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Chronic long-term exposure to cadmium air pollution and breast cancer risk in the French E3N cohort

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Abbreviations: AEI: annual exposure index; BMI: body mass index; CIs: confidence intervals; CIE: cumulative index of exposure; CNIL: commission for data protection and privacy; ER: estrogen receptor; EPIC: European Prospective Investigation into Cancer and Nutrition; EMEP: European Monitoring and Evaluation Program; GIS: geographic information system; HRT: hormone replacement therapy; IARC: International Agency for Research on Cancer; IGN: National Geographic Institute; ORs: odds ratios; PR: progesterone receptor; OMINEA: Organization and Methods of the National Inventories of the Atmospheric Releases; SD: standard deviation; wκ: weighted kappa.

Key words: airborne cadmium, geographic information system, hormone receptor status, breast cancer risk,

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Novelty and Impact

Epidemiological studies suggested a role of cadmium in breast cancer risk, but findings have been inconsistent. In this prospective cohort study, airborne cadmium was not significantly associated with the overall risk of breast cancer. However, statistically significant inverse associations were found for ER- breast tumors, but the possibility of false positive findings as a result of multiple testing could not be excluded. This study highlights a paradoxical effect of both carcinogenicity and anti-carcinogenicity of cadmium.

ABSTRACT

Cadmium, due to its estrogen like activity, has been suspected to increase the risk of breast cancer, however epidemiological studies have reported inconsistent findings. We conducted a case-control study (4,059 cases and 4,059 matched controls) nested within the E3N French cohort study to estimate the risk of breast cancer associated with long-term exposure to airborne cadmium pollution, and its effect according to molecular subtype of breast cancer (estrogen receptor negative/positive (ER-/ER+) and progesterone receptor negative/ positive (PR-/PR+)). Atmospheric exposure to cadmium was assessed using a Geographic Information System (GIS) based metric, which included subject's residence-to-cadmium source distance, wind direction, exposure duration and stack height. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. Overall, there was no significant association between cumulative dose of airborne cadmium exposure and the risk of overall, premenopausal and postmenopausal breast cancer. However, by ER and PR status, inverse associations were observed for ER- ($OR_{Q5\ vs\ Q1}$ = 0.63; 95% CI: 0.41-0.95, P trend = 0.043) and for ER-PR- breast tumors ($OR_{Q4\ vs\ Q1}$ = 0.62; 95% CI: 0.40-0.95, $OR_{Q5\ vs\ Q1}$ = 0.68; 95% CI: 0.42-1.07, P trend = 0.088). Our study provides no evidence of an

association between exposure to cadmium and risk of breast cancer overall, but suggests that cadmium might be related to a decreased risk of ER- and ER-PR- breast tumors. These observations and other possible effects linked to hormone receptor status warrant further investigations.

INTRODUCTION

Ambient air pollution is one of the leading contributors to global burden of disease, and its contribution remained relatively stable from 1990 to 2015 [1]. Evidence from the International Agency for Research on Cancer (IARC) and epidemiological studies have shown that long term exposure to ambient air pollution was associated with higher risk of cardiovascular, respiratory diseases and cancer [2,3]. Of those, cadmium, due to its estrogenic properties, has been suspected to increase the risk of breast cancer, the most common cancer among women [4]

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Cadmium is a common environmental contaminant and a metal belonging to group IIB of the periodic table, which has an estrogen like activity [5]. Cadmium is emitted in the environment as a result of both natural and anthropogenic activities. Natural sources include volcanic activity, weathering of cadmium-containing rocks, sea spray, and cadmium deposited in soils,

sediments and landfills. The anthropogenic sources, which represent the major part of cadmium present in the atmosphere, include tobacco smoking, mining and smelting of zinc-bearing ores, combustion of fossil fuels, waste incineration and releases from tailings piles or municipal landfills [6]. Human cadmium exposure is essentially through inhalation and ingestion. Inhalation is a far smaller contributor to total cadmium body burden except for smokers, however a greater proportion of inhaled cadmium is retained by the body in comparison to ingested cadmium. Cadmium accumulates primarily in the kidneys, and its estimated biological half-life in humans is 10–35 years [7].

Overall, cadmium and its compounds have been classified by IARC as carcinogenic to humans (Group 1), reporting that there was sufficient evidence for their carcinogenicity in humans, specifically for lung cancer [8]. A growing number of case-control epidemiological studies have shown that higher urinary level of cadmium significantly increases the risk of breast cancer [9,10]. A 2016 random effect meta-analysis reported that higher level of urinary cadmium was associated with a higher risk of breast cancer, pooled odds ratio (OR) of highest versus lowest quantile was 2.24, 95% confidence interval (CI): 1.49-3.35)[11]. Similarly, a dose response meta-analysis by Larsson et al. found a pooled OR of 2.24 (95CI: 1.50-3.34) for the highest versus lowest category of urinary cadmium concentration and 1.66 (95%CI: 1.23-2.25) for each 0.5 µg/g creatinine increase of cadmium concentration [12]. However, data from the prospective Danish cohort study based on 900 incident breast cancers cases showed no association between urinary concentration of cadmium and subsequent risk of postmenopausal breast cancer [13]. Similarly, in the prospective Women's Health Initiative cohort study, Adams et al. reported no association between urinary cadmium evaluated by

creatinine-normalized urinary cadmium concentration and risk of postmenopausal breast cancer [14]. Also, the majority of studies on dietary cadmium intake did not support the hypothesis that cadmium increases the risk of breast cancer [15,16]. Nevertheless, a small number of studies found a statistically significant relationship between dietary exposure to cadmium and an increased risk of developing breast cancer [17,18].

A limited number of studies [19] have investigated the effect of long-term exposure to airborne cadmium. Furthermore, cadmium exposure and cancer relationships may also be different according to the molecular subtypes of breast cancer. The only study conducted on airborne cadmium exposure and breast cancer risk found no evidence for overall increased breast cancer risk, with the exception of an increase in risk of ER-PR- breast cancer among non-smokers ($HR_{Q5\ vs\ Q1}$ = 1.00; 95%CI: 0.9-1.2 for all cancers and $HR_{Q5\ vs\ Q1}$ = 1.60; 95%CI: 1.1-2.5 for ER-PR-) [19]. Due to these inconsistent results, further analyses of the role of long-term exposure to airborne cadmium in breast cancer etiology are needed taking into consideration the molecular subtypes.

Using data from a case-control study nested within the E3N (Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale) cohort, this study aimed to assess the risk of breast cancer associated with long-term exposure to cadmium air pollution, and to investigate whether this association differs according to molecular subtypes of breast cancer.

METHODS

The E3N cohort study

E3N is an ongoing prospective cohort study launched in 1990 to investigate the main risk factors for cancer and severe chronic conditions in women [20]. Participants were recruited between June 1990 and November 1991 among women aged 40-65 years, living in France and insured with the MGEN, a national health insurance plan covering mostly teachers. E3N is the French part of EPIC (European Prospective Investigation into Cancer and Nutrition), a vast European study coordinated by the IARC involving nearly 500,000 Europeans in 10 countries [21]. At recruitment, 98,995 E3N participants replied to a baseline self-administered questionnaire, which included information about lifestyle and reproductive factors, anthropometry, past medical history, and familial history of cancer. Follow-up questionnaires were sent approximately every 24-36 months thereafter. Until now, eleven questionnaires have been sent to the participants (participation rate at each questionnaire ~80%). Between 1994 and 1998, participants were invited to give a blood specimen. Blood samples were collected from 25,000 women and saliva samples from an additional 47,000 women. Occurrence of cancer was self-reported in each questionnaire, and a small number of cancers were further identified from the insurance files or information on causes of death obtained from the National Service on Causes of Deaths. The pathology report used to confirm the diagnosis of invasive breast cancer (our primary outcome), was obtained for 93% of declared cases and the proportion of false-positive self-reports was low (<5%). The addresses of the subjects selected for the study have been recorded at baseline questionnaire (1990) and at follow-up questionnaires 5 to 9 (years 1997, 2000, 2002, 2005, 2008 and 2011). Postal codes of participants were recorded at follow-up questionnaires 3 and 4 (1993 and 1994). In

addition, participants' place of birth (postal code and commune) was obtained from the first questionnaire and assigned an urban/rural status based on data from the closest national census [22]. Informed consent was obtained from all participants and the study was approved by the French National Commission for Data Protection and Privacy (CNIL).

The nested case control study

The present analysis is based on a nested case-control subset of the E3N cohort. The study involved 5397 histologically confirmed incident breast cancer cases, identified during the follow-up 1990 to 2008. Women were included if they had completed their home address at baseline, lived in the metropolitan French territory during the follow-up time, and had never been diagnosis with any cancer at baseline. Women with phyllodes tumors or tumors with missing morphological codes were excluded (N=18). Women with more than one missing address, as well as women with incomplete address were additionally excluded (N=847). For each breast cancer case, one control was randomly selected using incidence density sampling, thus among cohort participants at risk of breast cancer at the time when the case was diagnosed. The time was the delay elapsed since entry into the cohort. Controls were further individually matched to cases on residential area (French "département"), age (± 1 year), date (± 3 months) and menopausal status at blood collection for participants who gave a biological sample, or at baseline for participants without a blood sample. The latter were additionally matched for existence or not of a saliva sample. Women with missing data on matching variables were excluded (N=3). Overall, the current analyses were carried out in a subsample of 4529 women diagnosed with a primary invasive breast cancer and 4529 matched controls with complete information on confounding variables and home address at baseline.

Information on estrogen receptor (ER) and progesterone receptor (PR) status was obtained from the pathology report. ER and PR status were available for 76.7% (ER- =697, ER+ =2775, and unknown = 1057) and 74.1% (PR- =1214, PR+ = 2142, and unknown = 1173) of cases, respectively.

Covariates assessment

Data on established and potential breast cancer risks factors were available from the self-administered questionnaires at baseline. Regularly updates have been collected on smoking, anthropometry (height, weight), physical activity, diabetes, high blood pressure, benign breast disease, gynecological follow-up, breast cancer family history, education, age at menarche and at menopause, use of exogenous hormones, number of children, age at first full-term pregnancy, and breastfeeding. Body mass index (BMI) was calculated as weight (kg) divided by height (meter) squared. Physical activity was measured in metabolic equivalents (METs) per week. Daily alcohol intake was estimated from a validated semi quantitative dietary questionnaire. Education level was used as a proxy for socioeconomic status.

Assessment of long term exposure to airborne cadmium

The residential history of the study subjects, from their recruitment in the cohort until the index (breast cancer diagnosis for cases, selection for controls) was used to estimate atmospheric exposure to cadmium. Atmospheric exposure to cadmium was assessed using a Geographic Information System (GIS), which required a retrospective inventory of industrial sources, the estimation of their emission intensity, the geocoding of the participants' residential history and of the industrial sources, as well as the computation of local

meteorological data. The detailed methods used to assess exposure to cadmium have been recently described in two separate articles [23,24]. Briefly, cadmium industrial sources were first inventoried between 1990 and 2008, over the whole metropolitan France. Sources were identified through institutional and public databases, industrial unions and nationally recognized associations (OMINEA database (Organization and Methods of the National Inventories of the Atmospheric Releases in France) [25] and the EMEP database (European Monitoring and Evaluation Program) [26]. Overall, 2,700 cadmium sources were inventoried over the French national territory from 1990 to 2008 [23].

The participants residential history and emitting sources were geocoded (X and Y coordinates, addresses) using the ArcGIS Software (ArcGIS Locator version 10.0, Environmental System Research Institute – ESRI, Redlands, CA, USA) and its reference street network database, BD Adresse®, from the National Geographic Institute (IGN) [27]. Overall, 28,511 residential addresses in metropolitan France collected from the follow-up questionnaires (1990-2008) were geocoded [27]. A total of 78.1% of the subject's residences were geocoded to the address, 26% were manually checked, of which 17.4% have been corrected. All automatically geocoded locations were manually checked and repositioned at the stack using aerial photography from IGN.

A GIS-based metric was used to estimate airborne cadmium exposure [24] . Several parameters were tested to be included in the GIS-based metric to characterize exposure and to classify study subjects according to their airborne cadmium exposure. More specifically, the annual exposure index (AEI) to cadmium was estimated using the following GIS-based metric:

$$\text{AEI}\ (mg/m^2) = \sum_{j}^{J}\sum_{i}^{I} t_j \times \frac{1}{d^2{}_{ij}} \times EI_i \times F_i \times \left(\frac{h_{median}}{h_i}\right)^a$$

where j was the place of residence (j=1,…,J); i was the industrial source (i=1,…,I), EI was the annual cadmium emission intensity (in kg/year); t was the emission period duration (in year); d was the residence-to-source distance (in m); Fi was the factor taking into account the percentage of time during which the wind was blowing in a direction so as to induce a transport from the industrial source *i* to the participant's resident *j* (accounting for the weighted contribution of the sector of the buffer in which the participant was located); h_i was the stack height (in m); h_{median} was the median value of the other sources' stack height (in m) in a 10 km buffer, a was taking into account only when h_i was greater than 90 m. The exposure to cadmium was computed for each individual and for each calendar year. For each individual, their cumulative index of exposure (CIE) to cadmium was calculated by cumulating their AEI from their entry into the cohort to their index date.

The reliability of the GIS-based metric has been compared to SIRANE, a validated Gaussian atmospheric dispersion model, by calculating weighted kappa statistics (wκ) and coefficient of determination (R^2) [24]. SIRANE is an urban dispersion model that integrates a specific module to simulate pollutant dispersion within a built environment, considering local meteorological conditions and geometry of the streets. The comparison of this dispersion model with measured designs of NO2, PM10, dioxin and cadmium in the Lyon metropolitan area, showed consistent results [23,28]. Overall findings showed strong concordance between the GIS-based metric and the dispersion models, with wκ ranging from 0.69 (0.64 - 0.73) to 0.86

(0.82 - 0.91) and R^2 from 0.65 to 0.86 [24]. This metric has also been recently applied in a study on dioxin exposure and breast cancer risk among French women [29].

Statistical analyses

Baseline subject characteristics were compared between cases and controls using univariate conditional logistic regression models, and according to quintiles of the CIE to cadmium exposure using ANOVA test for continuous variables and Chi-square test for categorical variables. Conditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for cadmium exposure, in relation to risk of breast cancer. Models were conditioned on the matching factors including date of blood collection or of the return of the first questionnaire, age, department of residence, menopausal status at blood collection or at baseline and existence of a biological sample (blood, saliva, none). Multivariable models were additionally adjusted for variables including physical activity, smoking status, level of education, body mass index (BMI), previous family history of breast cancer, history of personal benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use (HRT) and status of birthplace (see Table 1 for the categories). Missing values in any of the categorical covariates were included as a separate category.

Statistical analyses for quintiles of the CIE to cadmium were performed for all subjects and separately for pre and post-menopausal women at the index date, using the first category as the reference value. Quintile cut-points of the CIE to cadmium were based on the distribution of the CIE to cadmium in control subjects. For each variable, the *P* for linear trend was the p-

value associated with the regression coefficient of the continuous variable based on the median value of each quintile. Further subgroup analyses were conducted according to hormone receptor status (ER and PR) of the breast tumors. Heterogeneity of associations across hormone receptor subgroups was assessed using polytomous logistic regression [30].

The potential non-linearity of the relationship between CIE to cadmium and breast cancer risk was investigated using restricted cubic splines [31]. Four knots were placed at 5th, 35th, 65th, and 95th percentiles of the distribution of CIE to cadmium [32], and the minimum value was chosen as a the reference. These models were also stratified according to menopausal status, and to hormone receptor status (ER and PR) of the breast cancer.

The effect modification by birthplace status (urban or rural), BMI (<25 kg/m^2/ ≥ 25 kg/m^2), smoking (never/ever), oral contraceptives use (no/yes) and HRT use (no/yes) was assessed using interaction terms and likelihood ratio tests.

All statistical tests were two-sided and *P* values < 0.05 were considered statistically significant. All analyses were performed using STATA version 14 (College Station, Texas, USA).

RESULTS

Baseline characteristics of the study participants

Table 1 summarizes the sociodemographic, reproductive and lifestyle characteristics of study participants by case–control status. Level of alcohol intake was higher among cases than controls ($P = 0.001$). Cases were more likely to be born in an urban area ($P = 0.041$), to be

less physically active (P = 0.006), to report having university education (P < 0.001), to be HRT users (P = 0.004), to be nulliparous (P < 0.001), to have a family history of breast cancer (P < 0.001) and a personal history of benign breast disease (P < 0.001).

The distributions of known risk factors for breast cancer by quintiles of CIE to cadmium are reported in **Supplementary Table S1**. Age, use of oral contraceptives, use of HRT, age at menarche, breastfeeding and history of personal benign breast disease were similar across quintiles. Compared to women in the lower quintiles, women in the upper quintiles of CIE to cadmium had a higher level of alcohol intake (P = 0.001), were more frequently current or former smokers (P < 0.001), were physically less active (P < 0.001), were more nulliparous (P = 0.001), had a higher educational level (P < 0.001), were mainly born in urban area (P < 0.001) and had a family history of breast cancer (P = 0.040).

Associations of cumulative airborne cadmium exposure with breast cancer risk

Table 2 and **3** show the relationship between quintiles of cumulative airborne cadmium exposure and overall breast cancer risk, by menopausal status and hormone receptor status. Overall, there was no significant association between CIE to cadmium and the risk of overall, premenopausal and postmenopausal breast cancer (**Table 2**). We found a statistically significant heterogeneity of the results by ER status (ER-/ER+) (P heterogeneity < 0.001). Across strata of ER and PR status, we observed an inverse linear relationship between CIE to cadmium and risk of breast cancer ($OR_{Q5\ vs\ Q1}$ = 0.63; 95% CI: 0.41-0.95, P trend = 0.043) for ER- breast cancer in all women (pre- and post-menopausal combined). An inverse association was observed for ER-PR- breast cancer but only for the fourth quintile of exposure ($OR_{Q4\ vs\ Q1}$

= 0.62; 95% CI: 0.40-0.95, P trend = 0.088). Test for heterogeneity of findings by ER-PR-/ER+PR+ status was statistically significant (P heterogeneity = 0.005). No statistically significant associations were observed between CIE to cadmium and risk of ER+, PR-, PR+ and ER+PR+ breast tumors. After stratification by menopausal status at index date, the inverse associations observed for ER- and ER-PR- remained significant only in postmenopausal women, but appeared to be nonlinear. Statistically significant associations were observed for the second versus the first quintile ($OR_{Q2\ vs\ Q1}$ = 0.57; 95% CI: 0.36-0.88, P trend = 0.300 and $OR_{Q2\ vs\ Q1}$ 0.55; 95% CI: 0.34-0.90, P trend = 0.254) for ER- and ER-PR- breast tumors, respectively in postmenopausal women. No statistically significant associations were found in premenopausal women (**Table 3**). The distributions of known risk factors for ER- breast cancer cases by quintiles of CIE to cadmium are reported in **Supplementary Table S2.**

The non-linear modeling of the relationship between cumulative airborne cadmium exposure and the risk of overall breast cancer, using four-knot cubic splines with the minimum value as the reference category is shown in **Figure 1.** These models were also stratified by menopausal status (see **Supplementary Figures S1 and S2**). Although not statistically significant, these figures confirm the non-linear effect of cumulative airborne cadmium exposure on the risk of breast cancer. However, the significant inverse associations appeared to be linear for ER- and ER-PR- breast tumors (see **Supplementary Figures S3 and S4**). Overall, findings from cubic splines analyses confirmed results observed in the analyses based on quintile categories.

Effect modification and sensitivity analyses

Given the potential effect of the residential areas (urban or rural status) on the risk of breast cancer, we reported the risk estimates accordingly (see **Supplementary Table S3**). There is some evidence that association of CIE to cadmium and breast cancer differed according to the urban/rural status of the birthplace, although the interaction was not statistically significant (P interaction = 0.197). The $OR_{Q2\ vs\ Q1}$ was 0.61; 95% CI: 0.39-0.95 and $OR_{Q3\ vs\ Q1}$ was 0.57; 95% CI: 0.35-0.92; P trend = 0.727 in women born in rural areas, while no significant associations were found among women born in urban areas. The association between CIE to cadmium and the risk of breast cancer was not modified by tobacco smoking status, BMI levels, oral contraceptive use, HRT use, age at menarche, age at first full term pregnancy, parity and breastfeeding (P interaction > 0.05, data not shown).

DISCUSSION

In this large nested case-control study, airborne exposure to cadmium was not significantly associated with the overall risk of breast cancer. However, in the stratified analyses, we observed that breast cancer risk associated to airborne cadmium exposure may vary according to menopausal status, and hormone receptor status of breast tumors. Statistically significant inverse associations were suggested for ER- and ER-PR- breast tumors.

Results of some case control epidemiological studies have shown that a high urinary cadmium level was associated with an increased risk of overall breast cancer [9,10,33]. In contrast, and in line with our results, several studies did not corroborate the hypothesis that cadmium increases the risk of overall breast cancer, although these were based on dietary estimated cadmium intake and measured urinary level of cadmium [13,14,34]. Consistent with our overall

findings, the only study conducted on airborne cadmium exposure and risk of breast cancer found a non-statistically significant association for overall breast cancer. By contrast, this study reported a positive association for ER- breast cancer [19], our results however suggested an inverse associations for ER- and ER-PR- breast tumors. The results of cubic splines were consistent with these findings. Only few studies investigated breast cancer risk stratified according to hormone receptor status. A number of studies reported that the increased risk associated with cadmium may be limited to ER+, or ER+PR+ breast cancers [34,35], however these were based on urinary level of cadmium. The study by Strumylaite et al. demonstrated that women with a greater urine level of cadmium (3rd quartile: 0.241-0.399 μg/g and 4th quartile: ≥ 0.4 μg/g) exhibited approximately twice the ER+ breast cancer risk compared with those having cadmium concentration lower than 0.147 μg/g (1st quartile) (OR = 1.9; 95 % CI: 1.31, 2.74) [35]. In contrast, findings by Julin et al. suggested a role for dietary cadmium in postmenopausal breast cancer development, with significant associations observed for overall (RR = 1.27; 95% CI, 1.07–1.50) and for ER+ tumors (RR = 1.25; 95% CI, 1.03–1.52) and no statistically significant association for ER− tumors (RR = 1.22; 95% CI, 0.76–1.93) [18]. Overall, these results should be interpreted with caution, since cadmium exposure information was only available since inclusion 1990 and not over the entire lifetime. The lack of historical air pollutant emission data makes it difficult to reconstruct past exposures and further research is needed to clarify the relationship between cadmium exposure and breast cancer risk. Additionally, the possibility of false positive findings as a result of multiple testing could not be completely ruled out, in particular for ER-PR- breast cancer, for which an inverse association was observed only for the fourth quintile of exposure. Overall, further studies

taking into account temporal exposure patterns that allow to capture the evolution of annual cadmium exposure over long periods prior to diagnosis are needed.

The underlying mechanisms linking exposure to cadmium and breast cancer risk in women are not fully elucidated, and it is possible that cadmium may have distinct roles in breast cancer carcinogenesis according to menopausal status and hormone receptor status. One of the main mechanisms may be related to the estrogenic effects of cadmium. Due to its properties, cadmium could interact with the hormone-binding domain of ER [36] to modulate target gene expression (expression of E2 regulated genes for example) [33], to activate ERK1/2 and p38 signaling [37,38], leading to breast cancer cell growth and cell proliferation. There is also evidence that cadmium induces estrogenic effects in rodents, including proliferation of mammary tissues [39]. In addition, cadmium has been reported to act through several ER independent mechanisms. Cadmium was able to induce the production of reactive oxygen species (ROS) and reduce the anti-oxidative defenses in breast tumor cells [40]. Also, cadmium can either damage DNA directly or alter the processes that control normal DNA replication or repair of DNA damage [41]. Overall, these hormonal, oxidative stress and genomic effects could facilitate tumor promoting effects associated with increasing cadmium exposure and breast cancer risk.

With respect to plausible biological mechanisms that could explain the observed inverse associations, it has been reported that the effects of cadmium on tumor angiogenesis in breast cancer cells and other tumor models, can be either stimulatory or inhibitory, depending on the concentrations [42,43]. Ultra-low concentrations of cadmium (< 0.5 μM) inhibit endothelial nitric oxide synthase (eNOS) activation, leading to reduced eNOS production and attenuated tumor

angiogenesis [44]. Additionally, cadmium in high concentrations (>10 μM) induces both endothelial cells apoptosis via the activation of caspase-3, resulting in destruction of tumor vasculature [45]. As angiogenesis is one of the key mechanisms in tumor carcinogenesis particularly in triple negative breast cancer [46], inhibition of tumor vessel growth by cadmium could reduce the tumor promoting growth, accounting in part for the inverse association between airborne cadmium exposure and risk of breast cancer observed in ER- and ER-PR- breast tumors. In contrast, low-dose cadmium (1-10 μM) up-regulates vascular endothelial growth factor (VEGF)-mediated tumor angiogenesis by exerting sub-apoptotic levels of oxidative stress on both tumor cells and endothelial cells [47]. The exact mechanisms underlying such effects are unclear, however the reported contradictory effects may partially explain the lack of consistency in the epidemiological findings regarding the association between cadmium exposure and breast cancer risk.

The strengths of our study comprise its prospective design of the E3N cohort allowing a high quality of information collected and the large number of cases, providing sufficient statistical power for most subgroup analyses. Availability of detailed information on lifestyle factors, reproductive factors and history of breast cancer, as well as information on the status of urban/rural at birth allowing for better control of confounding and further investigation of potential effect modifiers. Another strong point of our study includes detailed information on hormone receptor status, since breast cancer may develop according to distinct molecular pathway [48]. In addition to the most common cumulative exposure methods used in epidemiology, other alternative approaches taking into account the non-linearity of the relationship between CIE to cadmium and breast cancer risk was also considered using

restricted cubic splines. Also, while in many epidemiological studies, exposure is measured at a single point in time under the assumption that a single measure is an approximation for that exposure over a long time, we used in the present study the residential history to reconstruct exposure variation over time resulting both from changes in source emissions over time or from residential mobility of the study population. Furthermore, it should be noted that analyses comparing the distribution of demographics and risk factors between included cases and excluded cases (because of missing addresses) showed no important differences overall (data not shown). Compared to the included cases, excluded cases were less likely to be physically active, to have a higher educational level and to have a history of personal benign breast disease. However, there was no reason to believe that these minor differences could have modified any of the findings. The reliability of the GIS-based metric as compared to the SIRANE atmospheric dispersion model showed strong concordance, highlighting its ability to provide robust estimates of the subject's exposure in comparison to modelling results [23,24]. The inclusion of the wind speed in the parameters' combination of the GIS-based metric, did not further improve the agreement statistics although wind speed has been suggested to impact pollutant dispersion. However, integration of additional parameters, such as pluviometry or outdoor temperature, may further improve the performance of the GIS-based metric.

The limitations of this study include the lack of past residential history and historical airborne cadmium exposure estimates before 1990. This left truncation may bias the estimation of the exposure effect [49]. And this, according to the exposure effect model, may lead to an overestimation or underestimation of associations between exposure and the risk of disease [50].

We cannot exclude potential measurement errors in airborne cadmium exposure as other punctual and non-industrial sources (such as biomass fires, traffic-related exposure manufactured good burnings, outdoor burning and illegal landfills) were not included in this GIS-based metric due to the difficulty of their retrospective inventory at a fine geospatial scale, their geolocalization and the estimation of their cadmium emissions. However these restricted sources of cadmium represent overall a small proportion of cadmium exposure, while our GIS-based metric included almost all industrial sources of cadmium plus some miscellaneous sources including crematoria.

In conclusion, this study shows that, although there was no significant association for overall, premenopausal and postmenopausal breast cancer risk, increased airborne exposure to cadmium appeared to be associated with decreased risk of ER- and ER-PR- breast tumors. Our results suggest a paradoxical effect of cadmium in breast cancer which may be supported by mechanistic evidence reporting both carcinogenic and anti-carcinogenic effects of cadmium. Overall, these findings call for caution in evaluating breast cancer risk associated to cadmium exposure and highlight the need for further epidemiological studies, particularly in assessing the impact of lifetime cadmium exposure trajectories, taking into account postmenopausal status and hormone receptor status.

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Competing financial interests

The authors declare they have no actual or potential competing financial interests.

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Table 1: Baseline demographic and lifestyle characteristics of breast cancer cases and their matched controls in the case-control study nested within E3N cohort, France, 1990-2008

Characteristics	Cases (n=4,529)	Controls (n=4,529)	P value
CIE to cadmium (mg/m^2), median (p25-p75)	0.81 (0.07-4.18)	0.78 (0.07-3.79)	0.071
Age (years), mean ± SD	49.8 ± 0.1	49.7 ± 0.1	
Alcohol drinking (g/day), n (%)			
0	413 (9.1)	459 (10.1)	
> 0-6.7	1,269 (28.0)	1,319 (29.1)	
≥ 6.7	1,982 (43.8)	1,803 (39.8)	
Missing	865 (19.1)	948 (20.3)	0.001
Body Mass Index (kg/m^2), n (%)			
<25	3,762 (83.1)	3,741 (83.1)	
25-30	636 (14.0)	640 (14.1)	
≥ 30	131 (2.9)	148 (3.3)	0.567
Tobacco smoking status, n (%)			
Never	2,447 (54.0)	2,485 (54.9)	
Current	678 (15.0)	654 (14.4)	
Former	1,404 (31.0)	1,39 (30.7)	0.662
Status of birthplace, n (%)			
Rural	1,204 (26.6)	1,269 (28.0)	
Urban	2,902 (64.1)	2,790 (61.6)	
Missing	423 (9.3)	470 (10.4)	0.036
Physical activity (METs-h/week), n (%)			
< 25.3	1,145 (25.3)	1,068 (23.6)	
25.3-37.3	1,404 (31.0)	1,319 (29.1)	
37.4-56.9	1,187 (26.2)	1,254 (27.7)	
≥ 57.0	793 (17.5)	888 (19.6)	0.004
Education, n (%)			
Undergraduate	559 (12.3)	636 (14.0)	
Post-graduate with a 1- to 2-year university degree	2,301 (50.8)	2,423 (53.5)	
Post-graduate with a ≥ 3 year university degree	1,669 (36.9)	1,470 (32.5)	< 0.001
Menopausal status at index date, n (%)			
Premenopausal	2,679 (59.2)	2,690 (59.4)	
Postmenopausal	1,850 (40.8)	1,839 (40.6)	
Use of oral contraceptives, n (%)			
No	1,854 (40.9)	1,877 (41.4)	
Yes	2,675 (59.1)	2,652 (58.6)	0.583
Use of hormone replacement therapy, n (%)			

No	3,759 (83.0)	3,860 (85.2)	
Yes	770 (17.0)	669 (14.8)	< 0.001
Parity & age at first pregnancy (AFP, years), n (%)			
0	597 (13.2)	491 (10.8)	
0-2 & AFP < 30	2,196 (48.5)	2,227 (49.2)	
0-2 & AFP ≥ 30	515 (11.4)	412 (9.1)	
≥ 3	1,177 (25.9)	1,357 (29.9)	
Missing	44 (0.9)	42 (0.9)	< 0.001
Age at menarche (years)			
< 12	989 (21.8)	934 (20.6)	
12-14	2,360 (52.1)	2,320 (51.2)	
≥ 14	1,180 (26.1)	1,275 (28.2)	0.059
Breastfeeding, n (%)			
No	2,153 (47.5)	2,148 (47.4)	
Yes	2,376 (52.5)	2,381 (52.6)	0.915
Family history of breast cancer, n (%)			
No	3,717 (82.1)	4,024 (88.8)	
Yes	812 (17.9)	505 (11.2)	< 0.001
History of personal benign breast disease, n (%)			
No	3,189 (70.4)	3,514 (77.6)	
Yes	1,340 (29.6)	1,015 (22.4)	< 0.001

P values from univariate conditional logistic regression models, except for age and menopausal status which were matching factors

SD: Standard deviation, MET: Metabolic Equivalent of Task, HRT: menopausal hormone replacement therapy, CIE: cumulative index of exposure to cadmium. Menopausal status at index date: date of diagnosis of the case in the case-control pair

Table 2: Odds ratio and 95% confidence intervals (OR, 95% CI) for the association of quintiles of cumulative airborne cadmium exposure with breast cancer risk overall and by menopausal status at index date in the case-control study nested within the E3N cohort, France, 1990-2008

	Overall		Premenopausal		Postmenopausal	
Cumulative airborne cadmium exposure (mg/m^2)	n cases/ controls	OR (95%CI)	n cases/ controls	OR (95%CI)	n cases/ controls	OR (95%CI)
All						
≤ 0.033	917/906	Ref	254/226	Ref	663/680	Ref
> 0.033 - 0.357	860/907	0.92 (0.80-1.06)	211/193	0.88 (0.62-1.25)	649/714	0.92 (0.78-1.08)
> 0.357 - 1.48	924/904	0.96 (0.83-1.10)	198/163	1.13 (0.78-1.64)	726/741	0.93 (0.78-1.10)
> 1.48 - 5.47	872/907	0.90 (0.78-1.04)	127/123	0.86 (0.56-1.33)	745/784	0.91 (0.77-1.09)
> 5.47	956/905	0.98 (0.84-1.14)	98/119	0.72 (0.45-1.15)	858/786	1.06 (0.89-1.27)
P trend		0.717		0.310		0.531
P interaction						0.070

Multivariable models were adjusted for physical activity, smoking status, level of education, body mass index (BMI), previous family history of breast cancer, history of personal benign breast disease, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use (HRT) and status of birthplace

Menopausal status at index date: date of diagnosis of the case in the case-control pair

Table 3: Odds ratio and 95% confidence intervals (OR, 95% CI) for the association of quintiles of cumulative airborne cadmium exposure with breast cancer risk by hormone receptor status in overall pre- and post-menopausal, in the case-control study nested within the E3N cohort, France, 1990-2008

	Overall		Premenopausal		Postmenopausal	
Cumulative airborne cadmium exposure (mg/m^2)	n cases/ controls	OR (95%CI)	n cases/ controls	OR (95%CI)	n cases/ controls	OR (95%CI)
ER-						
≤ 0.033	168/137	Ref	52/43	Ref	116/94	Ref
> 0.033 - 0.357	132/144	0.68 (0.48-0.97)	41/29	1.28 (0.48-3.39)	91/115	0.57 (0.36-0.88)
> 0.357 - 1.48	141/140	0.73 (0.49-1.06)	28/34	1.06 (0.34-3.33)	113/106	0.80 (0.50-1.28)
> 1.48 - 5.47	136/147	0.66 (0.44-0.97)	23/39	0.64 (0.21-1.94)	113/108	0.74 (0.47-1.19)
> 5.47	120/129	0.63 (0.41-0.95)	18/21	0.75 (0.18-3.09)	102/108	0.66 (0.41-1.08)
P trend		0.043		0.391		0.300
ER+						
≤ 0.033	534/543	Ref	118/111	Ref	416/432	Ref
> 0.033 - 0.357	499/529	0.94 (0.78-1.13)	97/91	0.84 (0.48-1.49)	402/438	0.95 (0.76-1.18)
> 0.357 - 1.48	566/537	1.01 (0.84-1.22)	105/79	1.28 (0.73-2.26)	461/458	1.02 (0.82-1.26)
> 1.48 - 5.47	542/567	0.93 (0.76-1.13)	71/55	1.10 (0.57-2.12)	471/512	0.94 (0.76-1.18)
> 5.47	634/599	1.00 (0.82-1.22)	69/70	0.89 (0.47-1.67)	565/529	1.07 (0.87-1.34)
P trend		0.969		0.947		0.567
P heterogeneity		< 0.001		0.259		0.015
PR-						
≤ 0.033	249/239	Ref	47/54	Ref	202/185	Ref
> 0.033 - 0.357	230/261	0.80 (0.61-1.04)	47/41	0.90 (0.39-2.08)	183/220	0.69 (0.50-0.95)
> 0.357 - 1.48	260/230	0.97 (0.73-1.29)	36/33	1.31 (0.46-3.73)	224/197	0.89 (0.64-1.23)

> 1.48 - 5.47	236/250	0.86 (0.65-1.15)	32/45	0.79 (0.30-2.08)	204/205	0.85 (0.61-1.19)
> 5.47	239/234	0.89 (0.66-1.20)	26/33	1.40 (0.35-5.57)	213/201	0.87 (0.62-1.22)
P trend		0.581		0.966		0.812
PR+						
≤ 0.033	446/432	Ref	125/100	Ref	321/332	Ref
> 0.033 - 0.357	385/394	0.94 (0.76-1.16)	88/78	0.98 (0.55-1.76)	297/316	1.00 (0.78-1.27)
> 0.357 - 1.48	420/424	0.91 (0.74-1.12)	93/77	1.13 (0.63-2.02)	327/347	0.97 (0.76-1.23)
> 1.48 - 5.47	404/422	0.85 (0.68-1.06)	60/46	1.00 (0.51-1.97)	344/376	0.90 (0.70-1.16)
> 5.47	487/470	0.93 (0.74-1.15)	59/56	0.76 (0.40-1.48)	428/414	1.02 (0.79-1.31)
P trend		0.348		0.605		0.863
P heterogeneity		0.064		0.205		0.004
ER-PR-						
≤ 0.033	132/107	Ref	34/29	Ref	98/78	Ref
> 0.033 - 0.357	105/117	0.68 (0.46-1.02)	28/23	0.88 (0.26-2.92)	77/94	0.55 (0.34-0.90)
> 0.357 - 1.48	112/106	0.77 (0.50-1.17)	17/24	0.59 (0.12-2.75)	95/82	0.83 (0.50-1.38)
> 1.48 - 5.47	106/124	0.62 (0.40-0.95)	16/28	0.72 (0.18-2.94)	90/96	0.65 (0.39-1.09)
> 5.47	96/97	0.68 (0.42-1.07)	14/12	1.55 (0.21-11.5)	82/85	0.65 (0.38-1.12)
P trend		0.088		0.962		0.254
ER+PR+						
≤ 0.033	408/402	Ref	105/85	Ref	303/317	Ref
> 0.033 - 0.357	359/369	0.96 (0.78-1.19)	75/72	0.79 (0.42-1.47)	284/297	1.02 (0.80-1.31)
> 0.357 - 1.48	394/390	0.96 (0.77-1.18)	82/67	1.05 (0.56-1.98)	312/323	1.01 (0.79-1.30)
> 1.48 - 5.47	378/403	0.86 (0.69-1.08)	54/37	1.08 (0.52-2.25)	324/366	0.89 (0.69-1.15)
> 5.47	462/437	0.97 (0.78-1.22)	55/47	1.02 (0.50-2.07)	407/390	1.06 (0.81-1.36)
P trend		0.576		0.816		0.936
P heterogeneity		0.005		0.779		0.008

Multivariable models were adjusted for physical activity, smoking status, level of education, body mass index (BMI), previous family history of breast cancer, history of personal benign breast disease, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use (HRT) and status of birthplace.
Menopausal status at index date: date of diagnosis of the case in the case-control pair.

Figure legends

Figure 1: Cubic spline modelling of the relationship between cumulative airborne cadmium exposure and risk of overall breast cancer i**n the case-control study nested within the E3N cohort, France, 1990-2008.** Multivariable adjusted OR (continuous line) and 95% CI (dotted line) obtained using four-knot restricted cubic splines with the minimum value used as reference. Models were adjusted for physical activity, smoking status, level of education, body mass index (BMI), previous family history of breast cancer, history of personal benign breast disease, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use (HRT) and status of birthplace.

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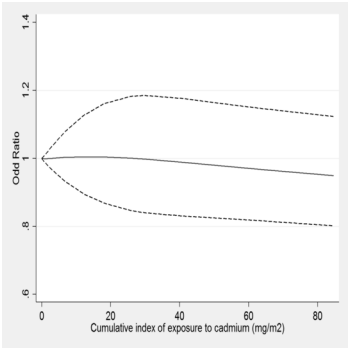
Cadmium is a common environmental contaminant that exerts estrogen-like activity in human cells. While this activity suggests that cadmium might influence breast cancer risk, the relationship between cadmium exposure and breast cancer remains unclear. In this study, the authors employed a Geographic Information System (GIS)-based metric to assess atmospheric cadmium exposure in women in France. No significant association was found between airborne cadmium and overall breast cancer risk. Risk varied, however, according to menopausal status and tumor hormone receptor status. Significant inverse associations were indicated for estrogen receptor-positive breast cancers. Additional research is needed to assess cadmium exposure-associated cancer risks.



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