Exposure to airborne cadmium and breast cancer stage, grade and histology at diagnosis: Findings from the E3N cohort study

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Abstract

Purpose

Molecular and cellular studies reported a role of cadmium in risk of advanced breast cancer (BC). However epidemiological evidence is limited. Our previous study suggests that cadmium might be related to a decreased risk of ER- and ER-PR- breast tumors. In this study, we further explored the association between long-term exposure to airborne cadmium and risk of BC by stage, grade of differentiation, and histological types at diagnosis.

Methods

A nested case-control study of 4,401 cases and 4,401 matched controls was conducted within the French E3N cohort. A Geographic Information System (GIS) based metric was employed to evaluate outdoor airborne exposure to cadmium. Multivariable adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression models.

Results

There was no statistically significant association between cadmium exposure and stage of BC in the multivariable analyses. The adjusted ORs for the fifth versus first quintile were 1.02 (95% CI: 0.83–1.25), 1.11 (95% CI: 0.84–1.49), and 0.67 (95% CI: 0.37–1.24) for stages I, II, and III-IV BC, respectively. The subgroup analyses showed no statistically significant association between cadmium exposure and grade of differentiation of BC at diagnosis. However, further analyses by histological type suggested a positive dose-response association between cadmium and risk of invasive tubular carcinoma (ITC) BC (OR for the fifth versus first quintile = 3.44 (95% CI: 1.10–10.7)).

Conclusions

Our results do not support the hypothesis that airborne cadmium exposure may have a role in advanced BC risk, but suggest that cadmium may be associated with an increased risk of ITC. However, these results should be considered with caution, and more epidemiological studies are needed to confirm our findings and to improve our understanding of the effects of cadmium exposure according to several clinic-pathological characteristics of BC.

Introduction

Worldwide, breast cancer (BC) is the most frequent cancer and the leading cause of cancer death among women worldwide, accounting for almost 1 in 4 (2.1 million) of all new cancer cases in 2018 [1]. BC is a heterogeneous disease at the histopathological and molecular levels, comprising different subtypes

defined by their distinct histological, biological features, and clinical behaviors [2, 3]. Current evidence suggests etiological heterogeneity with differential effects of risk factors on hormone receptor status, pathological grade, stage or histological type at diagnosis [4, 5]. For example, increased risks related to hormone and reproductive factors (including age at menarche, older ages at first birth, endogenous estrogens) have been consistently found for Estrogen receptor positive (ER+) and/or Progesterone receptor positive (PR+) breast tumors [6, 7]. In addition to well-known reproductive and lifestyle factors [8, 9], a growing number of studies has identified an increased risk of BC associated with exposure to environmental pollutants, in particular to pollutants with endocrine disrupting properties; and linked exposures to several endocrine-disrupting-chemicals (EDC) to tumors size, lymph nodes involvement, and development of tumor metastasis and other hallmarks of BC tumor aggressiveness [10–13]. Molecular and cellular studies suggest that cadmium due to its estrogenic properties, might play an important role in BC progression, tumor growth and invasion, as well as enhances the migratory ability of metastatic cells [14–17]. Also, a positive association of blood cadmium levels with distant metastasis has been reported [18].

Cadmium is an environmental contaminant that exerts toxic effects promoting several cancers including possibly BC. It is classified as a group 1 human carcinogen by the international agency for research on cancer (IARC) [19]. Cadmium is emitted to the atmosphere from both natural and anthropogenic sources, including tobacco smoking, mining, smelting and refining of non-ferrous metals, fossil fuel combustion, and waste incineration [20]. Major route of exposure is through inhalation or incidental ingestion from contaminated hands, food, or cigarettes [21]. Ponce et al. reported that chronic cadmium treatment increases cell spreading and cell migration and promotion [16]. Other experimental studies reported that cadmium stimulated cell proliferation by activating genes and signals associated with cancer migration and invasion BC cells [22, 23]. Wei et al. have shown that low concentrations of cadmium transformed the non-tumorigenic breast epithelial cells to a more mesenchymal-like morphology, suggesting a potential role of cadmium in promoting metastasis [24]. Moreover, in vitro studies have suggested that cadmium might contribute to enhancing the aggressiveness of breast tumors through stimulation of the transcription of oncogenic c-Myc and downregulating the tumor suppressor p21 [25]. Furthermore, a study investigating cadmium concentrations in BC tissues, reported that cadmium was positively associated with histological type of tumor, its size and grading [26]. However, current epidemiological studies have provided inconsistent evidence regarding the association of cadmium air pollution exposure with BC risk overall [27, 28] and no epidemiological study to date has investigated the impact of cadmium exposure on BC stage, grade of differentiation, or histological type at diagnosis. A recent dose-response meta-analysis based on four studies using cadmium urine levels and six studies on dietary exposure, showed no significant relation between dietary cadmium intake or urinary cadmium excretion and BC. Compared to no exposure, the summary risk ratio = 1.12 (95% CI: 0.80–1.56) and 0.89 (95% CI 0.38–2.14) at 20 µg/day of cadmium intake and 2 µg/g creatinine of cadmium, respectively [29]. Similarly, the sister study, including 2,587 BC cases with the mean follow-up of 7.4 years, found an HR of 1.1, 95% CI: 0.96–1.3 of developing postmenopausal BC when comparing the highest to lowest quintiles of air cadmium levels [30].

In our previous study based on the same population, we have estimated the risk of BC associated with long-term airborne cadmium exposure, and its effect according to molecular subtype of breast cancer (estrogen receptor negative/positive (ER-/ER+) and progesterone receptor negative/ positive (PR-/PR+)). Our results showed no evidence of an association between airborne exposure to cadmium and risk of overall BC, but suggested an inverse associations for ER-PR- BC [27].

In the present study, we further explored the association between long-term exposure to cadmium air pollution and risk of BC by stage, grade of differentiation and histological type at diagnosis.

Methods

Study design and participants

E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) is an ongoing prospective cohort study involving 98,995 French women, established in 1990 to investigate risk factors for cancer and severe chronic conditions in women [31]. 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 people working within the French education system and their families, and have been biennially followed-up with self-administered mailed questionnaires. At recruitment, participants filled in a self-administered questionnaire, which included items relative to lifestyle and reproductive factors, anthropometry, past medical history, and family history of cancer. To date, twelve 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, resulting in the collection from 25,000 women, and saliva samples were later collected 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 (CépiDC-Inserm). The pathology report for confirming diagnosis of the primary outcome (invasive BC) 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 reported in the baseline questionnaire (1990) and in the 5^{th} to 9^{th} follow-up questionnaires (years 1997, 2000, 2002, 2005, 2008, and 2011). In the 3^{rd} and 4^{th} follow-up questionnaires (years 1993 and 1994) only postal codes of participants were reported. In addition, participants' place of birth (postal code and municipality) was obtained from the first questionnaire and assigned an urban/rural status based on data from the closest national census [32]. 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 design

A nested case-control study was designed among women of the E3N cohort who had completed their home address at baseline, lived in the metropolitan French territory during the follow-up time, and had never been diagnosed with any cancer at baseline. Details of this study have been described elsewhere

[27]. After excluding women with phyllodes tumors, a total of 5,382 histologically confirmed incident BC cases were identified during the follow-up 1990 to 2008. From these, we excluded women with missing addresses (including women with more than one missing address and those for whom it was impossible to retrieve addresses, N = 981 cases). For each BC case, one control was randomly selected using incidence density sampling, i.e. among cohort participants at risk of BC at the time of case diagnosis, using the follow-up time since inclusion into the cohort as time axis. In order to best select appropriate controls according to the planned studies, two complementary groups of cases were set, according to availability of a biological sample (blood or saliva), for the first group of cases (with a blood sample), controls were matched to cases on the department of residence, age (± 1 year), date (± 3 months) and menopausal status at blood collection. Controls for the second group (without blood sample) were matched on the same criteria but collected at baseline, and additionally matched on the existence or not of a saliva sample. Finally, the nested case-control study involved 4,401 women diagnosed with a primary invasive BC and 4,401 matched controls with complete information on home address at baseline [27].

Assessment of staging, grading, histology and other covariates

Information on tumor-node-metastasis (TNM) stage was extracted from pathological reports or any other medical document (such as bone-scan, magnetic resonance (MRI) or X-ray radiography reports). Of the 4,401 BC cases, a total of 3,924 (89%) cases had stage information. Information on the grade of differentiation and histological subtype at diagnosis was collected based on pathological reports and available for 3,433 (78%) and 4,120 (93.6%) BC cases, respectively. Data on established BC risk factors and other potential confounding factors were obtained from the E3N self-administered questionnaires at baseline. Information collected at baseline on smoking, anthropometry (height, weight), physical activity, diabetes, hypertension, benign breast disease, gynecological follow-up, family history of BC (FHBC), education, age at menarche and at menopause, use of exogenous hormones, number of children, age at first full-term pregnancy (AFP), and breastfeeding [31]. Follow-up questionnaires were sent every 2-3 years thereafter. Daily alcohol intake (g/day) was estimated from the validated E3N self-administered diet history questionnaire (DHQ) in 1993. Physical activity was converted into metabolic equivalent task-hour per week (MET-h/w). Education level was used as a proxy for socioeconomic status.

Assessment of long-term exposure to airborne cadmium

The method employed to estimate airborne cadmium exposure at the individual residential address level have has been previously described in detail [33–35] and applied in two previous studies [27,36]. Briefly, the residential history of the women, from their enrolment in the E3N cohort until the index date (BC diagnosis for cases, date of diagnosis of the case in the case-control pair for controls) was used to estimate atmospheric exposure to cadmium, within a Geographic Information System (GIS).

A detailed retrospective inventory of industrial cadmium emitting sources over the entire metropolitan France between 1990 and 2008 was performed [33]. Sources of emissions were assessed using emission factors from the OMINEA (Organization and Methods of the National Inventories of the Atmospheric Releases in France) [37] and the EMEP (European Monitoring and Evaluation Program) [38] databases.

Overall, 2,700 cadmium sources were inventoried over the French national territory from 1990 to 2008 [33].

The participants residential history from 1990 to 2008 and inventoried cadmium 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) [35]..

To classify the study subjects according to their airborne cadmium exposure, a GIS-based metric was developed and calibrated using a set of parameters (local meteorological data, characteristics of industrial sources, e.g. emission intensity and stack height) [34]. Specifically, the annual airborne cadmium exposure index (AACEI) was estimated using the following GIS-based metric:

$$\text{AACEI}\ (mg/m^2) = \sum_{j}^{J} \sum_{i}^{I} \text{tj} \times \frac{1}{\text{d}^2_{\text{ij}}} \times \text{EI}_\text{i} \times \text{F}_\text{i} \times \left(\frac{\text{h}_{\text{median}}}{\text{h}_\text{i}}\right)^a$$

where j was the place of residence (j=1,…,J); i was the industrial source (i=1,…,I), EI was the source 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 accounting for the weighted contribution of wind direction from the industrial source *i* to the participant's residence *j*; 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, and was taken 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 airborne cadmium exposure index was calculated by cumulating their AACEI from their entry into the cohort to their index date. The cumulative airborne cadmium exposure index was then expressed from kg/m² to mg/m² [27].

Statistical analyses

Kruskal Wallis and Chi-square tests were used to assess BC cases characteristics differences according to stage, grade of differentiation, histological type with regard to continuous and categorical variables, respectively.

Conditional logistic regression models were used to estimate odds ratios (OR) and their 95% confidence intervals (95% CI) for risk of BC associated with cadmium exposure. 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). Two adjusted models were considered to account for predefined variables recognized as confounding and risk factors for BC. Using a directed acyclic graph to identify the

confounding variables, the first model was adjusted for physical activity (< 25.3, 25.3-37.3, 37.4-56.9, and ≥ 57.0 METs-h/week), alcohol intake (never, < 6.7, ≥ 6.7 g/day), level of education (secondary, 1 to 2-year university degree, ≥ 3 year-university degree), BMI (< 25, 25- < 30, and ≥ 30 kg/m²), age at menarche (< 12, 12-13, and ≥ 14 years), parity and AFP (0, 1-2 children & AFP < 30 years, 1-2 children & AFP ≥ 30 years, and ≥ 3 children), breastfeeding (ever, never), oral contraceptive use (ever, never), MHT (ever, never), status of birthplace (rural, urban) [9,32,36] and smoking status (never, current, and former). In the second multivariable model, we further adjusted for previous FHBC (yes, no) and history of personal benign breast disease (yes, no). Since there was no difference in the OR estimates between the two models, we only reported the results of the fully adjusted models in the main manuscript. For contraceptive and menopausal MHT variables, we considered the values collected in the last questionnaire before the date of diagnosis in cases, whereas all other adjustment variables were taken at E3N baseline questionnaire.

For covariates with less than 5% missing data, the latter were imputed by their modal or median value of the control population; and for variables with more than 5% of missing data (only alcohol intake and rural urban status at birth), a category of missing data was created.

Statistical analyses for quintiles of the cumulative airborne cadmium exposure index were performed by stage, grade of differentiation, and histological subtype of BC at diagnosis using the first quintile as the reference value. Quintile cut-points of the cumulative levels were based on the distribution in control subjects. For each variable, the *P* for linear trend was the p-value associated with the regression coefficient of the categorical variable used as continuous. The statistically significance of the global effect of the quintiles of the cumulative airborne cadmium was derived from the likelihood ratio test comparing the models including and excluding terms for quintiles. Heterogeneity of associations across BC stage at diagnosis was assessed using polytomous logistic regression and *P* values for heterogeneity were derived from Wald tests [39]. For sensitivity analyses, we repeated our analyses using the mean of the annual airborne cadmium exposure index (from entry into the cohort to the index date) of the cadmium exposure instead of the cumulative exposure. Additional adjustments for the mammographic examination before inclusion (yes, no) was also done. Cubic splines [40], with four knots placed at 5th, 35th, 65th, and 95th percentiles of the cumulative exposure to airborne cadmium distribution [41] were performed to explore the non-linearity of the relationship between cadmium and BC risk.

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

Results

Differences in cases sociodemographic, reproductive and lifestyle characteristics according to stage are summarized in Table 1. Among the 3,924 women who had stage information, the majority were diagnosed at stage I (2,370 cases) and at stage II (1,216 cases). In contrast, advanced BC was not frequent, only 311 and 27 cases were diagnosed at stages III and IV, respectively. Due to the small number

of stage IV BC, stage III and IV were combined in one category (338 cases) to have enough cases for statistical analyses. Women with stage I BC were more likely to be diagnosed older (P <0.001), to be postmenopausal (P < 0.001), to be MHT users (P = 0.003), to have FHBC (P = 0.035), and to have a personal history of benign breast disease (P = 0.026). In contrast, women with stages III-IV BC were more likely to be obese (BMI ≥ 30) (P = 0.002). Also, hormone negative BC (ER- and PR-) were more common among women with advanced stage (III-IV). The distributions of alcohol intake, smoking status, urban/rural status, physical activity, education level, oral contraceptive use, age at menarche, breastfeeding, parity and age at first pregnancy were similar across the three stage groups.

Analyses comparing the distribution of demographics and risk factors by grade of differentiation of BC at diagnosis showed no substantial differences overall (Additional Table 1). Differences across these groups were observed for rural/urban status at birth (P = 0.013), menopausal status at index date (P < 0.001), FHBC (P = 0.035), ER and PR status (P < 0.001).

Further analyses comparing the distributions of known risk factors for BC according to the histological type are shown in the Additional Table 2. Women with invasive tubular carcinoma (ITC) tend to have higher level of cumulative airborne cadmium exposure as compared to women with other histological types. However, ER and PR BC were more frequent among women with mixt histology (invasive ductal and lobular carcinoma) (P < 0.001 and P = 0.009, respectively).

Table 2 shows the association between cumulative airborne cadmium exposure index and risk of BC according to the stage in women. Overall, there was no statistical significant association between cumulative airborne cadmium exposure and BC risk differed by stage. According to stage, the multivariable adjusted ORs for the fifth versus first quintile were 1.02 (95% CI: 0.83-1.25) for stage I BC, 1.11 (95% CI: 0.84-1.49) for stage II BC, and 0.67 (95% CI: 0.37-1.24) for stages III-IV BC (Table 2). There was no statistically significant association between cadmium and risk of stage of BC among both premenopausal and postmenopausal women (data not shown).

The association between cumulative airborne cadmium exposure index and risk of BC by grade of differentiation is shown in **Table 3.** Overall, no statistically significant associations were observed between levels of cumulative airborne cadmium exposure index and risk of BC by grade of differentiation at diagnosis. The ORs comparing the fifth quintile to the reference category (first) = 1.19 (95% CI: 0.74-1.92) for grade 1 BC, 1.11 (95% CI: 0.84-1.47) for grade 2 BC and 0.89 (95% CI: 0.70-1.15) for grade 3 BC. There was no statistically significant heterogeneity of the results by grade of differentiation (P heterogeneity = 0.934).

With respect to the histological types, we found a suggestive evidence that the association between cadmium and BC risk varied by histology, although there was no statistically significant heterogeneity (P heterogeneity = 0.347) (**Table 4**). Cadmium was associated with higher risk of ITC with the adjusted OR for the fifth versus first quintile being 3.44 (95% CI: 1.10-10.7). No statistically significant relationships were found for invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) or mixt BC. Results of the additional cubic splines modelling using four knots with the minimum value as the reference

category, confirmed a dose-response relation between cumulative airborne BaP exposure and ITC risk (Additional Figure 1).

In sensitivity analyses, the multivariable risk estimates did not substantially change after further adjustment for mammographic examination before inclusion (data not shown). Similarly, using the mean annual cadmium exposure instead of cumulative airborne cadmium exposure showed similar findings (Additional Table 3).

Discussion

To the best of our knowledge, this is the first epidemiological study exploring the association between airborne cadmium exposure and risk of BC by stage, grade of differentiation, and by histological type. The results of this nested case-control study do not support the hypothesis that cumulative airborne exposure to cadmium increases the risk of advanced stage BC at diagnosis. Further analyses by grade of differentiation of BC at diagnosis also showed no evidence of an association between airborne cadmium and risk of BC by grade. In contrast, we found an increased risk of ITC BC, suggesting that the association of cadmium air pollution with BC may differ by histological types.

There is an increasing body of laboratory evidence supporting that cadmium promotes BC cell growth, particularly metastasis [17, 42, 43]. In our study, although the cumulative airborne cadmium exposure index was higher in advanced stages of BC, the multivariable analyses showed no statistically significant association. Overall, our results were not consistent with the findings from several experimental studies reporting that risk factor for BC associated cadmium may vary according to the stage [18, 44]. Likewise, Peng et al. reported that high cadmium exposure was observed in advanced stages of BC, indicating that it may promote the development of BC [45]. Also, the lack of association between airborne cadmium and grade of differentiation of BC is not in line with mechanistic evidence suggesting that cadmium may play a role in the differentiation of BC cells and tissues [26]. The inconsistency observed between our results and experimental findings is likely to be explained by the size of some of the subgroups that was too small to provide an accurate estimate of the effect, particularly for the analyses by stage. Further epidemiological studies with more information on the stage and grade of BC are warranted. Also, in our population, even if women were chronically exposed for long periods, they are generally exposed to low doses that may not be reflected by the short-term high cadmium doses that were shown to induce aggressiveness and transformation of non-cancerous human mammary epithelial cells in experimental studies [22, 46, 47].

The results of the present study suggested that women had a higher risk of ITC BC associated with higher exposure to cadmium. These women also had significantly higher levels of cadmium as compared to women with other histological subtypes of BC. A stronger risk of ITC compared to the risk of other histological types has been reported previously for current MHT use [48, 49]. Only one study has assessed the association between cadmium and risk of BC by histological subtype, reporting an increased risk of ductal BC with an adjusted OR of 1.18 (95% CI: 0.89–1.58) in the intermediate and 1.53

(95% CI: 1.15–2.04) in the highest category of urinary cadmium as compared to the lowest tertile. However this study did not investigate tubular BC [50].

The results of the present study add to the current evidence that risk may vary across histological BC types, and suggest a role of cadmium in the etiology of ITC. However, although the cubic splines modelling confirmed the dose response relation between cadmium exposure and ITC, our results should be interpreted with caution, due to the small numbers of ITC and the possibility of false positive findings as a result of multiple testing.

Independently of these clinico-pathological characteristics, several epidemiological studies have reported an increased risk of overall BC associated with higher cadmium levels in urine [51, 52] or dietary cadmium [53, 54], although other studies reported no or null statistically significant associations [46, 55]. A 2016 random effect meta-analysis reported that higher level of urinary cadmium was associated with a higher risk of BC, pooled OR of the highest versus lowest quantile was 2.24 (95% CI: 1.49–3.35) [56]. A more recent meta-analysis did not support an association between cadmium and overall BC, although they suggested marginal positive relation between dietary cadmium intake and breast cancer [29].

The exact mechanisms linking cadmium and BC development are still unclear. Several potential mechanisms have been proposed, involving both estrogen mediated pathways and ER independent mechanisms. Cadmium has been shown to interfere with a number of normal estrogen-sensitive pathways. In particular, cadmium can interact with the hormone-binding domain of ER [57, 58] to regulate several genes and transcription factors involved in BC cell growth and proliferation [59, 60]. Recently, Bloomfield demonstrated that chronic cadmium exposure, even at low levels, can increase the malignancy of BC cells by decreasing their dependency on ERα and increasing the adaptability of the cancer cells [61]. Additionally, cadmium can promote the development of cancer through several ER independent mechanisms. Cadmium has been shown to activate the production of reactive oxygen species (ROS) and reduce the anti-oxidative defenses in breast tumor cells, one of the major mechanisms of breast carcinogenesis [62]. Furthermore, cadmium induces genotoxic effects, including DNA modifications due to cadmium-induced oxidative damage [63]. Also, cadmium has been found to alter DNA repair and cause genomic instability [63].

Strengths of our study include the prospective design of the E3N cohort study and the high quality information collected. One of the most important strength of our study is the accurate geocoding of the residential history to reconstruct exposure variation over time, resulting from changes in source emissions over the study period as well as from the subjects' residential moves. Unlike our study, the majority of epidemiological studies considered exposure at a single point in time under the assumption that a single measure represents a proxy for that exposure over a longer time. Also, the reliability of the exposure method assessment was evaluated in comparison with the results provided by SIRANE, a Gaussian atmospheric dispersion model [64–66] by calculating weighted kappa statistics (wκ) and coefficient of determination (R^2). Overall findings showed strong concordance between the GIS-based metric and the dispersion model, 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 [34]. Another essential strength of our study is the availability of detailed information on individual reproductive and lifestyle factors allowing extensive consideration of potential confounding, particularly socioeconomic status, tobacco smoking, BMI, and urban rural status factors. As discussed in our previous study on airborne and BC risk [27], a further important strength is the reliability of our GIS-based metric as compared to the SIRANE atmospheric dispersion model, stressing the performance of our exposure assessment method to provide vigorous estimates of the subject's airborne exposure [34]. Limitations of our study comprise the lack of earlier residential history and historical airborne cadmium exposure estimates before inclusion into the cohort in 1990 [33]. This left truncation of exposure data has been reported to lead to a loss of accuracy of exposure estimates and may be associated with potential overestimation or underestimation of the relation between exposure and the risk of disease [67, 68]. Further limitations include the lack of biological sampling of cadmium and dietary estimates, and the potential uncertainties in airborne cadmium exposure, since punctual and non-industrial sources (such as biomass fires, traffic-related exposure, manufactured good burnings, outdoor burning and illegal landfills) were not included in the GIS-based metric due to the difficulties in their geolocalization and in finding a reliable retrospective inventory [33]. Also, compared to dietary exposure, inhalation is a far smaller source of cadmium exposure except for smokers. However a larger proportion of inhaled cadmium is retained by the body than of ingested cadmium; according to world health organization (WHO) findings, 2–6% of ingested cadmium is absorbed by the body while in the case of inhalation, 30–60% is absorbed [21]. Nevertheless these sources of cadmium constitute a small part of cadmium exposure emissions during the study period [33, 69], whereas the GIS-based metric included almost all industrial sources of cadmium as well as some miscellaneous sources such as crematoria.

Conclusions

Our study do not support the hypothesis that cadmium air pollution exposure may have a role in the risk of advanced stage of BC and in the differentiation of breast tumor cells, which have been suggested in experimental studies. In contrast, we found a suggestive positive association between cadmium and ITC BC. However, these findings should be interpreted with caution and further epidemiological studies taking into account clinico-pathological characteristics of BC are warranted to evaluate whether cadmium may be associated to specific histological subtypes of BC, in particular ITC.

Abbreviations

AACEI: annual airborne cadmium exposure index; AFP: age at first full-term pregnancy; BMI: body mass index; BC: breast cancer; CIs: confidence intervals; CNIL: commission for data protection and privacy; DHQS: diet history questionnaires; E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; ER: estrogen receptor; EPIC: European Prospective Investigation into Cancer and Nutrition; EMEP: European Monitoring and Evaluation Program; EDC: endocrine-disrupting-chemicals; FHBC: family history of breast cancer; GIS: geographic information system; IDC: invasive ductal carcinoma; invasive lobular carcinoma (ILC); ITC: invasive tubular carcinoma; IARC: International

Agency for Research on Cancer; MHT: menopausal hormone therapy; MET: metabolic equivalent task; IGN: National Geographic Institute; ORs: odds ratios; PR: progesterone receptor; OMINEA: Organization and Methods of the National Inventories of the Atmospheric Releases; SD: standard deviation; TNM: tumor-node-metastasis; TCDD: tetrachlorodibenzo-p-dioxin; wκ: weighted kappa; WHO: world health organization.

Declrations

Ethics approval and consent to participate

The study was approved by the French National Commission for Data Protection and Privacy (CNIL), and informed consent was obtained from all individual participants included in the study.

Consent for publication

All of the authors have read and approved the article.

Availability of data and materials

Not applicable for that section. The datasets generated and/or analyzed during the current study are not publicly available for ethical reasons, permission by the participants to use their data, according to the signed informed consent, and from the MGEN, their insurance company, is restricted to the team in charge of the cohort, which can be extended to collaborators with a specific research agreement.

Competing interests

We declare that they have no potential conflicts of interest

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Authors' contributions

All authors contributed to the study conception and design. AA: participated to the conception and design of the work, performed statistical analyses and interpretation, and drafted the first article. DP: helped with

the data collection and results interpretation, and revised the article. TC: participated to the data collection, exposure assessment, and critical revision of the article. AMND: participated to the conception and design of the work, and data collection. EF: participated to the data collection and data analysis (geocoding and spatial analyses) and revised the article. KL: helped with the data analysis and interpretation. GS: participated to the conception and design of the work, and data collection. PS: participated to the conception and design of the work. FRM: helped with the data interpretation. BF: was responsible for the conception and design and supervising the work, and data interpretation. All authors read, revised and approved the final manuscript.

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Tables

Table 1: Demographic and lifestyle characteristics of cases according to the stage of breast cancer at diagnosis in the case-control study nested within the E3N cohort, France, 1990-2008.

Characteristics	Stage I n (%)=2,370 (60.4)	Stage II n (%)=1,216 (31.0)	Stages III-IV n (%)=338 (8.6)	*P* value
Cumulative airborne cadmium exposure (mg/m^2), mean ± SD	12.6 ± 58.5	12.9 ± 57.3	14.9 ± 103	0.436
Age at recruitment (years), mean ± SD	49.9 ± 6.1	49.6 ± 6.4	49.5 ± 6.7	0.061
Age at diagnosis (years), mean ± SD	59.6 ± 7.5	59.0 ± 7.8	57.5 ± 8.3	<0.001
Alcohol drinking (g/day), n (%)				
Never	219 (9.2)	102 (8.4)	35 (10.4)	
< 6.7	687 (29.0)	348 (28.6)	88 (26.0)	
≥ 6.7	1,047 (44.2)	522 (42.9)	151 (44.7)	
Missing	417 (17.6)	244 (20.1)	64 (18.9)	0.511
Body Mass Index (kg/m^2), n (%)				
< 25	2,006 (84.6)	987 (81.2)	271 (80.2)	
25 - <30	313 (13.2)	185 (15.2)	50 (14.8)	
≥ 30	51 (2.2)	44 (3.6)	17 (5.0)	0.003
Smoking status, n (%)				
Never	1,270 (53.6)	657 (54.0)	189 (55.9)	
Current	362 (15.3)	187 (15.4)	48 (14.2)	
Former	748 (31.3)	372 (30.6)	101 (29.9)	0.945
Status of birthplace, n (%)				
Rural	616 (26.0)	333 (27.4)	93 (27.5)	
Urban	1,535 (64.8)	766 (63.0)	224 (66.3)	
Missing	219 (9.2)	117 (9.6)	21 (6.2)	0.305
Physical activity (METs-h/week), n (%)				
< 25.3	581 (24.5)	303 (24.9)	78 (23.1)	
25.3 - 37.3	763 (32.2)	357 (29.4)	119 (35.2)	
37.4 - 56.9	613 (25.9)	332 (27.3)	88 (26.0)	
≥ 57.0	413 (17.4)	224 (18.4)	53 (15.7)	0.444
Education, n (%)				

Secondary	292 (12.3)	143 (11.8)	39 (11.5)	
1 to 2 year university degree	1,194 (50.4)	623 (51.2)	176 (52.1)	
≥ 3 year university degree	884 (37.3)	450 (37.0)	123 (36.4)	0.962
Menopausal status, n (%)				
Premenopausal	406 (17.1)	254 (20.9)	99 (29.3)	
Postmenopausal	1,964 (82.9)	962 (79.1)	239 (70.7)	<0.001
Use of oral contraceptives, n (%)				
No	976 (41.2)	490 (40.3)	135 (39.9)	
Yes	1,394 (58.8)	726 (59.7)	203 (60.1)	0.829
Use of MHT, n (%)				
No	1,924 (81.2)	1,003 (82.5)	299 (88.5)	
Yes	446 (18.8)	213 (17.5)	39 (11.5)	0.004
Parity & Age at First Pregnancy (AFP), n (%)				
0	311 (13.1)	168 (13.8)	40 (11.8)	
1-2 & AFP < 30	1,190 (50.2)	585 (48.1)	168 (49.7)	
1-2 & AFP ≥ 30	268 (11.3)	143 (11.8)	37 (11.0)	
≥ 3	601 (25.4)	320 (26.3)	93 (27.5)	0.873
Age at menarche, n (%)				
< 12	500 (21.1)	275 (22.6)	66 (19.5)	
12 - 13	1,233 (52.0)	637 (52.4)	193 (57.1)	
≥ 14	637 (26.9)	304 (25.0)	79 (23.4)	0.285
Breastfeeding, n (%)				
No	1,133 (47.8)	566 (46.6)	162 (47.9)	
Yes	1,237 (52.2)	650 (53.4)	176 (52.1)	0.760
Family history of breast cancer, n (%)				
No	1,931 (81.5)	976 (80.3)	293 (86.7)	
Yes	439 (18.5)	240 (19.7)	45 (13.3)	0.026
History of personal benign breast disease, n (%)				
No	1,643 (69.3)	850 (69.9)	259 (76.6)	

Yes	727 (30.7)	366 (30.1)	79 (23.4)	0.023
Mammography before inclusion, n (%)				
No	478 (20.2)	275 (22.6)	103 (30.5)	
Yes	1,892 (79.8)	941 (77.4)	235 (69.5)	<0.001
ER status, n (%)				
ER -	345 (14.6)	205 (16.9)	89 (26.3)	
ER +	1,590 (67.1)	837 (68.8)	187 (55.3)	
Missing	435 (18.3)	174 (14.3)	62 (18.3)	<0.001
PR status, n (%)				
PR -	647 (27.3)	357 (29.4)	128 (37.9)	
PR +	1,225 (51.7)	646 (53.1)	142 (42.0)	
Missing	498 (21.0)	213 (17.5)	68 (20.1)	<0.001

The analyses were done on the three stages after excluding cases with missing stage information (477 cases)

P values were estimated based on Kruskal Wallis test for continuous variables and Chi-square test for categorical variables
SD: Standard deviation, MET: Metabolic Equivalent of Task, MHT: menopausal hormone replacement therapy, Menopausal status at index date: date of diagnosis of the case in the case-control pair, ER: estrogen receptor, PR: progesterone receptor

Table 2: Odds ratio and 95% confidence intervals (OR, 95% CI) for the association of quintiles of the cumulative airborne cadmium exposure with risk of breast cancer according to breast cancer stage in the case-control study nested within the E3N cohort, France, 1990-2008.

Cumulative airborne cadmium exposure (mg/m^2)	n cases/ controls	OR (95% CI) [a]	*P* trend	*P* likelihood	*P* heterogeneity
Stage I					
≤ 0.072	454/481	Ref			
> 0.072 - 0.767	491/464	1.12 (0.93-1.35)			
> 0.767 - 2.822	491/462	1.16 (0.95-1.40)			
> 2.822 - 11.07	470/492	1.05 (0.86-1.27)			
> 11.07	464/471	1.01 (0.82-1.24)	0.882	0.502	
Stage II					
≤ 0.072	257/242	Ref			
> 0.072 - 0.767	217/265	0.81 (0.62-1.05)			
> 0.767 - 2.822	253/242	1.05 (0.80-1.37)			
> 2.822 - 11.07	236/237	0.95 (0.72-1.25)			
> 11.07	253/230	1.10 (0.83-1.47)	0.296	0.208	
Stages III-IV					
≤ 0.072	78/63	Ref			
> 0.072 - 0.767	69/70	0.83 (0.48-1.42)			
> 0.767 - 2.822	66/85	0.62 (0.37-1.05)			
> 2.822 - 11.07	63/55	0.76 (0.42-1.38)			

> 11.07	62/64	0.70 (0.38-1.28)	0.253	0.470	0.455

[a] Multivariable models were adjusted for physical activity, tobacco smoking status, alcohol intake, level of education, body mass index, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, status of birthplace, previous family history of breast cancer and personal history of benign breast disease

P likelihood: P-values from likelihood ratio test comparing the statistically significance of the global effect of the quintiles

P heterogeneity: comparing heterogeneity of associations across breast cancer stage at diagnosis

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

Cumulative airborne cadmium exposure (mg/m^2)	n cases/ controls	OR (95% CI) [a]	*P* trend	*P* likelihood	*P* heterogeneity
Grade 1					
≤ 0.072	101/104	Ref			
> 0.072 - 0.767	116/114	1.19 (0.80-1.78)			
> 0.767 - 2.822	116/108	1.17 (0.76-1.78)			
> 2.822 - 11.07	107/122	0.97 (0.63-1.48)			
> 11.07	108/100	1.19 (0.74-1.91)	0.861	0.760	
Grade 2					
≤ 0.072	262/264	Ref			
> 0.072 - 0.767	251/251	1.01 (0.78-1.30)			
> 0.767 - 2.822	248/261	1.02 (0.79-1.32)			
> 2.822 - 11.07	237/236	1.04 (0.79-1.36)			
> 11.07	265/251	1.10 (0.83-1.45)	0.516	0.972	
Grade 3					
≤ 0.072	321/323	Ref			
> 0.072 - 0.767	318/335	0.96 (0.76-1.20)			
> 0.767 - 2.822	345/306	1.08 (0.86-1.36)			
> 2.822 - 11.07	335/332	0.97 (0.77-1.22)			
> 11.07	302/325	0.90 (0.70-1.15)	0.481	0.632	0.934

[a] Multivariable models were adjusted for physical activity, tobacco smoking status, alcohol intake, level of education, body mass index, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, status of birthplace, previous family history of breast cancer and personal history of benign breast disease

P likelihood: P-values from likelihood ratio test comparing the statistically significance of the global effect of the quintiles

P heterogeneity: comparing heterogeneity of associations across breast cancer grade at diagnosis

Table 4: Odds ratio and 95% confidence intervals (OR, 95% CI) for the association of quintiles of the cumulative airborne cadmium exposure with risk of breast cancer according to the histological type in the case-control study nested within the E3N cohort, France, 1990-2008.

Cumulative airborne cadmium exposure (mg/m^2)	n cases/ controls	OR (95% CI) [a]	*P* trend	*P* likelihood	*P* heterogeneity
Invasive ductal carcinoma					
≤ 0.072	580/608	Ref			
> 0.072 - 0.767	608/595	1.09 (0.92-1.28)			
> 0.767 - 2.822	614/586	1.11 (0.94-1.32)			
> 2.822 - 11.07	572/573	1.06 (0.90-1.26)			
> 11.07	566/578	1.01 (0.84-1.22)	0.929	0.695	
Invasive lobular carcinoma					
≤ 0.072	145/131	Ref			
> 0.072 - 0.767	110/140	0.80 (0.55-1.15)			
> 0.767 - 2.822	136/130	0.99 (0.68-1.43)			
> 2.822 - 11.07	150/142	1.01 (0.70-1.45)			
> 11.07	135/133	0.95 (0.64-1.41)	0.790	0.706	
Invasive tubular carcinoma					
≤ 0.072	18/28	Ref			
> 0.072 - 0.767	25/28	1.71 (0.62-4.71)			
> 0.767 - 2.822	32/29	1.53 (0.58-4.01)			
> 2.822 - 11.07	26/21	2.55 (0.79-8.25)			
> 11.07	31/26	**3.44 (1.10-10.7)**	0.034	0.257	
Ductal-lobular BC					
≤ 0.072	25/21	Ref			
> 0.072 - 0.767	21/15	1.32 (0.40-4.38)			

> 0.767 - 2.822	19/22	0.77 (0.23-2.59)			
> 2.822 - 11.07	18/24	0.50 (0.15-1.69)			
> 11.07	26/27	0.97 (0.26-3.60)	0.436	0.648	0.347

[a] Multivariable models were adjusted for physical activity, tobacco smoking status, alcohol intake, level of education, body mass index, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use, status of birthplace, previous family history of breast cancer and personal history of benign breast disease

P likelihood: P-values from likelihood ratio test comparing the statistically significance of the global effect of the quintiles

P heterogeneity: comparing heterogeneity of associations across histological type of breast cancer

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AddionalMaterialEnvhealth.docx