were excluded. Samples from total diet studies (TDS; <1% samples from the full initial dataset) were not included since in those studies foodstuffs are analyzed "as eaten", i.e. ready to be consumed. Indeed, results obtained by the TDS are not directly comparable with results obtained when analyzing food items not prepared as to be consumed, thus contamination data obtained applying different approaches/methods should not be mixed. Analytical results with missing or inappropriate

mode of expression (88% dry matter in the European regulation used for feeds (*Commission Regulation (EU) 2017/644 of 5 April 2017 laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No 589/2014 (Text with EEA relevance.)*, 2017)) were excluded. Analytical results with unreliable quantified values below the reported Limit of Detection (LOD) or Limit of Quantification (LOQ) were excluded, as well as analytical results with missing information for both LOD and LOQ. Following the approach presented in the scientific opinion of EFSA (Knutsen et al., 2018), analytical results with LOD or LOQ above 1/5 of European Regulatory Maximum levels or 1/3 of Actions levels were excluded as they did not comply with the analytical performance criteria following European Commission Regulation (EU) No 2017/644 (*Commission Regulation (EU) 2017/644 of 5 April 2017 laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No 589/2014 (Text with EEA relevance.)*, 2017). The final contamination dataset included 821,983 analytical results for 967 food items coded in the FoodEx classification system related to 17 dioxins (PCDD/Fs), 12 DL-PCBs, and 40 NDL-PCBs and collected through the annual EFSA calls of chemical contaminant occurrence data in food between 2000 and 2018.

Two scenarios were investigated to deal with left-censored values: (1) a middle bound (MB) scenario, where non-detected values were imputed by limit of detection (LOD)/2 and non-quantified values by limit of quantification (LOQ)/2; and (2) a lower bound (LB) scenario, where a null value was assigned to all left-censored values. The median occurrence value among each food group was used in order to limit the impact of extreme values on the aggregated EFSA PCB and dioxin values.

The occurrence levels for dioxins and DL-PCBs were transformed using the World Health Organization's (WHO) 2005 toxic equivalence factors (TEF) scheme weighting the toxicity of the less toxic compounds as fractions of the toxicity of the most toxic TCDD (van den Berg et al., 2006). The amounts of each toxic compound are multiplied with their (TEF) and then added together as a "sum of dioxins"; "sum of dioxins and DL-PCBs" and "sum of DL-PCBs".

2.4. Assessment of dietary intake of dioxins and PCBs

The FoodEx classification system was developed by EFSA to facilitate the assessment of dietary intake by allowing accurate matching of the chemical occurrence and food consumption datasets. It contains 20 main food groups that are further divided into subgroups, leading to 1,800 food items at the most refined level 4 (EFSA (European Food Safety Authority), 2011). For each individual congener and food item at FoodEx level 4 (the most detailed level available), the median contamination value was combined with the daily consumption of the corresponding food item for each EPIC participant, as described in Supplementary Tables 3 and 4. EPIC food consumption datasets were combined with EFSA occurrence data at FoodEx level 4 (the most detailed level available) and per individual congener to calculate dietary intake. The 11,858 items of the EPIC dietary questionnaires have been matched with FoodEx. FoodEx was then automatically converted into FoodEx2 using the Interpreting tool provided by EFSA. Manual corrections were performed at IARC to more closely fit FoodEx classification. Regarding processing, special attention was given to food items that may be available dried or in powder as well as fresh or reconstituted/whole to distinguish those two states and apply conversion/hydration factors provided by EFSA when needed (European Food Safety Authority, 2018). When there was no exact match between food items as reported in the EPIC food consumption database and food items as reported in the EFSA occurrence database, an alternative match was found taking into account the fact that processing may impact the contamination level (Rawn et al., 2013). Therefore a new link was created with a brother or parent item, i.e. with the same level of processing. For example a flour type could be replaced by another flour type assuming similar contamination levels but not with the corresponding grain. In case the same food was reported in two different states in the EPIC and EFSA database, for example « dried tea leaves» and « tea (beverage) », a dilution factor was applied. In case no alternative could be found in the EFSA occurrence database, we assumed the food item did not contain contaminants.

2.5. Intake calculation

The dietary intake of each compound was estimated for each participant using the following formula:

$$Averagedailyintake\left(\frac{pg}{day}\right) = \sum_{eachfood} (Averagefooddailyconsumptioning/day) \times (medianofcontaminationlevelforfoodin\frac{pg}{g}food)$$

When estimating individual dioxin and PCB intakes, we did not take into account information on the country where the food sample was purchased and/or where the analysis was conducted.

Four indicators have been calculated by summing the individual daily intake for each group of congeners: sum of 17 dioxins (pg TEQ/day), sum of 12 DL-PCBs (pg TEQ/day), sum of 29 DL-PCB and dioxins (pg TEQ/day), and a sum of 6 main NDL-PCB (pg/day). NDL-PCB group was restricted to six PCBs-101, 138, 153, 180, 28, 52, since these are the most frequently analyzed and this group corresponds to 50% of total NDL-PCBs measured in food according to EFSA (Knutsen et al., 2018). The full list of dioxins and PCBs provided by EFSA is available in the Supplementary Table 5.

2.6. Statistical analyses

Participants' baseline characteristics were described for cases and non-cases and according to quintile groups of dioxin/PCB intakes. The modal value (for categorical variables) or the median (for continuous variables) was used to impute missing values for covariates for which<5% of values were missing. When the proportion of missing values was higher than 5%, a separate category indicating missing data in the model for these variables was created to avoid massive imputation. This was the case for use of age at first birth (4.6%), menopausal hormone therapy (6.8% missing values), physical activity (5.7%), breastfeeding (11%), and mother's history of breast cancer (52.8%).

The main analyses were performed using PCB and dioxin food contamination levels collected between 2000 and 2018 applying the middle bound scenario.

Cox proportional hazards regression models were used to quantify the association between the dietary estimated intake of dioxins and PCBs (coded as a continuous variable for an increment of 1 Standard Deviation (SD) or as quintile groups) and breast cancer incidence. Age at recruitment was the primary time variable. Time at exit was age at diagnosis of breast cancer or any other cancer, death, loss to follow-up, or end of follow-up, whichever occurred first. The proportional hazards assumption was assessed with Schoenfeld residuals and tested using the cox.zph function in the survival package in R. All models were stratified by age at recruitment (1-year intervals) and center (the baseline hazard functions h0 (t) in Cox models is different between the age and center groups) and were built separately for each indicators (dioxins, dioxins + DL-PCBs, DL-PCBs and NDL-PCB).

A first model (Model 1) was adjusted for breast cancer risk factors identified and based on previous knowledge: body mass index (BMI; WHO categories (<18,5; 18,5–25; 25–30; >30 kg/m^2)), smoking (never, former, smoker), education (none, primary school, secondary school, technical or professional school, University degree), energy intake without alcohol (kcal/day), alcohol intake (g/day), combined total physical activity based on occupational activity and recreational/household activity (inactive, moderately active, moderately inactive,

active, missing).

A second model (Model 2) was further adjusted for the hormone-related risk factors: the use of oral contraceptive (yes, no), the use of menopausal hormone therapy (yes, no), menopausal status (pre-menopause, perimenopause [women who did not have regular menses over the past 12 months or who reported menses but were no longer menstruating at the time of recruitment], postmenopause, artificial menopause), age at menarche (≤12 years, 13–14 years, ≥15 years), mother's breast cancer history (yes, no, missing), breast-feeding (yes, no, missing) and age of first full-term pregnancy (no pregnancy, <22 years, 22–23 years, 24–26 years, ≥27 years, missing).

To disentangle the effects due to exposure to food contaminants from those due to the overall quality of the diet, models were further adjusted for the consumption of the food groups that mainly contributed to dioxin and/or PCB intake (dairy products and fish and shellfish), for lipids and then for adherence to an healthy dietary pattern or an unhealthy Western dietary pattern derived from Principal Component Analysis using proc princomp in SAS.

2.6.1. Subgroup analyses

To investigate potential geographic differences, we ran separate models by country and then we pooled hazard ratios for the continuous intake from each country using a random-effect model with inverse variance weighting. Heterogeneity across countries was assessed with I^2 tests. We also investigated a potentially differential relationship according to estrogen receptor status of the tumor ER– vs. ER+ (i.e. for ER + cox model, participants with ER- or unknown estrogen receptor status were censored). Subgroup analyses were also performed by the median follow-up time (14.9 years): (<14.9 years vs. ≥ 14.9 years) to explore long-term effects: in a first analysis, the follow-up was stopped at the median and individuals with a longer follow-up were censored and in the second analysis, we excluded the participants with follow-up shorter than 14.9 years. We also stratified models by menopausal status (excluding perimenopausal status and surgical operation), since some dioxins and PCBs may mimic hormonal effects, and by BMI, since body fat is a reservoir of PCB and some dioxins. Subgroup analyses were also performed using a combination of menopausal status (premenopausal and postmenopausal) and BMI (<25 and ≥ 25 kg/m^2). Finally, we performed stratified analyses based on the median consumption of the food groups identified as the main contributors of dietary intake of dioxins/PCBs, and on the median of adherence to a healthy dietary pattern based on Principal Component Analysis.

2.6.2. Sensitivity analyses

Further analyses based on model 2, using occurrence data collected over different time periods (2005–2018 and 2010–2018) were conducted to test the potential impact of increasing quality of occurrence data and data reporting. The year 2005 refers to 3 years after EFSA creation and 2010 to the year of data collection harmonization. These analyses also allowed testing the impact of the decreasing occurrence level over time. In order to avoid reverse causation bias, breast cancer cases diagnosed during the first five years of follow-up were excluded. A contaminant residual (energy-adjusted) model was used to remove variation due to total energy intake (Willett et al., 1997): dioxin and PCB intakes were regressed on total energy intakes, then residuals from the regression were used as an intake variable.

A complete case set (i.e., excluding participants with missing data on covariates) was conducted as sensitivity analyses to test various handling missing variable effects.

All tests were two sided and we considered $P < 0.05$ to be statistically significant. SAS version 9.4 (SAS Institute) and R version 3.6.2 were used for the analyses.

3. Results

3.1. Characteristics of the study population

A total of 318,607 women were included in this study. The mean ± SD age at baseline was 50.7 ± 9.7 years. Median follow-up was 14.9 years (IQR = 13.5–16.4). Overall, 13,241 incident invasive breast cancers were diagnosed and validated, of which 7,452 ER + and 1,677 ER- breast cancers, while ER status was unknown for 4,112 cases. Baseline characteristics of the study population, overall and by quintile groups of dietary intake of the sum of dioxins and DL-PCBs (dioxins + DL- PCBs), are described in Table 1. Compared with participants in the lowest quintile, those in the highest quintile group of dioxin/DL-PCBs intake tended to be older, more educated, more frequently report a history of breast cancer for their mother, use of menopausal hormone therapy, and oral contraceptive use. Baseline characteristics for quintile groups of dietary intake of dioxins only, DL-PCBs only, and NDL-PCBs, as well as for cases and non-cases, are described in Supplementary Tables S6, S7, S8, and S9.

3.2. Dioxins and PCBs intakes in EPIC

In the whole EPIC population, median (IQR) dietary intakes for dioxins, DL-PCBs, dioxins + DL-PCBs, and NDL-PCBs were 19 (13.9–25.5) pg TEQ/day, 40.1 (28.6–56.4) pg TEQ/day, 60.1 (44.1–82.0) pg TEQ/day, and 572 (319–732) ng/day, respectively (Table 2). The food groups that contributed the most to dietary intakes of dioxins according to the middle bound scenario were dairy products (38.1%). Similarly, for both dioxins + DL-PCBs and DL-PCBs, dairy products represented the main contributor (32% and 29.2%, respectively). For NDL-PCBs, fish and shellfish were the main food contributor (41.5%) (Table 3).

3.3. Relationship between estimated intakes of dioxins and PCBs and breast cancer risk

We found no statistically significant association between dietary intakes of dioxins and/or PCBs and breast cancer risk. In model 1, which was adjusted for socio-demographic factors, dietary intake of dioxins, dioxins + DL-PCBs, DL-PCBs, and NDL-PCBs were not associated with breast cancer incidence, with the following hazard ratios (HRs) and 95% confidence intervals for an increment of 1 SD: $HR_{dioxins} = 1.00$ (0.98 to 1.02), $HR_{dioxins+DL\text{-}PCB} = 1.01$ (0.98 to 1.03), $HR_{DL\text{-}PCB} = 1.01$ (0.99 to 1.03), and $HR_{NDL\text{-}PCB} = 1.01$ (0.99 to 1.03), respectively (Table 4). Similarly, there was no statistically significant association in model 2, which was further adjusted for hormonal and reproductive factors, with $HR_{dioxins} = 1.00$ (0.98 to 1.02), $HR_{dioxins+DL\text{-}PCB} = 1.01$ (0.98 to 1.03), $HR_{DL\text{-}PCB} = 1.01$ (0.98 to 1.03), and $HR_{NDL\text{-}PCB} = 1.01$ (0.99 to 1.03) (Table 4). We also found no statistically significant association when analysing the data grouped in quintiles of dietary intakes of dioxins, dioxins + DL-PCBs, DL-PCBs, or NDL-PCBs (Table 4). After adjusting for the main food contributors (fish and shellfish, dairy products), and for adherence to a Western or a healthy dietary pattern, the results remained virtually unchanged (Table 5).

Cause-specific Cox regression analysis yielded no statistically significant association between dietary intakes of dioxins, dioxins + DL-PCBs, DL-PCBs, and NDL-PCBs and the risks of ER + or ER- breast cancer (Supplementary Table S10).

When model 2 was run separately by country, we also found no statistically significant association between dietary intakes of dioxins or/and PCBs and breast cancer risk, except for Spain where HRs were $HR_{Dioxins\text{-}DL\text{-}PCB} = 1.10$ (1.00 to 1.20), $HR_{DL\text{-}PCB} = 1.11$ (1.01 to 1.21), and $HR_{NDL\text{-}PCB} = 1.20$ (1.02 to 1.42) (Fig. 1). Nevertheless, there was no statistically significant heterogeneity across countries ($I^2 = 4.3\%$, $P_{dioxins} = 0.4$; $I^2 = 39.4\%$, $P_{dioxins\text{-}DL\text{-}PCB} = 0.2$; $I^2 = 32.7$ %$P_{DL\text{-}PCB} = 0.1$, and $I^2 = 3.9\%$, $P_{NDL\text{-}PCB} = 0.4$). When running all other stratified analyses by menopausal status, BMI, median follow-up time, fish or dairy

Table 1
Baseline characteristics of study participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort for the overall population and by quintile groups of dietary intake of dioxins and dioxin-like PCBs.

	All N = 318,607	**Q1 N = 63,721**	**Q2 N = 63,722**	**Q3 N = 63,721**	**Q4 N = 63,722**	**Q5 N = 63,721**
Dioxins and DL-PCBs (pg TEQ/day, min–max)	**0.8–653**	**0.8–40.8**	**80.8–53.5**	**53.5–67.6**	**67.6–88.4**	**88.4–653**
Age at recruitment (year) (mean ± SD)	50.7 ± 9.7	49.7 ± 9.8	50.2 ± 9.6	50.6 ± 9.6	51.1 ± 9.6	52 ± 9.5
Kcal without alcohol (kcal/day) (mean ± SD)	1879.2 ± 529.8	1524.8 ± 407.7	1763.4 ± 440.5	1899.6 ± 471.9	2009.6 ± 498	2198.6 ± 560.3
Alcohol (g/day) (mean ± SD)	8.1 ± 11.7	7 ± 11.3	8.1 ± 11.9	8.3 ± 11.6	8.4 ± 11.6	8.8 ± 12.2
Total food intake (kg/day) (mean ± SD)	2,6 ± 0,9	2.1 ± 0.8	2.4 ± 0.9	2.6 ± 0.9	2.8 ± 0.8	3.2 ± 0.9
Vegetable (g/day) (mean ± SD)	208.5 ± 131.3	138.1 ± 95.7	169.6 ± 98.1	195.2 ± 103.6	229 ± 115.3	310.6 ± 161.1
Fruits, nuts and seeds (g/day) (mean ± SD)	244.8 ± 177.5	186.3 ± 147.2	221.8 ± 158.3	244.7 ± 170.4	265.7 ± 178.6	305.8 ± 204.3
Dairy products (g/day) (mean ± SD)	328.1 ± 221.9	218.3 ± 171.5	281.9 ± 192.7	331.7 ± 210.5	373.3 ± 221.5	435 ± 242
Cereals and cereal products (g/day) (mean ± SD)	204.2 ± 100.1	186.4 ± 90.9	202.7 ± 96.9	207.5 ± 98.5	210.2 ± 101.4	213.9 ± 109.6
Meat and meat products (g/day) (mean ± SD)	88.2 ± 52.6	66.7 ± 40.2	81.4 ± 43.9	88.2 ± 48.5	94.9 ± 53.3	109.8 ± 63.7
Fish and shellfish (g/day) (mean ± SD)	38.2 ± 36.8	25.6 ± 24.3	33.9 ± 29.9	38.2 ± 34	41.5 ± 38.1	52 ± 47.9
Fat products (g/day) (mean ± SD)	23.5 ± 14.4	20.8 ± 12.4	23.8 ± 13.5	24.6 ± 14.6	24.5 ± 15.3	23.6 ± 15.7
Healthy dietary pattern (mean ± SD)	−0.3 ± 1.2	−1.2 ± 0.9	−0.6 ± 0.9	−0.3 ± 1	0 ± 1.1	0.7 ± 1.3
Western dietary Pattern (mean ± SD)	−0.14 ± 1.2	−0.2 ± 1.1	−0.1 ± 1.1	−0.1 ± 1.2	−0.1 ± 1.2	−0.3 ± 1.3
Smoking status (%)						
Never	54.94	52.12	52.3	54.19	56.69	59.41
Former	23.35	21.23	22.95	23.72	24.33	24.5
Smoker	19.5	24.85	23.08	20.13	16.61	12.85
Unknown	2.21	1.8	1.67	1.96	2.37	3.24
Education degree (%)						
None	3.54	5.88	3.96	3.16	2.64	2.07
Primary school	23.02	29.27	26.24	23.16	19.47	16.97
Secondary school	28.09	21.5	23.59	26.81	31.03	37.5
Technical/profes	22.32	25.43	25.67	23.96	20.81	15.72
Longer education	23.03	17.93	20.54	22.92	26.04	27.74
Combined total physical activity index (%)						
Inactive	12.62	12.73	12.8	12.3	12.27	12.99
Moderately inactive	31.9	26.18	28.18	30.23	33.19	41.72
Moderately active	40.94	37.54	43.74	44.38	42.53	36.49
Active	8.9	7.48	9.29	9.93	10.01	7.8
Missing	5.64	16.07	5.99	3.15	1.99	1
Mother breast cancer (%)						
No	44.53	32.78	39.49	43.36	48.67	58.37
Yes	2.69	2.17	2.32	2.52	2.83	3.6
missing	52.78	65.06	58.19	54.12	48.5	38.02
Body Mass Index (%)						
BMI < 18,5	2.06	2.54	2	1.82	1.96	2
18,5 < BMI < 25	57.87	59.45	56.86	56.54	57.43	59.05
25 < BMI < 30	28.58	26.91	29.15	29.77	29.17	27.88
BMI ≥ 30	11.49	11.1	11.99	11.87	11.43	11.07
Menopausal status (%)						
Premenopausal	34.73	43.72	36.94	33.35	31.07	28.59
Postmenopausal	42.79	36.02	41.94	44.55	45.9	45.54
Perimenopausal	19.71	18.17	18.53	19.15	19.97	22.7
Surgical postmen	2.77	2.09	2.59	2.94	3.06	3.17
Hormone use during menopause (%)						
No	68.03	69.88	68.89	68.65	67.28	65.46
Yes	25.19	19.54	23.9	25.63	27.67	29.22
Missing	6.78	10.58	7.22	5.73	5.05	5.32
Age at menarche (%)						
≤12 years	35.26	32.8	34.4	35.22	35.7	38.2
13–14 years	46.12	44.34	46.19	46.78	46.99	46.29
≥15 years	15.25	14.8	15.92	15.72	15.57	14.25
missing	3.37	8.07	3.49	2.27	1.74	1.26
Ever pill use (%)						
No	37.91	32.84	36.63	38.98	40.18	40.89
Yes	62.09	67.16	63.37	61.02	59.82	59.11
Breastfeeding (%)						
No	25.14	25.44	23.35	23.72	25.5	27.71
Yes	63.83	63.22	65.55	64.74	63.16	62.49
Missing	11.02	11.34	11.10	11.54	11.34	9.81
Age at first full term pregnancy (%)						
No pregnancy	14.69	19.44	15.55	14.26	13.06	11.16
First pregnancy at < 22 years	17.89	17.77	18.06	17.84	17.52	18.25
First pregnancy at 22–24 years	15.35	13.37	14.89	15.33	16.06	17.12
First pregnancy at 24-<27 years	22.64	18.82	22.14	23.37	24.23	24.64
First pregnancy at >=27 years	24.79	21.49	25.31	26.29	26.18	24.66
missing	4.64	9.12	4.05	2.91	2.95	4.18

Table 2
Estimated dietary intake of dioxins and PCBs according to the middle bound scenario in the different EPIC countries.

	Non-cases	Incident breast cancer cases	Overall	Dietary intake (median (IQR)) (Middle Bound scenario)			
	N = 303,772 (%)	N = 14,934 (%)	N = 318,706 (%)	Dioxins (pg TEQ/day)	Dioxins/DL-PCB (pg TEQ/day)	DL-PCB (pg TEQ/day)	6NDL-PCB (ng/day)
France	64,079 (20.98)	3,309 (24.99)	67,388 (21.15)	26.3 (19.6–34.1)	80.4 (59.9–104.7)	53.2 (39.4–69.9)	561 (360 – 1,018)
Italy	29,302 (9.60)	1,197 (9.04)	30,499 (9.57)	17.8 (14.1–22.5)	48.4 (38–61)	30.2 (23.4–38.4)	285 (232 – 344)
Spain	24,195 (7.92)	649 (4.90)	24,844 (7.80)	19.9 (14.4–26.4)	54.7 (39.5–74.5)	33.9 (23.9–48.1)	412 (308 – 576)
United Kingdom	50,686 (16.60)	1,872 (14.14)	52,558 (16.50)	17.7 (12.8–23.3)	71.6 (52.2–95.2)	52.4 (37.1–72.8)	545 (406 – 710)
The Netherlands	25,863 (8.47)	1,043 (7.88)	26,906 (8.44)	17.4 (13.7–21.6)	64.1 (50.7–79.9)	45.8 (35.6–58)	330 (268 – 430)
Germany	26,562 (8.70)	812 (6.13)	27,374 (8.59)	15.8 (12–21.3)	53.1 (40.1–70.7)	36.6 (27.3–48.8)	327 (250 – 436)
Sweden	25,054 (8.20)	1,307 (9.87)	26,361 (8.27)	14.1 (9.9–20.8)	53.6 (39.3–73.6)	38.4 (27.5–52.6)	1,120 (543 – 2,118)
Denmark	26,851 (8.79)	1,853 (13.99)	28,704 (9.01)	19.9 (15.9–24.8)	50.6 (40.3–63.1)	30.2 (23.8–38.2)	573 (400 – 1,034)
Norway	32,774 (10.73)	1,199 (9.06)	33,973 (10.66)	17.4 (13.2–22.7)	50.1 (37.8–66)	32.3 (24.1–43.1)	519 (394 – 676)
Overall	303,772 (100)	14,934 (100)	**318,706** (100)	19 (13.9–25.5)	60.1 (44.1–82.0)	40.1 (28.6–56.4)	572 (319 – 732)

Table 3
Percentage of contribution to dioxins and PCBs dietary intake for the main food groups in EPIC.

Epic Food Classification	Middle Bound				Lower Bound			
	Dioxins, DL-PCBs (%)	Dioxins (%)	DL-PCBs (%)	NDL-PCBs (%)	Dioxins, DL-PCBs (%)	Dioxins (%)	DL-PCBs (%)	NDL-PCBs (%)
Potatoes and other tubers	3.5	3.8	3.3	1.6	2.9	4.9	2.4	3
Vegetables	20.1	3.4	27.9	9.4	24	3.2	30.1	0.2
Fruits, nuts and seeds	4.1	6.1	3.1	3.1	0.7	1.1	0.6	0.2
Dairy products	32	38.1	29.2	19.1	35	49.5	30.7	5.6
Cereal and cereal products	1.5	0.7	1.8	2.7	0.3	0	0.3	4
Meat and meat products	15.9	20.8	13.6	9.4	15.3	19	14.2	5.5
Fish and shellfish	15.4	14.7	15.7	41.5	17.5	18	17.4	74.6
Fat	4.7	7.2	3.6	7.6	2.7	1.2	3.1	2.8
Others	2.8	5.2	1.8	5.6	1.6	3.1	1.2	4.1

Others: legumes, egg and egg products, sugar and confectionary, cakes, biscuits, nonalcoholic beverages, alcoholic beverages, condiment, sauces, soups, bouillons.

product intakes, adherence to a healthy dietary pattern, no considerable differences were observed compared with the main analyses (Supplementary Tables S11, S12, and S13).

Further sensitivity analyses (exclusion of breast cancer cases diagnosed during the first 5 years of follow-up, use of dioxin and/or PCB residuals derived from energy adjustment methods, use of the lower-bound scenario) did not modify the findings (Supplementary Tables S14, S15, and S16). When using food contamination data obtained during different periods of food sampling (2005–2018 and 2010–2018), the relationship between dietary intakes of dioxins, dioxins + DL-PCBs, DL-PCBs, and NDL-PCBs and breast cancer risk remained unchanged (Supplementary Table 17). The complete case analysis to handle missing data showed no differences in the results compared with the main analyses (Supplementary Table S18). When we ran model 2 for individual congeners, no statistically significant association was found with breast cancer risk (Supplementary Table S19).

4. Discussion

In this large European prospective cohort, we found no association between dioxins, DL-PCB, and NDL-PCB estimated from reported dietary intakes and breast cancer risk. The results were similar when adjusting for the consumption of food groups identified as the main contributors to dietary intakes of dioxins and PCBs, or for adherence to a healthy or a Western dietary pattern, as well as in stratified analyses per BMI, menopausal status, country, or ER status. The association also remained null when including food contamination data collected during different time periods, or when adjusting for energy using the residuals method, or with different methods to handle missing values.

This overall absence of a relationship between dietary intake of PCBs and breast cancer risk is in agreement with the results from a Swedish prospective cohort, including 36,777 participants from the general population, which observed no association between dietary intake of PCB-153 and breast cancer risk (Donat-Vargas et al., 2016). Several case-control and nested case-control studies in the general population also observed no relationship between PCBs levels measured in serum and adipose tissue and breast cancer risk (Gammon et al., 2002; Gatto et al., 2007; Holmes et al., 2014; López-Carrillo et al., 2002; Pavuk et al., 2003; Raaschou-Nielsen et al., 2005; Rubin et al., 2006; Wolff et al., 2000), whereas some others have observed an increased risk with serum levels of $\sum$ 5 PCBs in Groenland (Wielsøe et al., 2017), PCB-203 in the USA (Cohn et al., 2012), PCB-152 in China (Zhang et al., 2013), $\sum$ 35 PCBs serum levels in Mexico (Recio-Vega et al., 2011), as well as with plasma levels of $\sum$ 35 PCBs only among African-American in the USA (Millikan et al., 2000), PCB-118 and PCB-156 in Québec (Demers et al., 2002), and with the $\sum$ 16 PCBs in adipose tissue in Long Island (Muscat et al., 2003) (Cohn et al., 2012; Demers et al., 2002; Muscat et al., 2003; Recio-Vega et al., 2011; Wielsøe et al., 2017; Zhang et al., 2013). These conflicting results may be explained by the small number of breast cancer cases (<700 cases) included in most case control studies, by the different congeners or sum of congeners investigated (making the comparisons difficult), the different exposure levels, and different risk of

Table 4
Hazard ratios and 95% confidence intervals for breast cancer risk according to dietary intake of Dioxins (pg TEQ/d), Dioxins-DL-PCBs (pg TEQ/d), DL PCB (pg TEQ/d) and 6NDL PCB (ng/d) using Cox multivariate regression models in EPIC (N = 318,607) (Middle bound scenario).

Sum of dioxins		Number of cases/ non-cases	Age and center adjusted	M1	M2
Continuous + 1SD		13,241/ 305,366	1.01 (0.99 to 1.03)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
Quintiles (min–max)	Q1 (0.4–13.1)	2,244/ 61,477			
	Q2 (13.1–17.2)	2,592/ 61,130	1.04 (0.99 to 1.11)	1.03 (0.97 to 1.1)	1.03 (0.97 to 1.09)
	Q3 (17.2–21.7)	2,675/ 61,046	1.02 (0.96 to 1.08)	1.01 (0.95 to 1.07)	1.00 (0.94 to 1.06)
	Q4 (21.7–28.0)	2,754/ 60,968	1.01 (0.95 to 1.07)	1.00 (0.93 to 1.06)	0.99 (0.93 to 1.05)
	Q5 (28.0–250.8)	2,976/ 60,745	1.04 (0.98 to 1.11)	1.01 (0.95 to 1.09)	1.01 (0.94 to 1.08)
P-trend			0.5	0.8	0.7
Sum of dioxins/ DL-PCB					
Continuous + 1SD		13,241/ 305,366	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.03)	1.00 (0.98 to 1.03)
Quintiles	Q1 (0.8–40.1)	2,523/ 61,198			
	Q2 (40.1–53.5)	2,525/ 61,197	0.96 (0.91 to 1.02)	0.95 (0.9 to 1)	0.95 (0.89 to 1)
	Q3 (53.5–67.6)	2,654/ 61,067	0.99 (0.94 to 1.05)	0.98 (0.92 to 1.03)	0.97 (0.92 to 1.03)
	Q4 (67.6–88.4)	2,663/ 61,059	0.98 (0.93 to 1.04)	0.96 (0.9 to 1.02)	0.95 (0.9 to 1.01)
	Q5 (88.4–653.0)	2,876/ 60,845	1.02 (0.96 to 1.08)	0.99 (0.92 to 1.05)	0.98 (0.92 to 1.05)
P-trend			0.4	0.8	0.7
Sum of DL-PCB					
Continuous + 1SD		13,241/ 305,366	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.03)
Quintiles	Q1 (0.3–26.3)	2,586/ 61,135			
	Q2 (26.3–35.3)	2,616/ 61,106	1.00 (0.95 to 1.05)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)
	Q3 (35.3–45.6)	2,600/ 61,121	0.99 (0.94 to 1.05)	0.97 (0.92 to 1.03)	0.97 (0.91 to 1.02)
	Q4 (45.6–61.4)	2,633/ 61,089	0.99 (0.94 to 1.05)	0.97 (0.91 to 1.03)	0.96 (0.91 to 1.03)
	Q5 (61.4–452-8)	2,806/ 60,915		0.99 (0.93	0.99 (0.93
			1.03 (0.97 to 1.09)	to 1.06)	to 1.06)
P-trend			0.5	0.7	0.6
Sum of NDL-PCB					
Continuous + 1SD		13,241/ 305,366	1.02 (1 to 1.04)	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)
Quintiles	Q1 (39.6–295.5)	2,508/ 61,213			
	Q2 (295.5–395.2)	2,523/ 61,197	0.98 (0.92 to 1.03)	0.96 (0.9 to 1.02)	0.96 (0.9 to 1.01)
	Q3 (395.2–542.0)	2,675/ 61,048	1.03 (0.97 to 1.09)	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)
	Q4 (542.0–838.0.2)	2,623/ 61,099	1.00 (0.94 to 1.06)	0.96 (0.9 to 1.02)	0.96 (0.9 to 1.02)
	Q5 (838.2–29,723)	2,912/ 60,809	1.01 (0.95 to 1.07)	0.95 (0.89 to 1.02)	0.95 (0.89 to 1.02)
P-trend			0.7	0.2	0.2

1 sd (Dioxins) = 10 pg TEQ.
1 sd (Dioxins DL PCB) = 32.2 pg TEQ.
1 Sd (DL PCB) = 24 pg TEQ.
1 sd (6 NDL PCB) = 676 429 pg = 676 ng.
Model 1 (M1) was stratified on age at baseline and center and adjusted for BMI, smoking status, education level, energy without alcohol, alcohol intake, physical activity. Age was also used as time-scale.
Model 2 (M2) was M1 further adjusted for oral contraceptive use, use of menopausal hormone therapy, menopausal status, age of menarche, mother breast cancer history and age of first full term pregnancy.

disease progression when concentrations in biological samples are collected near the time of diagnosis. systematic review (mainly based on case-control studies and occupational exposure) found 29 studies showing no association between PCBs exposure and breast cancer risk and 19 studies with a positive association (Wan et al., 2021). A meta-analysis assessed exposure limited to specific congeners, and identified an increased risk of breast cancer for higher plasma/adipose tissue levels of three NDL-PCBs (99,183,187), but no relationship was observed for three NDL-PCBs (118,138,170) or DL-PCB-180 (Leng et al., 2016). In our analyses by individual congener (Supplementary Table S14), none of congeners was significantly associated with breast cancer risk. Finally, two meta-analyses found no association between total PCBs measured in the serum, plasma, or adipose tissue and breast cancer risk (Zani et al., 2013; Zhang et al., 2015).

The evidence available on the association between dioxins and breast cancer risk is consistent with our findings. A study conducted in E3N cohort, which represents the French component of EPIC and which used contamination data published in 2000 from the French High Council for Public Health, highlighted no association between dietary intake of dioxins and breast cancer risk among 63,830 participants (Danjou et al., 2015). Additionally, results from a *meta*-analysis showed that TCDD exposure was not associated with breast cancer risk (analyses based on 3 studies) (Xu et al., 2016).

4.1. Strengths and limitations

Several limitations should be taken into account when interpreting the results from the present study. Dietary exposure was investigated

Table 5
Hazard ratios and 95% confidence intervals for breast cancer risk according to dietary intake of Dioxins (pg TEQ/d), Dioxins-DL-PCBs (pg TEQ/d), DL PCB (pg TEQ/d) and 6NDL PCB (ng/d) using Cox multivariate regression models in EPIC (N = 318,607) adjusting for the main food contributors to dioxins and PCBs dietary intake (Middle bound scenario).

Sum of dioxins		No of cases/non-cases	M2 + lipids	M2 + dairy products	M2 + Fish and shellfish	M2 + Healthy dietary pattern	M2 + Western dietary pattern
Continuous + 1SD		13,241/305,366	1.00 (0.98 to 1.02)	1.00 (0.97 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
Quintiles	Q1 (0.4–13.1)	2,244/61,477					
	Q2 (13.1–17.2)	2,592/61,130	1.03 (0.97 to 1.09)	1.03 (0.97 to 1.09)	1.03 (0.97 to 1.09)	1.03 (0.97 to 1.09)	1.03 (0.97 to 1.09)
	Q3 (17.2–21.7)	2,675/61,046	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)
	Q4 (21.7–28.0)	2,754/60,968	0.99 (0.93 to 1.05)	0.98 (0.92 to 1.04)	0.99 (0.92 to 1.05)	0.99 (0.93 to 1.05)	0.98 (0.92 to 1.05)
	Q5 (28.0–250.8)	2,976/60,745	1.00 (0.94 to 1.08)	0.99 (0.93 to 1.06)	1.00 (0.93 to 1.07)	1.00 (0.94 to 1.07)	1.00 (0.94 to 1.07)
P-trend			0.6	0.4	0.5	0.6	0.6
Sum of dioxins/DL-PCB							
Continuous + 1SD		13,241/305,366	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.03)
Quintiles	Q1 (0.8–40.1)	2,523/61,198					
	Q2 (40.1–53.5)	2,525/61,197	0.95 (0.89 to 1)	0.94 (0.89 to 1)	0.94 (0.89 to 1)	0.94 (0.89 to 1)	0.95 (0.89 to 1)
	Q3 (53.5–67.6)	2,654/61,067	0.97 (0.92 to 1.03)	0.97 (0.91 to 1.03)	0.97 (0.92 to 1.03)	0.97 (0.92 to 1.03)	0.97 (0.92 to 1.03)
	Q4 (67.6–88.4)	2,663/61,059	0.95 (0.9 to 1.01)	0.95 (0.89 to 1.01)	0.95 (0.89 to 1.01)	0.95 (0.9 to 1.01)	0.96 (0.9 to 1.02)
	Q5 (88.4–653.0)	2,876/60,845	0.98 (0.92 to 1.05)	0.97 (0.91 to 1.04)	0.98 (0.91 to 1.04)	0.98 (0.91 to 1.04)	0.99 (0.93 to 1.05)
P-trend			0.7	0.5	0.6	0.6	0.9
Sum of DL-PCB							
Continuous + 1SD		13,241/305,366	1.01 (0.98 to 1.03)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.03)	1.01 (0.99 to 1.03)
Quintiles	Q1 (0.3–26.3)	2,586/61,135					
	Q2 (26.3–35.3)	2,616/61,106	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)
	Q3 (35.3–45.6)	2,600/61,121	0.97 (0.91 to 1.02)	0.96 (0.91 to 1.02)	0.96 (0.91 to 1.02)	0.96 (0.91 to 1.02)	0.97 (0.91 to 1.03)
	Q4 (45.6–61.4)	2,633/61,089	0.96 (0.91 to 1.02)	0.96 (0.9 to 1.02)	0.96 (0.9 to 1.02)	0.96 (0.9 to 1.02)	0.97 (0.91 to 1.03)
	Q5 (61.4–452-8)	2,806/60,915	0.99 (0.93 to 1.06)	0.98 (0.92 to 1.05)	0.98 (0.92 to 1.05)	0.98 (0.92 to 1.05)	1.00 (0.93 to 1.07)
P-trend			0.6	0.5	0.5	0.5	0.8
Sum of NDL-PCB							
Continuous + 1SD		13,241/305,366	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.03)
Quintiles	Q1 (39.6–295.5)	2,508/61,213					
	Q2 (295.5–395.2)	2,523/61,197	0.96 (0.9 to 1.01)	0.96 (0.9 to 1.01)	0.95 (0.9 to 1.01)	0.95 (0.9 to 1.01)	0.96 (0.9 to 1.01)
	Q3 (395.2–542.0)	2,675/61,048	0.99 (0.94 to 1.06)	1.00 (0.94 to 1.06)	0.99 (0.93 to 1.06)	0.99 (0.93 to 1.06)	1.00 (0.94 to 1.06)
	Q4 (542.0–838.0.2)	2,623/61,099	0.96 (0.9 to 1.02)	0.96 (0.9 to 1.02)	0.95 (0.89 to 1.02)	0.95 (0.89 to 1.02)	0.96 (0.9 to 1.03)
	Q5 (838.2–29,723)	2,912/60,809	0.95 (0.89 to 1.02)	0.95 (0.89 to 1.02)	0.94 (0.88 to 1.01)	0.95 (0.88 to 1.01)	0.96 (0.89 to 1.02)
P-trend			0.2	0.2	0.2	0.2	0.3

1 sd (Dioxins) = 10 pg TEQ.
1 sd (Dioxins DL PCB) = 32.2 pg TEQ.
1 Sd (DL PCB) = 24 pg TEQ.
1 sd (6 NDL PCB) = 676 429 pg = 676 ng.
Model 2 (M2) was stratified on age at baseline and center and adjusted for BMI, smoking status, education level, energy without alcohol, alcohol intake, physical activity, oral contraceptive use, use of menopausal hormone therapy, menopausal status, age of menarche, mother breast cancer history and age of first full term pregnancy. Age was also used as time-scale.

since it is not feasible to measure serum concentrations in such a large population. Food consumption data were collected through one food survey at baseline, which assumes constant dietary habits. Even if questionnaires were validated using comparisons with multiple 24 h-recalls (Supplementary Material 1), it has to be acknowledged that this tool is subject to measurement errors. The measurement errors are mainly due to difficulties in recalling and estimating the average food intakes over a long term period of time (memory bias) and reported intakes may be influenced by psychological factors such as social desirability. It is considered that the dietary measurement error is the result of the sum of measurement error related to the true intake and random variation, each of them having opposite effects on the estimate. Indeed participants with high dietary intake tend to underport their intakes, while participants with low dietary intakes tend to overreport ("flattened-slope effect"). This brings to inflation of the estimated HR. Conversely, the random variation, which can be considered non-differential measurement error, tends to attenuate the estimated HR. It has been reported by previous authors that this non-differential error plays more important role in the overall bias (Thiébaut et al., 2007). This is why in prospective studies, such as the present study, dietary

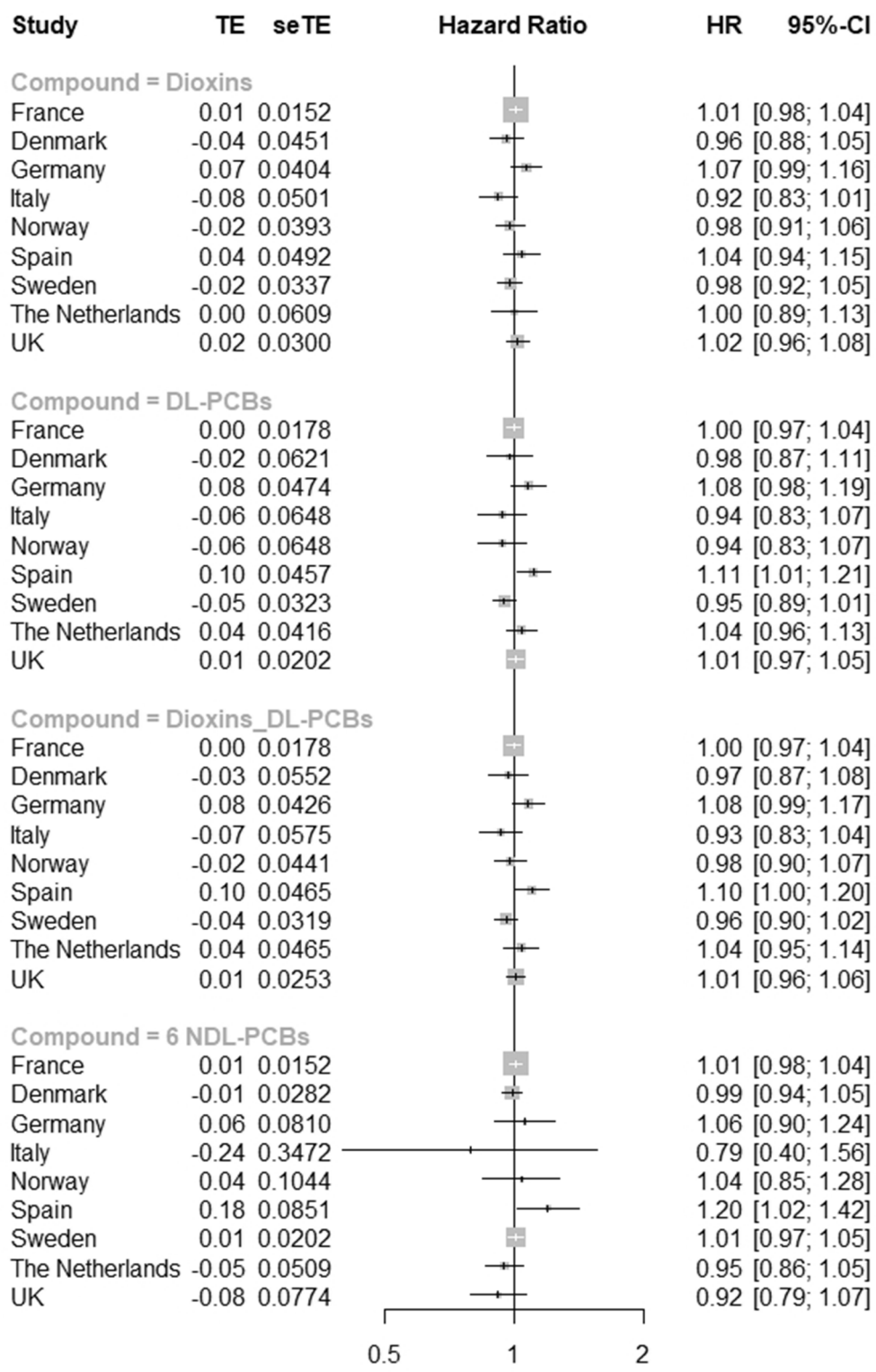

Fig. 1. Forest plot presenting the hazard Ratios (HRs) and 95% confidence intervals (Cis) for an increment of + 1 standard deviation in dietary intakes of dioxins and PCBs in relation to breast cancer risk; stratified analyses by EPIC country (n = 318,607). Heterogeneity across the countries was estimated using random-effect meta-analysis model: $I^2 = 4.3\%$, $P_{dioxins} = 0.4$; $I^2 = 39.4\%$, Pdioxins-DL-PCB = 0.2; $I^2 = 32.7$ %$P_{DL\text{-}PCB} = 0.1$, and $I^2 = 3.9\%$, $P_{NDL\text{-}PCB} = 0.4$. **Legend 1:** The analyses were stratified on age and center and adjusted for BMI, smoking status, education level, energy without alcohol, alcohol intake, physical activity, use of oral contraceptives, use of menopausal hormone therapy, menopausal status, age of menarche, mother's breast cancer history, and age at first full-term pregnancy (as in model 2). TE = estimated effect; seTE = standard error of estimate.

measurement error are considered non-differential and lead to a global attenuation of the final association with the outcome of interest. Additionally, there was a time gap between the available food contamination data, collected between 2000 and 2018, and consumption data, collected in the 1990's, which may lead to exposure misclassification. Dioxins and PCBs are persistent contaminants with long half-lives, limiting wide variations in contaminations over the years. Indeed, dioxins and PCBs food contamination levels tend to decrease slowly over time, thus limiting the impact of timing on dietary intake estimations. As such, our sensitivity analyses using food contamination data collected at different time periods showed similar results. Moreover, it should be noted that dietary data were collected following different methods and validated by the different centers included in the EPIC cohort. Nevertheless, validation of the estimated intakes of dioxins and PCBs in the EPIC cohort by comparisons with measurements of internal biomarkers of exposure in EPIC participants would have been of great value. However, it should be underlined that the use of human biomonitoring studies can be more complicated to interpret since their concentrations

can be influenced by between-individual variation (e.g. different capacities to metabolize the contaminants, variations regarding to the fat mass, weight changes) and the these studies do not allow to discriminate the contribution of different sources of exposure (Vaclavik et al., 2006). Geographical differences in food contamination levels have not been taken into account in the exposure estimation, which may lead to an over-estimation or an under-estimation of exposure. However, it is not possible to know the origin of the consumed food products, thus we assumed an EU food market where not only the products from the home country are consumed. Moreover, dioxins and PCBs are ubiquitous in the environment which may limit the geographic heterogeneities. The EPIC cohort is not nationally representative of the general population and participants may be more health conscious, which could question the generalizability of these findings. Finally, potential residual confounding cannot be ruled out, which may include dioxins and PCB exposure from other sources than diet, co-exposure to other chemicals, or population genetic variability. For the time being, information concerning PCBs and dioxins exposure due to air contamination is not available for the entire EPIC cohort that is why we could not estimate combined exposure.

This study also presents several strengths. This is the largest prospective study to date on dietary exposure to dioxins and PCBs in relation to breast cancer risk, including the highest number of validated breast cancer cases (n = 13,241). This important population size allowed strong statistical power to detect low effects and to conduct numerous sensitivity and stratified analyses, underlying the robustness of our results. Access to histologic characteristics of the tumors allowed us to perform separate analyses based on tumor ER status. The availability of 14.9 years of median follow-up enabled to take into account long-term effects of dietary exposure to PCBs and dioxins. This is the first study that used detailed and comprehensive food contamination and food consumption databases covering different dietary patterns in Europe. Indeed, EPIC food consumption data reflect a broad diversity of dietary patterns across Europe. Additionally, our estimations of dietary exposure to dioxins and PCB are in range with the other dietary assessment studies (Supplementary Table S20). Finally, the EFSA dataset contained >500,000 analytical results for individual dioxins and PCBs, which improved representativeness of European food contamination levels.

5. Conclusions

In conclusion, this study does not support the hypothesis that dietary intakes of dioxins and/or PCBs increase the risk of female breast cancer in the European general population. Nevertheless, these results need to be replicated in other populations. Moreover, we cannot rule out an association with the risk of breast cancer in highly exposed populations or due to exposure during sensitive time periods (perinatal, puberty, pregnancy…), or risk associated with exposure to dioxins and PCBs in combination with other chemicals.

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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Contributors

TF, FRM, IH conceived the study and defined the analytical strategy. TF, FRM, IH, CC, GN, ZSH participated to the data cleaning process for occurrence data and participated to the construction of the dietary exposure database. TF performed statistical analyses and provided preliminary interpretation of findings. TF and the writing group (IH, MK, FRM, CC, GN) drafted the manuscript. All authors critically interpreted the results, revised the manuscript, provided relevant intellectual input, and read and approved the final manuscript.

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Data sharing

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of the International Agency for Research on Cancer (IARC), WHO, and the EPIC centres. The primary responsibility for accessing the data, obtained in the frame of the present publication, belongs to the EPIC centres that provided them. The use of a random sample of anonymised data from the EPIC study can be requested by contacting epic@iarc.fr . The request will then be passed on to members of the EPIC Steering Committee for deliberation and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107213.

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