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Associations between dietary exposure to profiles of metalloestrogens and estrogen-receptor positive breast cancer risk in the French E3N cohort

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Abstract

Metalloestrogens are ionic metals and metalloids that can activate estrogen receptor, and are suspected to play a role in breast cancer occurrence. This study explored the relationship between dietary exposure profiles to metalloestrogens and estrogen-receptor positive breast cancer (ERP-BC) risk among women in the French E3N cohort.

A prospective study was conducted involving 66 722 women who completed a food frequency questionnaire in 1993. Food consumption data were combined with food contamination data obtained from the Second French Total Diet Study, to estimate the dietary intake of 14 metalloestrogens. A principal component analysis was performed to identify the main dietary exposure profiles to metalloestrogens. The retained principal components were included in Cox regression models, used to estimate Hazard Ratios (HR) and their 95% confidence intervals (95% CI) for the associations between the adherence to the identified profiles and ERP-BC risk identified until 2014, adjusted for confounding factors selected using a directed acyclic graph.

After an average follow-up of 17.7 years, 3 739 incident cases of ERP-BC were identified. Four principal components were retained, explaining 80.5% of the variance. A statistically significant positive association between the third principal component, mainly characterized by dietary intake of inorganic arsenic and vanadium, and ERP-BC risk was estimated (HR: 1.04, 95% CI: 1.00–1.07, p-value: 0.03). No statistically significant association was found when evaluating the effect of each metalloestrogen individually.

The results suggests that even relatively low levels of exposure to inorganic arsenic and vanadium, when combined, could increase the risk of ERP-BC.

Keywords Metalloestrogens, Breast cancer, Principal component analysis, Dietary exposure to contaminants, Food frequency questionnaire, Prospective cohort

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Introduction

Breast cancer is a public health issue in France and worldwide. Defined as the uncontrolled proliferation and spread of abnormal cells from the mammary gland, it is a major cause of morbidity and mortality among women. Indeed, about one in eight women will be affected by breast cancer during her lifetime (K. [48]). It was the most frequently diagnosed cancer worldwide in 2020, with 2.3 million new cases [7]. This situation underscores the importance of understanding the factors that contribute to the development of this disease. In addition to the already known risk factors, which include genetic and non-genetic factors such as lifestyle, age, alcohol, tobacco, and hormonal context [30, 57, 70], environmental contaminants are suspected to be linked to breast cancer. In particular, hormone-dependent breast cancer mainly stimulated by endogenous estrogens [69], could see its development favored by environmental contaminants that mimic the action of these hormones [16].

Among these environmental contaminants, metalloestrogens are ionic metals and metalloids capable of activating the estrogen receptor and mimicking the action of physiological estrogens [18]. These metal(oid)s (aluminum, antimony, arsenic, barium, cadmium, chromium, cobalt, copper, tin, mercury, nickel, lead, selenium, and vanadium) are natural components of the Earth's crust and are found in all aspects of the environment, including air, water, soil, and plants [35]. Human activities, particularly in industry, contribute to the release and accumulation of metalloestrogens in the environment. Indeed, certain metalloestrogens are extensively used in metallurgy and are subsequently emitted as fine particles during industrial processes [41]. They are then transported by wind, disseminated in soils and aquatic environments, and thus contaminate fauna, flora, and the food chain [28]. Metalloestrogens are not biodegradable, and some of them can bioaccumulate in living organisms, in particular cadmium, mercury, lead, arsenic and antimony [11, 26, 34]. Diet represents a major route of exposure for the general population to metalloestrogens. For example, ingestion of contaminated food or water represents the main source of exposure to arsenic, and to cadmium for non-smokers (EFSA Panel on Contaminants in the Food Chain (CONTAM) et al., [23]; [31]). Other sources of exposure are linked to their presence in cosmetics [51], and plastics or food packaging [12]. Some metals, such as arsenic, mercury, chromium, lead and cadmium, are already known to be toxic, exhibiting effects on bone, kidney, the cardiovascular system, and the nervous system [6, 19]. Others, like selenium, copper, chromium, nickel, vanadium, and cobalt are essential trace elements necessary for the proper functioning of the body, but can become toxic at high concentrations [4]. Some of these metalloestrogens are recognized as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer (IARC), such as arsenic, cadmium, nickel compounds, and chromium VI. Other have been classified as probably carcinogenic (Group 2A) such as inorganic compounds of lead, soluble cobalt(II) salts, and trivalent antimony. Finally, some have been classified as possibly carcinogenic (Group 2B) such as methylmercury, cobalt(II) oxide, and vanadium pentoxide (Group 2B) [32, 56]. Cadmium and arsenic are also classified as potential endocrine disruptors based on evidence from in vivo rodent and in vitro human experiments [59].

Given the role of estrogens in the development and progression of breast cancer and the carcinogenicity of some metals to several sites, the ability of metalloestrogens to bind and activate estrogen receptors suggests that they may also contribute to breast carcinogenesis [13, 18, 71]. In vitro and ex vivo, it has been shown that metalloestrogens stimulate the proliferation of MCF7 breast cancer cells [1, 8, 40, 66].

Regarding studies in human populations, the levels of metalloestrogens in human tissues, such as blood, adipose tissue, hair, and nails, were generally higher in breast cancer cases compared to non-cases [2, 17, 38].

Regarding the relationship between dietary exposure to metalloestrogens and breast cancer, most research focuses on cadmium. A recent meta-analysis of 17 studies did not find an association between dietary cadmium intake and the risk of breast cancer (OR: 1.05, 95% CI: 0.91–1.21, $I^2 = 69\%$) [25]. The association of dietary exposure to other metalloestrogens and the risk of breast cancer has also been studied. For example, two cohort studies on dietary arsenic did not show a statistically significant association with breast cancer [52, 72]. Another recent review evaluated the effects of dietary exposure to selenium, copper, and cadmium, and highlighted positive, negative or no associations for studies in cadmium, and no association for most studies on selenium [33].

Few studies have evaluated the combined effects of multiple metalloestrogens on the risk of breast cancer. For example, a study have been conducted on airbone exposure to multiple metals [37], but most studies have focused on the individual effects of metalloestrogens. Considering dietary exposures, to our knowledge, no prospective study has evaluated the association between dietary exposure profiles to metalloestrogens and the occurrence of breast cancer.. However, metals often occur as mixtures in the environment, and their combined effects, even at low doses, may result in health impacts that are not apparent when each metalloestrogen is studied separately [5, 68]. Therefore, the main objective of this study was to explore the effect of dietary exposure profiles to the 14 metalloestrogens on the risk

of developing estrogen receptor-positive breast cancer in the E3N cohort.

Materials and methods

The E3N Cohort

The E3N study is an ongoing prospective cohort of women covered by the French national health insurance plan for people working for the national education system, the Mutuelle Générale de l'Éducation Nationale (MGEN), that began in 1990. The MGEN mainly covers teachers or teachers' spouses, but also other professions within the French education system. It included 98 995 women, born between 1925 and 1950, residing in mainland France. This study evaluates the effect of lifestyle, diet, environment, and medical treatments on women's health. Participants have completed paper questionnaires every two to three years about their lifestyle, environment, and health status. The participation rate has remained high (77% to 92%), with only 3% loss of follow-up since 1990 [14, 15].

Study population

This study included participants who responded to the dietary questionnaire sent in 1993 ($N=74\ 522$). We excluded participants with prevalent cancer at the start of follow-up ($N=4\ 709$), those who did not complete any questionnaire after the dietary questionnaire ($N=568$), because their follow-up time would be zero, those who declared extreme energy intake values, i.e., below the 1st or above the 99th percentile of the ratio between energy intake and energy requirement ($N=1\ 366$), and breast cancer cases for which estrogen receptor information was unavailable ($N=1\ 157$). Our final study population consisted of 66 722 participants.

Estimation of dietary intake of metalloestrogens

Dietary consumption data were collected from the third questionnaire, sent out to women in 1993. This semi-quantitative food frequency questionnaire comprised 238 food items and was previously validated on 119 women aged 36–65 years and employees of a large anti-cancer hospital in France [65]. The questionnaire collected information on the consumption of foods and beverages over the past year, based on typical French eating habits, with questions covering 8 meals (breakfast, morning snack, aperitif before lunch, lunch, afternoon snack, aperitif before dinner, dinner, and post-dinner snack). It was constituted in two part: the first part focused on the frequency and quantity of consumption of each food group, while the second part gathered more details on the foods and beverages consumed within the food groups of the first part, as well as information on condiments and added fats.

Food contamination data come from the Total Diet Study 2 (TDS2) [4]. This study was conducted by the French National Agency for Food, Environmental and Occupational Health and Safety (ANSES) between 2007 and 2009, and measured the dietary contaminations of more than 445 different substances in 212 types of food, including the 14 metalloestrogens (aluminum, antimony, arsenic, barium, cadmium, chromium, cobalt, copper, tin, mercury, nickel, lead, selenium, and vanadium). A total of 20 280 food items were collected in 8 regions of mainland France, leading to 1 352 composite samples which were "prepared as consumed" and in which substances levels were measured. Non-quantified values of metalloestrogens were replaced by their limit of detection, and non-detected values by 0, corresponding to the lower-bound scenario. They are presented in Supplementary Table 1.

In the case of arsenic, chromium and mercury, only certain forms are potentially toxic for human health [4, 6]: inorganic arsenic, chromium VI and methylmercury respectively. Inorganic arsenic contamination levels were estimated from total arsenic levels measured in TDS2 food items, by multiplying these contamination levels by a coefficient corresponding to the proportion of inorganic arsenic in total arsenic for the corresponding food item. For water, fish and shellfish food items, these proportion are known (i.e., 1.00, 0.01 and 0.02 respectively) [54]. For other foods, one of the scenarios suggested by EFSA (considering a proportion of 0.50) was adopted (EFSA Panel on Contaminants in the Food Chain [20]. Similarly, methylmercury contamination levels were estimated by multiplying total mercury levels by the assumed proportions of methylmercury in different foods (1.00 in fish and shellfish, 0 in other foods) [53]. In the case of chromium, the available information did not allow us to estimate levels of chromium VI, so total chromium was used for the analyses.

Dietary consumption and contamination data were merged, as detailed in a previous article [39]. In short, a direct correspondence between TDS2 and E3N food items was established for 146 E3N food items. For 56 E3N food items for which there was no direct correspondence, the most similar TDS2 food item available was matched. Finally, 36 food items of the E3N database were excluded due to the lack of possible match with TDS2.

For each participant, the average daily dietary intake of metalloestrogens (µg/day) was estimated by multiplying the average daily amounts consumed of each

food component by the average contamination levels of the corresponding food component.

Identification of estrogen-receptor positive breast cancer cases

A case was defined as the occurrence of estrogen receptor-positive (ERP) breast cancer during the study period (1993–2014). Cases were primarily identified through self-reports via E3N questionnaires. Additional cases were reported through spontaneous declarations by relatives and the national registry of medical causes of death (CépiDC). For all cases, attempts were made to contact the participants' doctors to obtain pathology reports. Information on tumor characteristics was extracted from these reports, allowing to validate the diagnosis and to identify ERP breast cancer. Only validated cases were included in this study.

Covariates

The adjustment variables included in the Cox model described below were selected using a directed acyclic graph (Supplementary Fig. 1) to estimate the total effects of dietary intake of metalloestrogens on the risk of ERP breast cancer. Some of the adjustment variables described in the next paragraph were collected in several questionnaires in the E3N study. In our study, only the value available at the start of follow-up was used. Indeed, for a covariate to be considered as confounding factor, it must have been able to have an influence on the outcome, but as well on the exposure, so it is preferable not to use information measured after the latter has been collected.

Information on birth generation ($\leq$1930, (1930–1935], (1935–1940], (1940–1945], >1945) and education level (<12 years, 12 to 14 years, >14 years) was collected in the first questionnaire sent in 1990. Data on body mass index (BMI, <18.5, (18.5–22.5], (22.5–25], (25–30], >30 kg/m^2), smoking status (non-smoker, former smoker, current smoker), history of contraceptive pill use (yes/no), parity and age at first full-term pregnancy (nulliparous, one or two children and age at first full-term pregnancy <30 years, more than three children and age at first full-term pregnancy <30 years, age at first full-term pregnancy $\geq$30 years), cumulative breastfeeding duration (no breastfeeding, less than 6 months of breastfeeding, at least 6 months of breastfeeding), menopausal status and recent use of hormone replacement therapy (HRT) (premenopausal, post-menopausal with recent use of HRT, i.e., less than a year ago, post-menopausal without recent use of HRT) were obtained from the second questionnaire sent in 1992. Finally, information on physical activity (continuous, in metabolic equivalent of task per hour/week), daily alcohol intake (continuous, in g/day), daily fat intake (continuous, in g/day), total daily energy intake (continuous, in kcal/day), and consumption of the main food groups (i.e., bread and salty cereal products, cakes and sweet cereal products, charcuterie, cheese, coffee, eggs, fish, fresh dairy, fruits, meat, offal, oil, butter and other fats, cream, pizza, quiche, salted pies, sandwich, hamburger, seafood, soda, starch food, sugar products, sweet dairy, teas, vegetables, vinaigrette, water) (continuous, in g/day) were obtained from the dietary part of the third questionnaire sent in 1993. Adherence to "Western" and "Prudent" dietary patterns derived from principal component analysis were also obtained from the dietary questionnaire, as described elsewhere [67]. Adherence to the French dietary recommendations, using the simplified "Programme National Nutrition Santé—guidelines score 2" (PNNS score) was also estimated using data from the dietary questionnaire [10].

For the main analyses, covariates with less than 5% missing values were imputed by the mode (for categorical variables) or the median (for continuous variables). A "missing data" category was created for covariates with $\geq$5% of missing values (only BMI and recent use of HRT).

Descriptive analyses

Baseline characteristics (median and interquartile ranges for continuous variables, numbers and proportions for categorical variables) were described in the study population. Number or proportion of missing values were also provided before imputation. For each metalloestrogen, its distribution (median, interquartile range, minimum, and maximum) in the study population was described. In addition, the contributions of the main food groups to the intake of each metalloestrogen were estimated. Spearman's correlation coefficients between metalloestrogens intake were calculated and presented.

Main analyses

A principal component analysis was performed on the 14 standardized metalloestrogens intake variables (i.e., aluminum, antimony, inorganic arsenic, barium, cadmium, chromium, cobalt, copper, lead, methylmercury, nickel, selenium, tin, and vanadium), to identify principal components representing the main dietary exposure profiles to metalloestrogens. A maximum number of 14 principal components was identified, and the final number of principal components to be retained was chosen using several criteria. Firstly, the interpretability of the profiles obtained was considered, so that each metalloestrogen had a high loading in at least one principal component, and if possible, in only one principal component. Secondly, the variance explained by each principal components was considered, corresponding to its eigenvalue divided by the sum of the eigenvalues of all

principal components. The Spearman rank correlation coefficient between the main food group consumptions and the retained principal components were estimated. Then, Cox proportional hazards models with age as the timescale were fitted to estimate the Hazard Ratios (HR) and their 95% confidence intervals (95% CI) for the association between each retained principal components and the risk of ERP breast cancer. The time of entry into the study was the age of response to the dietary questionnaire. The time of exit was the age at diagnosis of breast cancer (for cases), the age at the last completed questionnaire before death or loss to follow-up, the age at diagnosis of another cancer, or the age at the end of the follow-up period, whichever occurred first.

Model 1 was only adjusted for age as the timescale. Model 2 included socio-anthropometrics and hormonal characteristics, i.e., birth generation, level of education, BMI, parity and age at first full-term pregnancy, cumulative duration of breastfeeding, history of contraceptive pill use, and menopausal status and recent use of HRT. Model 3 (the main model) was supplementary adjusted for lifestyle factors and dietary habits, i.e., smoking status, physical activity, daily alcohol intake, daily fat intake, total daily energy intake (without alcohol or fat) and adherence to the French dietary recommendations, in order to include of potential confounders identified by the DAG.

For continuous variables, a test of deviation from linearity was performed by modeling them with penalized splines in the main model (model 3). If the test was non- statistically significant, only the linear terms were retained; if it was statistically significant, the corresponding variable was modeled with penalized splines using four degrees of freedom.

All statistical tests were two-sided, and the threshold for statistical significance was set at 5%. Statistical analyses were performed using R software, version 4.3.3, the survival package version 3.6–4 and the FactoMineR package version 2.11 [36, 44, 61, 62].

Sensitivity analyses

A sensitivity analysis was performed by adjusting the main model on adherence to a Prudent dietary pattern (continuous) and adherence to a Western dietary pattern (continuous) instead of adherence to the French dietary recommendations (continuous). To prevent a potential reverse causality bias and to take into account latency between exposure and diagnostic, a sensitivity analysis was performed by starting follow-up 5 years after completion of the dietary questionnaire. In order to explore a differential effect depending on whether breast cancer occurs pre- or post-menopausal, a sensitivity analysis considering only post-menopausal ERP breast cancer cases was carried out. Breast cancer cases arising before menopause were censored at the date of diagnosis. Finally, a sensitivity analysis performing the PCA the total form of all metalloestrogens (i.e., mercury instead of methylmercury, and arsenic instead of inorganic arsenic) was conducted.

Interaction analyses

In order to explore potential effect modification by smoking status, interaction tests between the latter (in three categories: current, former, never) and each of the retained principal components were performed in the main model (model 2). Indeed, smoking increases hematocrit, which enhances the blood's capacity to carry various substances, including metalloestrogens [60]. Additionally, interaction tests between menopausal status at baseline and each of the retained principal components were carried out in the main model (model 3). Indeed, menopausal status is suspected of modifying the effects of dietary exposure to certain metals such as cadmium, higher iron levels after menopause may reduce gastrointestinal absorption of cadmium [64].

Secondary analyses

The associations between each metalloestrogen and ERP breast cancer risk were estimated. A separate Cox model for each metalloestrogen was fitted, using age as the timescale and adjusted on the same covariates than the main analyses.

Results

Characteristics of the study population

The study population was constituted of 66 722 participants followed for an average of 17.7 years (standard deviation: 5.3 years), equivalent to 1 180 979 person-years. Among these women, 4 259 developed breast cancers during follow-up (6.8% of the population), including 3 739 ERP breast cancers (5.6%).

The characteristics of the participants at inclusion are described in Table 1. At inclusion, the women had a median age of 51.5 years with a median BMI of 22.2 kg/m^2. The majority (85.3%) had a level of education of at least 12 years, 51.5% had never smoked and 52.6% were pre-menopausal.

Dietary intake of metalloestrogens

Distributions of estimations of daily dietary intakes of each metalloestrogen are shown in Supplementary Table 1. Aluminum was the metalloestrogen to which the participants were the most exposed with an estimated median daily dietary intake of 3 489 µg/day, while antimony was the one to which the participants were the

Table 1 Characteristics of the study population: 66 722 women in the French E3N cohort study

	Median [Interquartile range] or Number (Percent)
Sociodemographic characteristics	
Age at baseline (years)	51.50 [47.08, 57.5]
Birth generation	
≤ 1930	6414 (9.6%)
(1930; 1935]	8931 (13.4%)
(1935; 1940]	13,354 (20.0%)
(1940; 1945]	16,459 (24.7%)
> 1945	21,564 (32.3%)
School educational level (years)	
Missing value	2272 (3.4%)
< 12	7524 (11.3%)
[12–14]	33,036 (49.5%)
> 14	23,890 (35.8%)
Hormonal and lifestyle characteristics	
Physical activity (metabolic equivalents of task-hours/week)	36.0 [21.5, 57.7]
Missing value	433 (0.6%)
Smoking status	
Never	34,379 (51.5%)
Former	21,312 (31.9%)
Current	8464 (12.7%)
Missing value	2567 (3.8%)
Body mass index (kg/m^2)	22.2 [20.6, 24.2]
Missing value	3628 (5.4%)
Menopausal status and recent HRT use	
Premenopausal	35,106 (52.6%)
Postmenopausal and recent HRT use (less than a year ago)	9444 (14.2%)
Postmenopausal and no recent HRT use	18,592 (28.4%)
Postmenopausal and missing data on recent HRT use	3220 (4.8%)
Parity and age at first full-term pregnancy (FFTP)	
Nulliparous	7788 (11.7%)
One or two children and age at FFTP < 30 years	32,880 (49.3%)
At least 3 children and age at FFTP < 30 years	18,993 (28.5%)
Age at FFTP ≥ 30 years	7061 (10.6%)
Contraceptive pill use (current or past)	
Ever	39,179 (58.7%)
Never	25,113 (37.6%)
Missing value	2430 (3.6%)
Cumulative duration of previous breastfeeding	
No breastfeeding	25,246 (37.8%)
Cumulative duration of breastfeeding < 6 months	26,105 (39.1%)
Cumulative duration of breastfeeding ≥ 6 months	12,243 (18.3%)
Missing value	3128 (4.7%)
Dietary habits	
Alcohol consumption (g/day)	6.9 [1.6, 16.5]
Adherence to French dietary recommendations (PNNS score)	3.9 [1.9, 5.9]
Meat consumption (g/day)	120.2 [81.3, 104.9]
Fish consumption (g/day)	28.7 [17.1, 44.4]
Fruits and vegetables consumption (g/day)	655.6 [443.4, 901.5]
Dairy food consumption (g/day)	328.0 [224.5, 462.7]
Starches consumption (g/day)	146.6 [94.0, 209.4]

Number (percentage) of missing data are indicated in an additional line, if any

PNNS: "Programme National Nutrition Santé"- guidelines score 2

least exposed with an estimated median daily dietary intake of 2 µg/day.

The contributions of the food groups to the intake of each metalloestrogen are shown in Supplementary Table 2. Aluminum was mainly provided by vegetables (25.1% of dietary intake of aluminum comes from vegetables), antimony by coffee (13.6%), arsenic by fish (49.3%) while inorganic arsenic was mainly provided by water (24.1%), barium by fruits (18.4%), cadmium by vegetables (26.3%), chromium from fresh dairy products and vegetables (9.9% each), cobalt from coffee (18.5%), copper from coffee (21.6%), tin from fruits (35.6%), mercury and methylmercury from fish (72.2% and 97.2% respectively), nickel from fruits (18.9%), lead from vegetables (17.7%), selenium from fish (48.9%) and vanadium from water (20.2%).

The Spearman rank correlation coefficients between dietary intake of the 14 metalloestrogens are shown in Supplementary Fig. 2. The metalloestrogens were positively correlated with each other, with coefficients ranging from 0.07 (tin-methylmercury) to 0.92 (nickel–cobalt), with a median of 0.54.

Main analyses

The first four principal components were retained, explaining 80% of the total variance (Supplementary Fig. 3). The first principal component (PC 1), which explained 54% of the total variance, was characterized by high loading factors (i.e., > 0.5) for all metalloestrogens except the tin and methylmercury, i.e., aluminum [0.83], antimony [0.71], inorganic arsenic [0.63], barium [0.89], cadmium [0.84], cobalt [0.83], chromium [0.92], copper [0.65], nickel [0.88], lead [0.88], selenium [0.51], and vanadium [0.74]. The second principal component (PC 2), explaining 12% of the total variance, was mainly composed of methylmercury [0.85] and selenium [0.83]. The third principal component (PC 3), explaining 8% of the total variance, was essentially made up of vanadium [0.61] and inorganic arsenic [0.69]. Finally, the fourth principal component (PC 4), explaining 7% of the total variance, was mainly composed of tin [0.90] (Supplementary Table 3).

Correlations between these four principal components and food group consumptions are presented in Supplementary Fig. 4. The first principal component was positively and moderately correlated with all food groups. The second principal component had a strong positive correlation with fish (0.73) and moderate positive correlations mainly with seafood (0.33) and offal (0.32). The third principal component was mainly correlated with water (0.40). The fourth principal component had moderate positive or negative correlations with several food groups.

Associations between each principal component and ERP breast cancer risk are presented in Table 2. A statistically significant and positive association was found between the third principal component, characterized mainly by vanadium and inorganic arsenic, and the risk of developing ERP breast cancer (HR: 1.04, 95% CI: 1.00–1.07, p-value: 0.026). No statistically significant association was found for the other principal components.

Sensitivity analyses

The results of the sensitivity analyses adjusted for the Western and Prudent dietary patterns are presented in

Table 2 Associations between dietary exposure profiles to metalloestrogens (PC 1 to PC 4) obtained by principal component analysis and ERP breast cancer risk. Hazard Ratios (HR) and their 95% confidence intervals (95% CI) are estimated by Cox models (N = 66 722)

	Model 1		Model 2		Model 3	
	HR [95%CI]	p-value	HR [95%CI]	p-value	HR [95%CI]	p-value
PC 1, for one SD increase	**1.03 [1.00–1.07]**	**0.04**	1.03 [0.99–1.06]	0.09	0.97 [0.92–1.03]	0.30
PC 2, for one SD increase	1.01 [0.98–1.04]	0.68	1.01 [0.97–1.04]	0.73	1.00 [0.97–1.03]	0.96
PC 3, for one SD increase	**1.05 [1.02–1.08]**	**0.002**	**1.05 [1.02–1.09]**	**0.002**	**1.04 [1.00–1.07]**	**0.026**
PC 4, for one SD increase	1.00 [0.97–1.03]	0.96	1.00 [0.97–1.04]	0.83	1.01 [0.98–1.04]	0.57

SD: Standard Deviation

Model 1: Adjusted for age (as the timescale) only

Model 2: Adjusted for age (as the timescale), birth generation (≤ 1930, (1930–1935], (1935–1940], (1940–1945, > 1945]), level of education (< 12 years, 12 to 14 years, > 14 years), current or past user of contraception (no, yes), BMI (missing data, < 18.5, (18.5–22.5], (22.5–25], (25–30], > 30 kg/m^2)parity and age at first full-term pregnancy (FFTP) (nulliparous, 1 or 2 children and age at FFTP > 30 years, more than 2 children and age at FFTP < 30 years, age at FFTP ≥ 30 years), menopausal status and recent use of hormone replacement therapy (HRT) (pre-menopausal, post-menopausal with recent use of HRT, post-menopausal without recent use of HRT, post-menopausal with missing data on recent use of HRT), cumulative duration of breastfeeding (no breastfeeding, cumulative duration of breastfeeding < 6 months, duration of breastfeeding ≥ 6 months)

Model 3: Adjusted for Model 2 + smoking status (smoker, former smoker, never smoker), physical activity (in METs-hours/week, using linear terms), energy intake excluding fat and alcohol (in kcal/day, using linear terms), alcohol consumption (in g/day, modelled with penalized splines), fat consumption (in g/day, modelled with penalized splines) and adherence to the French dietary recommendation (using linear terms)

Supplementary Table 4 (Model 4). The results were very close to the main analysis: a positive association between the third principal component and the risk of developing ERP breast cancer was highlighted (HR: 1.04, 95% CI: 1.01–1.08, *p*-value: 0.013), without any significant association for the other principal components.

When the follow-up started 5 years after completion of the dietary questionnaire, the results remained similar to the main analyses, with broadly identical HRs and confidence intervals (Supplementary Table 4, Model 5).

When censoring participants who had developed ERP breast cancer before the menopause to consider only post-menopause ERP breast cancer, the association between the third principal component and ERP breast cancer risk was no longer significant (HR: 1.03, 95% CI [1.01–1.07], p-value: 0.06]) (Supplementary Table 4, Model 6).

When using the total form of the 14 metalloestrogens, three principal components were retained, explaining 70% of the total variance, so that each metalloestrogen had a high load in at least one principal component and, if possible, in only one principal component (Supplementary Table 5). The first principal component explained 54% of the total variance and was characterized by high loading factors (i.e., > 0.5) for all metalloestrogens except the tin. The second principal component, explaining 13% of the total variance, was mainly composed of arsenic. The third principal component, explaining 7% of the total variance, was essentially made up of tin. No significant association was found between these principal components and ERP breast cancer risk (Supplementary Table 6).

Subgroup analyses

The interaction between the first principal component and smoking status was close to statistical significance (p-value: 0.056). In subgroup analyses, the HR for the first principal component was higher in current smokers than in former smokers and non-smokers, but none of the associations were statistically significant (Supplementary Table 7). No significant interaction was observed for the other principal components.

Furthermore, none of the interactions between menopausal status and each principal component were significant.

Secondary analyses

None of the associations between each individual metalloestrogen and ERP breast cancer risk were statistically significant (Supplementary Table 8).

Discussion

This study identified the main dietary exposure profiles to metalloestrogens to which a population of French middle-aged women was mainly exposed. The main profile of exposure was characterized by all metalloestrogens except tin and methylmercury. Other profiles were characterized respectively by dietary exposures to methylmercury and selenium; vanadium and inorganic arsenic; and tin. The main finding was that ERP breast cancer was statistically significantly and positively associated with the third dietary exposure profile, mainly characterized by dietary intake of inorganic arsenic and vanadium. These results were robust to most sensitivity analyses, except the one that used the total form of metalloestrogens. Indeed, the exposure profile composed of arsenic and vanadium no longer existed, and none of the profiles identified showed any significant association. In a secondary analysis studying each metalloestrogen in separate models, no statistically significant association was observed. However, the two metalloestrogens with the highest HR were those characterizing the third principal component (i.e., inorganic arsenic and vanadium). The statistically significant association observed for the latter is therefore expected, and could be explained by the addition of their individual effects. The absence of significant association highlighted for other profiles is also consistent with the individual HR estimated when considering each metalloestrogens separately, the lack of association for the main profile could be explained by the addition of positive and negative HR for the many metalloestrogens that made it up.

In addition, an interaction close to statistical significance was found between smoking status and the first principal component, characterized by dietary intake of all metalloestrogens except tin and methylmercury. The effect size of the first principal component was higher in current smokers than in former and never smokers, but no statistically significant association was highlighted in the sub-group analyses.

The average dietary exposures to inorganic arsenic and vanadium in this study were in the same order of magnitude than estimates from the TDS2 study (mean in µg/kg/day: 0.24 in TDS2 vs 0.33 in E3N for inorganic arsenic; 0.86 in TDS2 vs 1.15 in E3N for vanadium) [4], which used similar contamination levels but relied on consumption data from the second Individual and National Study on Food Consumption INCA2 study (2005–2007) involving 1,918 adults representative of the French general population.

The carcinogenic potential of inorganic arsenic, classified in the Group 1 (i.e., carcinogenic to humans) by the

IARC [32], involves several mechanisms of action. It can generate reactive oxygen species that increase oxidative stress, causing cell damage, and inhibits the enzymes responsible for DNA repair [24]. Arsenic can also function as an endocrine disruptor, with in vitro studies showing it stimulates the growth of MCF-7 breast cancer cells [55]. As for vanadium, its carcinogenic potential is uncertain: some studies suggest it is mutagenic and carcinogenic [3, 47, 49], while others highlight its anticancer properties by promoting apoptosis and activating tumor suppressor genes [45, 46, 50]. Vanadium pentoxide, the form commonly used in industry, has been classified in the Group 2B (i.e., possibly carcinogenic to humans) by the IARC [32].

Several epidemiological studies have investigated associations between various forms of arsenic exposure and breast cancer risk. A recent review of the literature reported that ten case–control studies had been carried out on arsenic in urine, hair, blood or breast tissue, most concluding with statistically significant positive associations [43]. This review also identified 7 prospective studies conducted on airborne, toenail, dietary or blood arsenic, most of which showed no statistically significant association. Few studies have been conducted on vanadium. Three case control studies highlighted negative associations between urinary vanadium and breast cancer risk [27, 42, 58]. Lequy et al. investigated exposure to airborne vanadium and arsenic in non-urban participants of the French cohort GAZEL and did not find a statistically significant association with breast cancer risk, with hazard ratios of 1.35 (95% CI 0.88–2.07) for vanadium and 0.91 (95% CI 0.60, 1.37) for arsenic when comparing the fourth to the first quantiles of exposure [37]. Additionally, the study examined exposure profiles through PCA. Although the principal components identified differed from those obtains in the present study, the "crustal" PCA profile characterized by high exposure to arsenic and vanadium was not statistically significantly associated with breast cancer risk. It should be noted that this study probably lacked power, as only 208 breast cancer cases were included.

Our study has some limitations that need to be taken into account for correctly interpret the results. Firstly, the E3N cohort is made up of middle-aged women with a higher level of education than the general population. Extrapolation of the results must be done with caution. In addition, food consumption data was assessed in 1993, while food contamination data was measured as part of the TDS2 study between 2007 and 2009. Between 1993 and 2007–2009, food contamination levels may have changed, particularly as during this period regulatory limits for food contamination levels were lowered for several metalloestrogens such as lead, cadmium and inorganic arsenic, leading to imperfect estimates of dietary intake of metalloestrogens (EFSA Panel on Contaminants in the Food Chain (CONTAM), [20, 22]). However, it is likely that contamination levels have evolved in a similar way in all food groups, given that environmental contamination is ubiquitous. Consequently, the error in estimating participants' dietary exposure to a given metalloestrogen should be homogeneous among them. Thus, the absolute levels of exposure may have been underestimated, but this probably did not prevent the correct identification of participants with relatively higher or lower levels of exposure, thus ensuring correct classification among them. Furthermore, the resulting potential misclassification error should be non-differential, i.e., similar between breast cancer cases and non-cases, leading to an attenuation of the true association. In addition, the participants' dietary habits were assessed in 1993 only, whereas variations in dietary habits may have occurred during follow-up. However, it has been suggested by Thorpe et al. that dietary pattern of middle-aged women remains broadly stable over time [63]. The use of food frequency questionnaires, although validated, to estimate food consumption may also represent a potential source of error due to difficulties in remembering and estimating food consumption over a long period, and variations depending on the season in which the questionnaire was completed could have appeared. Moreover, the method of preparation is a source of variation in contamination levels (for example, the use of kitchen equipment containing aluminum). Although the food items were prepared as usually consumed by the French population in the TDS2 study, variations in exposure levels between participants due to their own habits were not taken into account, which may also have contributed to an imperfect estimate of exposure. Furthermore, despite our efforts to account for diet-related confounding by adjusting for various dietary variables and dietary patterns, we cannot exclude the risk of residual diet-related confounding. In addition, the adjustment variables were self-reported, which may have led to imperfect adjustments. Moreover, the absence of censorship on mastectomy could have led to a bias in the estimated HRs, since participants who had a mastectomy subsequently had a considerably reduced risk of breast cancer. However, this probably concerns a small number of participants, as prophylactic mastectomy is mainly performed in the case of a BRCA1/2 gene mutation, which is thought to affect 2 out of every 1,000 women in France [29]. Finally, it was not possible it was not possible to distinguish between the different ionic forms of metalloestrogens. Assumptions based on known proportions of inorganic arsenic and methylmercury in food have been made to estimate dietary exposure to these specific forms, but it should be noted that these proportions may

vary according to various factors (for example, region or environmental conditions). This may have led to imperfect estimates of exposure and introduced bias into the estimated associations. In addition, it was not possible to distinguish between the different species of inorganic arsenic (particularly the more toxic As^{3+}) or chromium (particularly the more toxic chromium VI), their specific effects could therefore not be estimated.

This study also has several strengths. It involved a very large number of participants, which gave us good statistical power. The long follow-up period (an average of almost 18 years) made it possible to study the long-term effects of metalloestrogens on women's health. In addition, prevalent cases of breast cancer at the start of the study were excluded, and a sensitivity analysis starting the follow-up 5 years after the estimation of dietary metalloestrogens intakes was performed. This ensured that the exposure was assessed before any diagnosis of breast cancer, thus preventing a potential reverse causality bias. Regarding cancer cases ascertainment, we believed we used the best available data possible, with the diagnosis of breast cancer being validated for all cases after access to pathology reports and identification of breast cancer subtypes, thereby providing us reliable and robust results. Breast cancer cases for which pathology reports were not available (<7%) have been excluded because it was not possible to determine their subtype. In addition, a large amount of information was collected in the E3N cohort, which made it possible to adjust the models for numerous potential confounding factors. In addition, this is the first epidemiological study to explore the effect of dietary exposure profiles to multiple metalloestrogens on ERP breast cancer. Populations are exposed to a large number of chemical substances at the same time, in particular through diet, so studying their combined effects is crucially important in epidemiology. Finally, although the estimation of dietary exposure may be imperfect, as discussed in the limitations, studying dietary exposure specifically could contribute to the elaboration of dietary recommendations.

This study has identified dietary exposure profiles to which a population of French middle-aged women were the most frequently exposed, and highlighted a positive association between a profile characterized by inorganic arsenic and vanadium and ERP breast cancer risk. Future research exploring the effect of joint dietary exposures to these two chemicals are needed to confirm our results. These findings could be used to formulate dietary recommendations, considering that the profile characterized by high intake of inorganic arsenic and vanadium was highly correlated with fish consumption. Nevertheless, such recommendations should also consider the positive effects of the nutrients present in the same foods. Indeed, the latter could have opposite effects counterbalancing those of metalloestrogens, or modify their effects by modulating their absorption [9]. Our results could also be used to revise regulatory limits for food contamination levels considering combined contaminations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01167-6.

Supplementary Material 1.

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Authors' contributions
Florian Saint-Martin: Methodology, Formal analysis, Writing—Original Draft. Chloé Marques: Writing—Review & Editing. Xuan Ren: Writing—Review & Editing. Emeline Lequy: Writing—Review & Editing. Conceptualization, Methodology, Writing—Review & Editing. Francesca-Romana Mancini: Conceptualization, Writing—Review & Editing, Supervision, Project administration. Pauline Frénoy: Conceptualization, Methodology, Formal analysis, Writing—Review & Editing, Supervision.

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Data availability
The data used in this study are not publicly available.

Declarations

Ethics approval and consent to participate
The E3N study was approved by the French National Commission for Data Protection and Privacy (ClinicalTrials.gov identifier: NCT03285230).

Informed consent
All participants included in the E3N study gave written informed consent.

Competing interests
The authors declare no competing interests.

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