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Longitudinal assessment of nitrate and trihalomethanes in drinking-water and breast cancer in the CONSTANCES cohort: a prospective population-based study in France

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ABSTRACT

Nitrate and trihalomethanes (THMs) in drinking water are widespread and potential human carcinogens. We evaluated the association between time-varying exposure to nitrate and THMs in drinking water and female breast cancer (BC) among adults from CONSTANCES, a large French population-based prospective cohort. Our analysis included 26,669 women (18.5–72.5 years old) enrolled in 2012–2020, followed until 2021, with information on residential history, type of water consumed, type of filter used, and bathing and showering frequency. We used water quality data for 2004–2020 from the drinking surveillance national database (SISE-Eaux). Annual median concentrations of nitrate, chloroform, chlorodibromomethane, bromodichloromethane, and bromoform at the participants' residential addresses were estimated. Waterborne ingested exposure was estimated considering type of water, filter used, and liters/day consumed. Estimated exposure in showers and baths combined residential concentrations with showers/baths duration and frequency. Incident BC cases were ascertained in the French national health data system (SNDS) for 2012–2021. Extended Cox models with attained age as time-scale and time-varying weighted average exposures, adjusted for individual and area-level covariables, were used to estimate hazard ratios (HR) and confidence intervals (CI) by exposure tertiles. Average age at enrolment was 49.3 years, and median exposure window was 13 years. Median follow-up was 5 years (153,742 person-years), resulting in 437 new BC diagnoses. Median residential nitrate, brominated (Br)-THMs and chloroform concentrations were, respectively, 15.8 mg/L, 14.2 μg/L, and 2.7 μg/L. HR (95 %CI) of BC associated with waterborne ingested nitrate (mg/day) for the second (>4.8–15.1) and third tertile (>15.1) compared to the first (≤4.8) were 1.35 (1.01–1.81) and 1.51 (1.10–2.07), respectively. Residential THM concentrations were not associated with BC, however HR (95 %CI) of BC for showering and bathing Br-THMs exposure (μg/L × min/day) was 1.18 (0.84–1.64) for the third (>125) vs. first tertile (≤51.5). Findings suggest that ingested nitrate could be a risk factor of BC.

1. Introduction

Breast cancer stands globally as the foremost cause of cancer-related fatality among women, with rising incidence rates (Siegel et al., 2023). In 2020, it was the most diagnosed neoplasia, with 2.3 million reported cases, constituting 11.7 % of all new cancer diagnoses (Sung et al.,

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2021). This disease exhibits a multifaceted pathology closely linked to sex hormones exposure, particularly estrogens, which drive a carcinogenic process through interaction with steroid receptors and other signaling pathways at different life stages. Reproductive factors such as early menarche, late menopause, delayed pregnancy, low parity, and short or absent lactation periods have been associated with increased endogenous estrogen exposure, contributing to breast cancer (Jasienska et al., 2017). Nonetheless, these factors combined with family history of breast cancer, account for only 40–50 % of cases, underscoring the potential influence of other lifestyle, dietary, and environmental risk factors (Barnes et al., 2011; Sprague et al., 2008).

Among environmental exposures, some elements in drinking water are potential carcinogens. Nitrate is a widespread groundwater contaminant due to its high water solubility and low soil retention (Bhatnagar and Sillanpää, 2011). While naturally occurring as part of the nitrogen cycle, nitrate levels have risen sharply due to human activities such as agricultural fertilizers, inadequately treated urban wastewater, industrial and animal waste, landfill leachate, and household septic systems. Nitrate from these sources can leach into groundwater or run off into surface waters, potentially contaminating drinking water supplies (Abascal et al., 2022). Human exposure to nitrate mainly occurs through ingestion of food and drinking-water (IARC, 2010). Nitrate intake has been a growing concern as a potential carcinogen due to nitrate acting as a precursor in the formation of N-nitroso compounds (NOC), many of which possess teratogenic and carcinogenic properties (Lijinsky, 1999; Swann, 1975). NOCs are endogenously formed through a complex nitrosation process influenced by a number of factors, including antioxidant presence and inflammatory conditions, among other (Hebels et al., 2011; Helser et al., 1992). Nitrate has been classified as 'probably carcinogenic' to humans by WHO-IARC, ingested under conditions that result in endogenous nitrosation (IARC, 2010). Exposure to industrial NOCs has been linked to DNA adduct formation and the incidence of both benign and malignant tumors in mammary glands in animal studies, suggesting a potential role as breast cancer risk factor (Malejka-Giganti et al., 2008; Ritter et al., 2002). Food additive nitrate in processed meats has been recently linked to a higher risk of breast cancer in the *NutriNet-Santé* cohort (Chazelas et al., 2022). More generally, high consumption of processed meat was associated with breast cancer incidence (Farvid et al., 2018). However, the four existing studies focusing on exposure to nitrate in drinking water and breast cancer risk, including the two ones based on the Iowa Women's Health Study (Inoue-Choi et al., 2012; Weyer et al., 2001), showed inconclusive evidence for an overall association (Brody et al., 2006; Espejo-Herrera et al., 2016), and contradictory results after stratification by folate consumption (Espejo-Herrera et al., 2016; Inoue-Choi et al., 2012).

Disinfectants added in drinking water treatment to inactivate microbial pathogens result in the formation of hundreds of unintended disinfection byproducts (DBPs) through reaction with naturally occurring organic matter (Richardson et al., 2000). Several DBPs are genotoxic *in vitro* and carcinogenic in animal experiments (Richardson et al., 2007; Wilbourn et al., 1999), and some DBPs are classified as possible human carcinogens by WHO-IARC (Chang, 1982; IARC, 2013). Chlorine is the most widespread disinfectant used worldwide, and trihalomethanes (THMs) and haloacetic acids are the DBPs formed at the highest concentrations after chlorination. THM levels serve as convenient indicator for this complex mixture (Mouly et al., 2009) as they are regulated contaminants and more easily available, unlike haloacetic acids that will be systematically monitored in France from January 2026 at the latest, following the European directive 2020/2184 and the 2022 French regulation (ANSES, 2023). In addition, a recent French report from ANSES stated that a correlation was found between brominated and chlorinated components of THMs and haloacetic acids in a national exploratory campaign (ANSES, 2023). Epidemiological studies examining the association between DBPs and breast cancer have methodological limitations including ecological design (Bean et al., 1982; Marcus et al., 1998). Additionally, some studies used mortality as an outcome measure, which may not accurately represent disease incidence (Vinceti et al., 2004; Young et al., 1981; Zierler et al., 1986). Furthermore, many investigators did not always adequately adjust for social or demographic variables, further complicating the interpretation of the findings (Bean et al., 1982; Marcus et al., 1998; Morris et al., 1992; Young et al., 1981). In the most recent case-control study, only chloroform exposure seemed to be linked to breast cancer, while brominated compounds or total THMs showed no association (Font-Ribera et al., 2018).

We aimed to assess the relationship between nitrate and THM exposure through drinking-water and female breast cancer, using a large prospective population-based French cohort.

2. Methods

2.1. Study design and population

CONSTANCES is a population-based prospective cohort including around 220,000 volunteers randomly selected among Social Security affiliates, aged 18 to 69 years at recruitment (2012–2020) in 21 health examination centers throughout France (Constances, 2023). Social Security covers around 85 % of the French population (the remaining 15 % include agricultural insurance systems affiliates and independent workers). Enrollment included a health examination and self-reported questionnaires to collect socio-demographics, lifestyle, socio-professional data, and medical history. Follow-up involved self-reported annual questionnaires covering a wide array of topics i.e. health, socio-demographics, occupation, environment, and lifestyle factors, and a health examination every four years (Zins et al., 2015). The type of water consumed at home, use of water filters, type filter, and frequency and duration of showers and baths was gathered at the 2020 follow-up. Residential addresses since enrollment were geocoded for all participants, and lifetime residential addresses prior to enrollment were collected and geocoded in a subset (N = 76,380) in 2020–2022.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures have been approved by the Institutional review board (IRB) of the French Institute of Health (Inserm) (Opinion n°01-011, then n°21-842), and authorized by the French Data Protection Authority ("Commission Nationale de l'Informatique et des Libertés", CNIL) (Authorization #910486). All participants signed a written consent form prior their participation in CONSTANCES. All information and regulatory authorizations relating to the publication are available on https://www.constances.fr/espace-volontaires/droits-et-protection-des-donnees/.

2.2. Cancer incidence

We ascertained incident breast cancer diagnoses (ICD-10 codes C50—Malignant neoplasm of breast, D05—Carcinoma in situ of breast) for 2012–2021 through linkage with the national health insurance system database (SNDS) (Tuppin et al., 2017) using algorithms created by the French Health Insurance. The quality of breast cancer identification was tested by using medical records among 265 cases, resulting in a positive predictive value of 92 % (95 %CI 88–95) (Rolland et al., 2023).

2.3. Nitrate and THM levels in drinking water

Routine monitoring data from SISE-Eaux, the French national database for drinking water quality surveillance, was obtained for 2000–2020. This covers almost entirely the French population given that drinking water supply in France is managed by the public administration, although it may be delegated to private companies (e.g. Veolia, ENGIE (former GDF Suez), Saur). In total, 26,322,366 measurements including nitrate and THM concentrations, sampling site and date, and

water source (ground, surface, mixed, or sea) were obtained. We used data from samples collected at the distribution network (e.g. tap), in private and public locations, to estimate annual median concentrations by surveillance area, i.e. subdivisions of water distribution unit with homogenous quality (SANDRE, 2009). Geographical characteristics of surveillance areas are available in Supplementals (Table S1, Fig. S1). In order to predict missing annual median concentrations, we developed linear mixed models with random intercepts, with surveillance area as clustering variable separately for nitrate and the four THM components (chloroform, chlorodibromomethane, bromodichloromethane, and bromoform) by region (Fig. S2). Interactions were considered to account for the different temporal trends by water source. Conditional predictions were used for surveillance areas included in the models (N = 56,149 for nitrates; N = 38,366 for total THMs). For the remaining surveillance areas, with all annual median concentrations missing, imputation was carried out using the corresponding water distribution unit's annual median if possible (N = 24,213 for nitrates; N = 38,019 for total THMs). Otherwise, missing values were left untouched (N = 22,675 for nitrates; N = 26,652 for total THMs). Comparison of concentrations measured in 100 samples with estimated annual concentrations showed a high correlation for nitrates (r = 0.85) in Paris, a highly dense urban city, and similar contrasts for nitrates and THMs between water distribution units in Rennes and Saint-Brieuc (two cities in Brittany) despite a period of drought in this region. We considered brominated THMs (Br-THMs) as the sum of chlorodibromomethane, bromodichloromethane, and bromoform concentrations. Complete procedures to collect, clean, and link water data to CONSTANCES is available elsewhere (Lafontaine et al., 2024).

2.4. Exposure period

THMs were routinely monitored since 2003, to comply with the French regulation following the European directive 98/83/CE of November 1998 (Mouly et al., 2009). THM measurements before 2004 were not systematic, and we thus excluded measurements before 2004 (also for nitrate, to be consistent). We implemented a 5-year lag to account for cancer latency, so the exposure period comprised 2004 until 5 years before the date of censorship (whichever came first: diagnosis, death, or end of study 2021), and used time-weighted cumulated averages for each exposure. For instance, for a participant included in 2012, exposure estimate at inclusion was the 2004–2007 mean concentration.

2.5. Individual residential exposures

The median number of residences was 6 in the lifetime and 2 for 2004–2016 period, where the last residence was also usually the longest (median of 11 years). Annual concentrations from the nearest surveillance area to the household were linked to participants with geocoded residential history (n = 76,380). The median distance (interquartile range) was 451 (651) meters. Residential geocodes relied on precise addresses for 63 % of study participants' residences, street-level for 26 %, neighborhood centers for 6 %, and postal code center for 5 %. In total, 85 % of residences were linked to surveillance areas geocoded by their actual geocodes, while the remaining 15 % were linked to surveillance areas with imputed geocodes using the municipality centroid. If a participant lived at two or more addresses in the same year, the time spent at each address was used to compute a time-weighted mean. Linkage was done even if there were missing values for a parameter to minimize misclassification. After linkage, 44 % of nitrate (46 % of total THM) annual values were based on model predictions, 34 % (16 %) on actual concentrations, and 22 % (38 %) on water distribution unit median values. Comparisons of measured, modeled and water distribution unit median values for nitrate and total THMs are reported by department in Supplementals (Fig. S3, Fig. S4).

2.6. Waterborne ingested exposure

We assigned residential concentrations to calculate waterborne ingested exposure when tap-water consumption without filter was reported. Drawing from previous studies on the efficacy of domestic water filtering devices (Carrasco-Turigas et al., 2013), we applied percentage reductions in THMs for users of activated carbon filters and reverse osmosis filters. For activated carbon pitcher-type filters, percentage reductions were computed for each THM component at different aging states: new (<1 L of water filtrated), moderately aged (>75 L), and aged (>150 L, maximum volume of use established by the manufacturer). We used the mean of these percentages as a global reduction percentage over the filter's lifespan to assign to activated carbon filters. In order to estimate nitrate reduction by domestic filters, we analyzed nitrate in samples before and after 2 reverse osmosis systems, and one activated carbon pitcher-type filter at different states of aging (new, 75L, 150L). We used the reduction percentage mean for activated carbon filters and reverse osmosis separately. For unspecified filtration systems connected to taps, we used the activated carbon and reverse osmosis reduction percentage mean, since these were the most frequent. For water softeners or other/unknown types of filters, no reduction was assumed. All reduction percentages are displayed in Table S2.

For study participants consuming bottled water we used nitrate levels in French bottled mineral water brands (except regional mineral water and hyper/supermarket brands), based on reported concentrations at the websites (24 brands, concentration range 0.25 to 7.3 mg/L). Concentrations were averaged using sales frequency in 2021 as a weight, leading to 3.2 mg/L of NO_3^- (Table S3). A zero THM level was assigned to bottled water consumers based on previous evidence (Font-Ribera et al., 2010). Participants who reported consuming water from other sources (e.g. private wells, rainwater collectors, etc.) or a combination of other sources with tap and/or bottled water were assigned missing concentrations (N = 185, including 97 who only consumed water from other sources).

The resulting annual median nitrate and THMs concentrations were multiplied by the average water intake (L/day) at the residence, including coffee and tea, to calculate waterborne ingested nitrate (mg/day) and THMs (μg/day). Consumption above the 99th percentile (3 L/day) was deemed implausible and treated as missing values (N = 206).

2.7. Exposure through showering and bathing

We multiplied annual residential THM levels in tap water by the average number of showers and baths per week and the duration (minutes) to calculate exposure through showering and bathing (μg/L × min/day). As frequency and duration of showers and baths were recorded using closed-ended categories, we took the middle of each category (e.g. 3.5 days per week for "3 to 4 times per week" category). The converted values are displayed in Table S4.

2.8. Covariables

Date of birth (month/year), height, education, physical activity, menopausal status, number of children and first-degree family history of breast cancer were obtained at the baseline questionnaire only. We used the International Standard Classification of Education (ISCED 2011) and considered three categories: low (levels 0–4: from "Early childhood education" to "Post-secondary non-tertiary education"), medium (levels 5–6: "Short-cycle tertiary education" and "Bachelor's") and high (levels 7–8: "Master's" and "Doctorate"). Physical activity off work was based on three questions about trips on foot or bicycle, practicing sports (excluding trips) and gardening/doing housework over the past 12 months. Intermediate scores were computed for each question: 0 for "no", 1 for "yes, less than 15 min per week" or "yes, less than 2 h per week" depending on the question, 2 for "yes, 15 min per week or more" or "yes, 2 h per week or more" depending on the question. The final

score was the sum of the three sub-scores, ranged from 0 ("Not at all") to 6 ("Highly active") and was categorized in low (0–2), medium (3–4), high (5–6).

Age, alcohol consumption, smoking status, and weight were obtained at inclusion and each follow-up. Alcohol consumption was defined as categories of daily number of glasses: less than one, 1–2, more than 2. Body mass index (BMI, kg/m^2) was calculated based on weight and height and categorized in 'underweight/normal' (BMI $<$ 25), 'overweight' (25 $\leq$ BMI $<$ 30), and 'obesity' (BMI $\geq$ 30). Smoking status was considered as never, former, or current smoker.

Diet was assessed at inclusion and in the 2017 questionnaire. Based on all the dietary information collected we created a dietary healthy score. We characterized food items as healthy or unhealthy based on a previous work in the cohort (Merle et al., 2018) and other studies (Farvid et al., 2018; Rodríguez-Ayala et al., 2024). Healthy foods considered were: 'fish or seafood', 'whole grain bread or breakfast rusks', 'fruits', 'vegetables', 'legumes', 'coffee' and 'tea'. Less healthy or unhealthy foods included: 'red meat (beef, lamb, pork)', 'sweet biscuits, chocolate bars or cereal bars', 'low-fat sweet biscuits', 'snacks (chips, crackers, peanuts, etc.)', 'shop-bought ready meals (tinned, frozen, etc.)' (low fat and high fat), 'hamburgers, kebabs, sandwiches, pizzas, quiches', 'fried foods (chips, crisps, doughnuts, battered meat or fish)', 'pastries, cakes', 'soda, fizzy drinks' (normal and diet/zero) and 'energy drinks'. For healthy food items, a score of 1 was assigned if consumption was 2–3 times per week or more, and −1 if consumption was less than 2–3 times per week. Conversely, for unhealthy food items, a score of −1 was assigned if consumption was 2–3 times per week or more, and 1 if consumption was less than 2–3 times per week. Subsequently, the scores for all items were summed up for each participant, creating a score ranging from −19 to 19. This dietary healthy score was then categorized into quartiles, representing diets ranging from least healthy to healthiest.

In order to use time dependent variables (alcohol consumption, smoking status, BMI and diet) in our models and since assessment of covariables differed over time, we applied a last observation carried forward approach for each covariate if necessary, whether values were missing or not.

Level of urbanicity was defined based on municipal density grid defined by the National Institute of Statistics and Economic Studies (INSEE, *Institut National de la Statistique et des Études Économiques*) in three categories: densely populated municipalities, municipalities with medium density, and rural municipalities. We calculated for each participant the time-varying percentage of time spent since 2004 in each of the three strata of urbanicity and used a 5-year lag to be consistent with the exposure windows. We considered urbanicity as a potential confounder, as it is a proxy of unmeasured variables such as artificial light at night that can be associated with breast cancer risk (Garcia-Saenz et al., 2018; Prajapati et al., 2025), or access to health care/healthcare seeking behaviors (Shi et al., 2021) that might impact a woman's likelihood to be diagnosed with breast cancer at an earlier stage. Also, urbanicity is linked to exposure, as concentrations of water parameters differ by water source (surface, ground, mixed) and surface sources are frequent in urban areas (Bean et al., 1982). We used urbanicity for the same exposure window as the drinking contaminants.

2.9. Missing values imputation

Missing data ranged between 0.8 % and 24.5 %, for first-degree family history of breast cancer and number of children, respectively. We used multiple imputation with chained equations to create five complete datasets (with five iterations) using MICE and MICEADDS R packages (van Buuren and Groothuis-Oudshoorn, 2011). We longitudinally imputed all variables using a 2-level model with participant identifiers as a cluster variable. The functions "2L.pmm" and "2L.only.pmm" were used for time-varying and time-independent variables, respectively. All covariables were used as predictors, as well as the longest region of residence and ever use of oral contraceptives. Distributions of imputed covariates for each imputed dataset are available in Fig. S5. Estimates were pooled following Rubin's rules (Rubin, 1987). Some variables at inclusion (total red and processed meat consumption, fruit and vegetables consumption, smoking status) were also imputed by multiple imputation with the same predictors as before in order to do stratified analyses.

2.10. Statistical analysis

Out of 76,380 eligible participants, we excluded men (n = 35,101), individuals who did not provide consent to access SNDS data (n = 1,022), prevalent breast cancers (n = 1,300), and participants with no residential history data for the period of interest (n = 453). We excluded 123,545 person-years lacking all exposure parameters (n = 5,262 participants), 13,917 person-years with reported residence less than 90 % of the time (n = 326 participants). Furthermore, we excluded participants with less than 70 % of exposure data for the exposure period (n = 6,247). We then created exposure variables over the exposure period resulting in a final study population of 26,669 participants (153,742 person-years) and 437 incident breast cancer cases (Fig. 1). To evaluate waterborne ingestion, we further excluded women with lack of data on water use, yielding a subsample of 22,664 participants (132,112 person-years) and 387 breast cancer cases. To examine showering and bathing exposure, we focused on a subsample of 22,674 participants (132,212 person-years) and 385 breast cancer cases.

Person-years were grouped into time-varying exposure tertiles based on their distribution all over the exposure period. We used extended Cox models with attained age as underlying time scale, and with time-

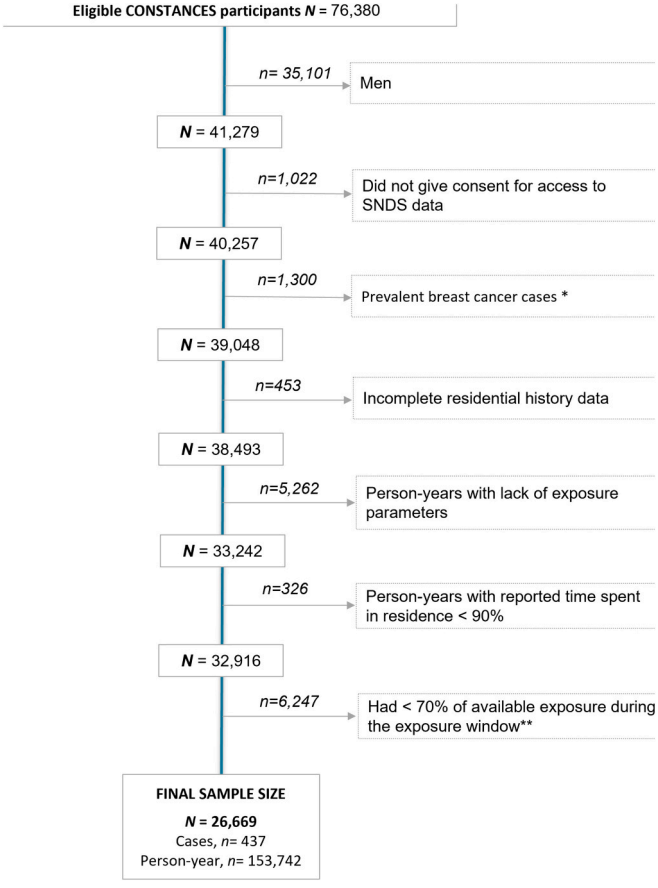

Fig. 1. Flow chart.

varying exposure to estimate hazard ratio (HR) and 95 % confidence intervals (CI) of breast cancer for the second and third tertile compared to the first tertile. To account for nonlinear relationships, we included restricted cubic splines (with three degrees of freedom) and visually assessed deviations from linearity. We also numerically assessed these deviations using likelihood ratio tests (Table S5). Since most relationships were not linear and results with continuous exposure were driven by extreme values, we did not report HRs for the continuous exposure. In order to have a better understanding of the shape of the relationships, we displayed splines for exposure below the 99th percentile. We graphically checked the proportional hazard assumption using scaled Schoenfeld residuals and observed no deviation.

All models were adjusted for education. Further adjustment included other potential confounders: alcohol consumption, BMI, dietary healthy score, smoking status, physical activity off work, self-reported family history of breast cancer, menopausal status, number of children, and urbanicity (percentage of time spent in densely populated municipalities and percentage of time spent in rural municipalities). As there was no multicollinearity (VIF < 2.5 for all considered exposures), an additional model was conducted with mutual adjustments between nitrate, chloroform and Br-THMs levels and considered as the main model.

As menopausal status was not yearly available through follow-up, to consider menopausal status as a potential effect modifier in our analyses, we stratified by age at censorship (whichever came first across diagnosis, death or end of study 2021) as a rough proxy. We chose 51 years old as a cut-off as it is the average age of menopause in France (Trémollieres et al., 2022). Stratified analysis by consumption of potential endogenous nitrosation precursors or inhibitors such as total red and processed meat (approximately once a week or less vs. two times per week or more), fruit and vegetables (approximately once a week or less vs. two times per week or more) and smoking (never-smoker, ever-smoker) at inclusion were conducted. As we stratified on imputed variables, we reported mean numbers of observations per strata across the imputed datasets. Stratified analysis by urbanicity were also conducted, based on four categories depending on the time spent during the exposure period in the different urbanicity strata: mostly urban (more than 90 % in densely populated municipalities), mostly *peri*-urban (more than 90 % in medium-density municipalities), mostly rural (more than 90 % in rural municipalities) and mixed. We ran sensitivity analyses by excluding participants that had more than 30 % of their annual concentrations coming from surveillance areas allocated to the centroid of their municipality (e.g. participants whose exposure has potentially more measurement error), participants who consumed bottled water as water consumption habits may be related to socio-economic factors, participants who consumed bottled water or used any filter. We also ran other analyses using quartiles instead of tertiles, and another one for exposure to THMs through showers and baths without adjusting for nitrate exposure. Finally, we redid our main analyses with a 10-year lag to account for cancer latency.

Presented p-values are two-tailed; <0.05 was considered statistically significant. All statistical analyses were performed with the R statistical software (R Core Team, 2024), version 4.3.1, using the 'survival' package (Therneau, 2001). Restricted cubic splines were performed with the 'rms' package (Harrell, 2024) using functions based on the previous package. Interaction p-values were computed comparing models with and without interaction, using a pooled Wald test based on χ^2 values obtained from tests done on each imputed dataset.

3. Results

We identified 437 breast cancer diagnoses over a median 5-year follow up (IQR:3.2; 132,212 person-years), range 1–10 years, with a median of 3.2 years (IQR: 3.3) and 0–9 years range for cases. The exposure period range was 4–13 years with a median of 11 years (IQR: 3) for cases and from 10 to 13 years with a median of 13 years (IQR: 0) for non-cases. Mean age at inclusion was 55 years among cases (min–max: 26–71) and 49 years for other women (min–max: 18.5–72.5) (Table 1). Breast cancer cases reported more family history of breast cancer than other participants (15.0 % vs. 8.5 %) and had a higher proportion of menopausal women at inclusion (61.4 % vs.46.0 %). They tended to eat less healthy (68.0 % had a dietary healthy score below the median vs. 57.1 %) and lived less in densely populated municipalities over the exposure period (median percentage of time in densely populated municipalities of 20 % vs. 40.9 %). About one quarter of the population lived exclusively in densely populated municipalities. Cases drank more bottled water than controls and less tap water without filter (Table 2). Median water consumption was 1.5 L/day (IQR: 0.5) among cases and 1.0 L/day (IQR: 0.5) among non-cases, while median time spent in showers and baths was similar in the two groups, 7.5 min/day (IQR: 5).

Correlations between average residential nitrate and THMs concentrations ranged between −0.07 and 0.34 (Fig. S6). Total THMs were more correlated with Br-THMs than with chloroform (0.95 and 0.61, respectively). Median (IQR) values for average residential nitrate concentrations (mg/L), Br-THMs (µg/L) and chloroform (µg/L) over the exposure period were 15.9 (18.9), 12.8 (11.7) and 1.9 (3.5), respectively in incident breast cancer cases and 15.4 (19.6), 12.8 (10.6) and 2.1 (3.5) in the rest of the cohort (Table 2). Median (IQR) average waterborne ingested nitrate (mg/day), Br-THMs intake (µg/day) and chloroform (µg/day) over the exposure period were 7.8 (18.1), 6.3 (15.8) and 0.7 (3.1), respectively in incident breast cancer cases and 6.9 (18.4), 6.0 (15.3) and 0.8 (3.2) in the rest of the cohort. Median (IQR) values for average showers and baths Br-THMs and chloroform exposure (µg/L × min/day) over the exposure period were 62.0 (85.5) and 7.6 (18.2), respectively, in breast cancer incident cases and 63.4 (83.5), 9.5 (20.4) in the rest of the cohort.

The included subset (n = 26,669) was similar to the women of the overall cohort (n = 110,111) in terms of smoking status, alcohol consumption, physical activity or BMI (Table S6). However, women in our study were slightly older (mean age of 49 vs. 47 years) and with higher education level (30 % of low educated women vs. 39 % in the overall cohort).

Overall, residential THM levels were not statistically significantly associated with breast cancer (Table 3). Residential nitrate levels were only statistically significantly associated with breast cancer for levels between 7.2 and 22.0 mg/L compared to below 7.2 mg/L (HR: 1.30 (1.01, 1.67)), revealing an inverse U-shaped relationship (Fig. 2). Waterborne ingested nitrate intake showed an exposure–response association with breast cancer (HR:1.35 (1.01, 1.81) for levels between 4.8 and 15.1 mg/day and 1.51 (1.10, 2.07) for levels above 15.1 mg/day compared to levels below 4.8 mg/day) (Table 3, Fig. 3). Ingested total THMs showed a significant association with breast cancer for levels between 2.9 and 15.2 µg/L compared to below 2.9 µg/L (HR: 0.75 (0.56, 0.99)). THM exposure from showers and baths was not significantly associated with breast cancer and Br-THMs exhibited an upward trend followed by a plateau effect, while being non-significant (Fig. 4). Main results were robust to potential sources of confounding other than water contaminants, as mono-pollutant results based on a crude adjustment were similar to the more adjusted ones.

Association between ingested nitrate and breast cancer was only significant among postmenopausal women, with HRs (95 %CI) of 1.48 (1.05, 2.09) and 1.53 (1.05, 2.25), respectively, for the second and third compared to the first tertile (interaction p-value = 0.26) (Table 4). Similarly, the inverse association between ingested total THMs identified in the intermediate tertile was only significant among postmenopausal women (HR: 0.68 (0.48, 0.97); interaction p-value = 0.27). However, statistical power was limited to n = 113 breast cancer diagnoses for premenopausal women.

We did not identify significant interactions between waterborne ingested nitrate and red and processed meat, fruit and vegetable consumption, or smoking status. Interaction p-values were respectively 0.53, 0.43, and 0.19 (Table S7). HR (95 % CI) for the third vs. first tertile

Table 1
Main characteristics of CONTANCES participants at inclusion unless stated otherwise in the variable column, 2012–2020.

	Non-cases (n = 26,232)	Cases (n = 437)	Total (n = 26,669)
Age, Mean ± SD	49.2 ± 12.7	54.8 ± 10.4	49.3 ± 12.7
Education, n (%)			
Low	7,810 (30.1 %)	139 (32.1 %)	7,949 (30.1 %)
Middle	11,242 (43.4 %)	201 (46.4 %)	11,443 (43.4 %)
High	6,881 (26.5 %)	93 (21.5 %)	6,974 (26.5 %)
Missing	299	4	303
Family history of breast cancer, n (%)			
No	23,813 (91.5 %)	369 (85.0 %)	24,182 (91.4 %)
Yes	2,214 (8.5 %)	65 (15.0 %)	2,279 (8.6 %)
Missing	205	3	208
Smoking status, n (%)			
Never	13,719 (53.9 %)	222 (52.0 %)	13,941 (53.9 %)
Former	8,448 (33.2 %)	157 (36.8 %)	8,605 (33.3 %)
Current	3,265 (12.8 %)	48 (11.2 %)	3,313 (12.8 %)
Missing	800	10	810
Body Mass Index, n (%)			
Underweight/normal	17,425 (67.4 %)	272 (62.7 %)	17,697 (67.3 %)
Overweight	5,934 (22.9 %)	112 (25.8 %)	6,046 (23.0 %)
Obesity	2,504 (9.7 %)	50 (11.5 %)	2,554 (9.7 %)
Missing	369	3	372
Alcohol consumption, n (%)			
<1 glass/day	16,746 (71.2 %)	262 (67.0 %)	17,008 (71.1 %)
1–2 glasses/day	5,009 (21.3 %)	87 (22.3 %)	5,096 (21.3 %)
>2 glasses/day	1,776 (7.5 %)	42 (10.7 %)	1,818 (7.6 %)
Missing	2,701	46	2747
Dietary healthy score, n (%)			
Q1 (least healthy)	8,294 (32.0 %)	184 (42.4 %)	8,478 (32.2 %)
Q2	6,512 (25.1 %)	111 (25.6 %)	6,623 (25.1 %)
Q3	7,258 (28.0 %)	91 (21.0 %)	7,349 (27.9 %)
Q4 (healthiest)	3,860 (14.9 %)	48 (11.1 %)	3,908 (14.8 %)
Missing	308	3	311
Physical activity off work, n (%)			
Low	5,710 (22.4 %)	94 (22.4 %)	5,804 (22.4 %)
Middle	12,120 (47.5 %)	181 (43.1 %)	12,301 (47.4 %)
High	7,707 (30.2 %)	145 (34.5 %)	7,852 (30.3 %)
Missing	695	17	712
Menopausal status, n (%)			
Post-menopause	11,082 (46.0 %)	251 (61.4 %)	11,333 (46.2 %)
Pre-menopause	13,018 (54.0 %)	158 (38.6 %)	13,176 (53.8 %)
Missing	2,132	28	2160
Number of children, n (%)			
0	903 (4.6 %)	17 (4.6 %)	920 (4.6 %)
1	3,727 (18.9 %)	71 (19.2 %)	3,798 (18.9 %)
2	9,804 (49.6 %)	184 (49.7 %)	9,988 (49.6 %)
≥3	5,328 (27.0 %)	98 (26.5 %)	5,426 (27.0 %)
Missing	6,470	67	6537
Main region of residence over the exposure period, n (%)			
Auvergne-Rhône-Alpes	2,051 (7.8 %)	29 (6.6 %)	2,080 (7.8 %)
Ile-de-France	4,560 (17.4 %)	78 (17.8 %)	4,638 (17.4 %)
Bourgogne-Franche-Comté	88 (0.3 %)	0 (0.0 %)	88 (0.3 %)
Brittany	3,371 (12.9 %)	56 (12.8 %)	3,427 (12.9 %)
Centre-Val de Loire	1,980 (7.5 %)	44 (10.1 %)	2,024 (7.6 %)
Corse	3 (0.0 %)	1 (0.2 %)	4 (0.0 %)
Grand Est	975 (3.7 %)	16 (3.7 %)	991 (3.7 %)
Hauts-de-France	1,979 (7.5 %)	41 (9.4 %)	2,020 (7.6 %)
Normandy	1,388 (5.3 %)	13 (3.0 %)	1,401 (5.3 %)
Nouvelle Aquitaine	4,356 (16.6 %)	78 (17.8 %)	4,434 (16.6 %)
Occitanie	3,074 (11.7 %)	47 (10.8 %)	3,121 (11.7 %)
Pays de la Loire	1,665 (6.3 %)	25 (5.7 %)	1,690 (6.3 %)
Provence-Alpes-Côte-d'Azur	548 (2.1 %)	8 (1.8 %)	556 (2.1 %)
Mixed	194 (0.7 %)	1 (0.2 %)	195 (0.7 %)
Percentage of time spent in each level of urbanicity over the exposure period, Median (Q1-Q3)			
Densely populated municipalities	40.9 (0–100)	20.0 (0–100)	40.9 (0–100)
Municipalities with medium-density	0.0 (0–46.1)	0.0 (0–50.0)	0.0 (0–46.1)
Rural municipalities	0.0 (0–57.7)	0.0 (0–80.8)	0.0 (0–59.0)

were 2.48 (1.37, 4.47) for meat consumption ≤once/week, and 1.38 (0.90, 2.19) for meat consumption >once/week; 0.84 (0.49, 1.45) and 1.62 (1.14, 2.31), respectively for fruit and vegetable consumption ≤once/week and >once/week; and 1.45 (0.93, 2.26) for never smokers, and 1.64 (1.01, 2.60) for ever smokers.

No interaction was found between urbanicity and water contaminant concentrations, except for Br-THMs exposure through showers and baths ($p = 0.05$) (Table S8). After stratification, associations were stronger among participants who lived mostly in semi-urban or rural areas compared to those living mostly in urban areas. We also found significant associations between waterborne ingested nitrate and breast cancer only among participants who spent most of the exposure period in

Table 2
Water-use and exposure characteristics of CONTANCES participants.

	Non-cases (n = 26,232)	Cases (n = 437)	Total (n = 26,669)
Type of water consumed (from 2020 follow-up), n (%)			
Tap water unfiltered	12,303 (54.3 %)	192 (48.4 %)	12,495 (54.2 %)
Tap water filtered	2,841 (12.5 %)	53 (13.4 %)	2,894 (12.6 %)
Bottled water	5,194 (22.9 %)	107 (27.0 %)	5,301 (23.0 %)
Unfiltered tap water + bottled	1,739 (7.7 %)	27 (6.8 %)	1,766 (7.7 %)
Tap water filtered + bottled	396 (1.7 %)	12 (3.0 %)	408 (1.8 %)
Other	85 (2.0 %)	3 (0.9 %)	79 (0.4 %)
Missing	3,580	40	3,620
Type of filter used (from 2020 follow-up), n (%)			
None	17,505 (77.5 %)	290 (73.0 %)	17,795 (77.4 %)
Pitcher-type	2,366 (10.5 %)	45 (11.3 %)	2,411 (10.5 %)
Faucet-mounted	492 (2.2 %)	12 (3.0 %)	504 (2.2 %)
Reverse osmosis	158 (0.7 %)	1 (0.3 %)	159 (0.7 %)
Water softener	1,363 (6.0 %)	31 (7.8 %)	1,394 (6.1 %)
Other	714 (3.2 %)	18 (4.5 %)	732 (3.2 %)
Missing	3,634	40	3,674
Average residential levels over the exposure period, Median (IQR)			
Nitrate (mg/L)	15.4 (19.6)	15.9 (18.9)	15.4 (19.6)
Total THMs (µg/L)	15.3 (12.3)	15.1 (13.3)	15.3 (12.3)
Br-THMs (µg/L)	12.8 (10.6)	12.8 (11.7)	12.8 (10.6)
Chloroform (µg/L)	2.1 (3.5)	1.9 (3.5)	2.1 (3.5)
Average waterborne ingested exposure over the exposure period, Median (IQR)			
Nitrate (mg/day)	7.2 (17.6)	7.9 (17.5)	7.2 (17.6)
Total THMs (µg/day)	8.2 (18.0)	8.3 (18.8)	8.2 (18.0)
Br-THMs (µg/day)	5.9 (14.2)	6.3 (15.1)	5.9 (14.2)
Chloroform (µg/day)	0.8 (3.0)	0.7 (3.0)	0.8 (3.0)
Average exposure through showers and baths over the exposure period, Median (IQR)			
Total THMs (µg/L × min/day)	83.3 (104)	81.2 (105.7)	83.3 (104.1)
Br-THMs (µg/L × min/day)	63.4 (83.5)	62.0 (85.5)	63.4 (83.6)
Chloroform (µg/L × min/day)	9.5 (20.4)	7.6 (18.2)	9.4 (20.4)
Follow-up time (years)			
Median (IQR)	5.0 (3.1)	3.2 (3.3)	5.0 (3.2)
Min-Max	0.7–9.9	0.0–9.2	0.0–9.9
Exposure period (years)			
Median (IQR)	13.0 (0.0)	11.0 (3.0)	13.0 (0.0)
Min-Max	10.0–13.0	4.0–13.0	4.0–13.0

densely populated municipalities (1.69 (1.01, 2.83) for the third tertile vs. first tertile).

When excluding participants with more than 30 % of water concentrations coming from a surveillance area allocated to the centroid of its municipality (Table S9), direction and magnitude of associations remained unchanged while the significance of the main results was lost. With the exclusion of participants who consumed bottled water, we obtained similar results for waterborne ingested nitrate (Table S10). However, exposure pattern became less evident for waterborne ingested brominated THMs (1.33 (0.94, 1.87) and 1.14 (0.77, 1.70) for the second and third vs. first tertile).

Results using quartiles instead of tertiles for the exposures (Table S11) and those limited to women who did not treat their tap water nor consumed bottled water (Table S12) were consistent with the main analyses. Not adjusting on nitrate for THMs models with exposure through shower and bath led to stronger associations with breast cancer risk (Table S13). More especially, we found a significant association for Br-THMs in the fourth quartile of exposure (1.51 (1.08, 2.10)). Main results using a 10-year lag to account for cancer latency led to similar findings.

4. Discussion

We evaluated breast cancer risk associated with widespread drinking water contaminants in a large country-wide prospective cohort in France. Long-term exposure to nitrate and THMs was assessed using centralized routine monitoring data of drinking water quality, residential history and personal information on water-related behavior of study participants. We estimated a set of relevant exposure indices including residential levels, waterborne ingestion, and showering-bathing exposure, all reflecting different and complementary exposure pathways. Our findings indicate a positive and exposure-dependent association between waterborne ingested nitrate and breast cancer risk. Associations for THMs were close to the null or showed non monotonic exposure–response patterns.

Residential levels provide a rough estimate of exposure through multiple routes (ingestion, inhalation, dermal) regardless of personal water use and drinking habits. Exposure through showers and baths informs specifically about dermal and inhalation exposure, that is particularly relevant for volatile and skin permeable THMs (Ashley et al., 2005; Costet et al., 2011; Gordon et al., 2006) but not for nitrate. Given than nitrate is only ingested, the waterborne ingested estimates that consider the type of water consumed (bottled, tap), use of filters and the amount of water ingested, provide the most relevant exposure marker for nitrate.

Compared to previous studies that evaluated breast cancer and exposure to nitrate in drinking water (Brody et al., 2006; Espejo-Herrera et al., 2016; Inoue-Choi et al., 2012; Weyer et al., 2001), there are differences in the methodology and exposure levels that hamper a direct comparison. Previous study designs were case-control in MCC-Spain (Espejo-Herrera et al., 2016) and Cape Cod study (Brody et al., 2006), and prospective cohort in the Iowa Women's Health Study (Inoue-Choi et al., 2012; Weyer et al., 2001). Among the four studies, three focused on residential levels or did not consider individual water consumption (Brody et al., 2006; Inoue-Choi et al., 2012; Weyer et al., 2001). Residential concentrations were lower in the studies conducted in the United States compared to our study (median of 15.4 mg/L): median concentration was 4.47 mg/L (equivalent to 1.01 mg/L nitrate-nitrogen) in the Iowa Women's Health Study, 1955–1988 (Inoue-Choi et al., 2012; Weyer et al., 2001), and percentile 60 was 4.87 mg/L (1.1 mg/L nitrate-

Table 3
Hazard ratio (HR) and 95 % confidence interval (CI) of breast cancer associated with average nitrate and trihalomethane (THM) exposure over the exposure period.

Exposure	Person-years	HR (95 % CI)[a]	HR (95 % CI)[b]	HR (95 % CI)[c]
Residential levels (N = 26,669 participants; 153,742 person-years; 437 breast cancer diagnoses)				
Nitrate (mg/L)				
≤7.21	51,266	Ref. 1	Ref. 1	Ref. 1
>7.21–22.0	51,229	1.23 (0.98, 1.55)	1.24 (0.98, 1.56)	1.30 (1.01, 1.67)
>22.0	51,247	1.12 (0.89, 1.42)	1.13 (0.89, 1.42)	1.19 (0.93, 1.53)
Total THMs (μg/L)				
≤11.9	51,248	Ref. 1	Ref. 1	Ref. 1
>11.9–19.7	51,247	0.89 (0.71, 1.13)	0.91 (0.71, 1.16)	0.85 (0.66, 1.10)
>19.7	51,247	0.96 (0.76, 1.20)	0.97 (0.77, 1.22)	0.88 (0.68, 1.13)
Brominated THMs (μg/L)				
≤9.46	51,248	Ref. 1	Ref. 1	Ref. 1
>9.46–15.7	51,293	0.83 (0.65, 1.05)	0.83 (0.65, 1.06)	0.78 (0.60, 1.01)
>15.7	51,201	0.96 (0.77, 1.20)	0.98 (0.78, 1.22)	0.96 (0.74, 1.24)
Chloroform (μg/L)				
≤1.00	51,282	Ref. 1	Ref. 1	Ref. 1
>1.00–3.35	51,213	0.83 (0.66, 1.05)	0.84 (0.67, 1.06)	0.84 (0.66, 1.07)
>3.35	51,247	0.83 (0.66, 1.04)	0.84 (0.67, 1.05)	0.80 (0.62, 1.03)
Waterborne ingestion (N = 22,664 participants; 132,112 person-years; 387 breast cancer diagnoses)				
Nitrate (mg/day)				
≤4.80	51,768	Ref. 1	Ref. 1	Ref. 1
>4.80–15.1	36,307	1.14 (0.88, 1.46)	1.16 (0.90, 1.49)	1.35 (1.01, 1.81)
>15.1	44,037	1.19 (0.94, 1.51)	1.23 (0.97, 1.55)	1.51 (1.10, 2.07)
Total THMs (μg/day)				
≤2.95	44,038	Ref. 1	Ref. 1	Ref. 1
>2.95–15.2	44,037	0.89 (0.70, 1.14)	0.91 (0.71, 1.16)	0.75 (0.56, 0.99)
>15.2	44,037	0.94 (0.74, 1.20)	0.98 (0.77, 1.24)	0.74 (0.53, 1.02)
Brominated THMs (μg/day)				
≤2.16	44,038	Ref. 1	Ref. 1	Ref. 1
>2.16–11.9	44,037	1.00 (0.78, 1.27)	1.01 (0.79, 1.29)	0.97 (0.67, 1.41)
>11.9	44,037	0.94 (0.74, 1.20)	0.97 (0.76, 1.25)	0.85 (0.54, 1.35)
Chloroform (μg/day)				
≤0.27	44,038	Ref. 1	Ref. 1	Ref. 1
>0.27–2.12	44,037	0.85 (0.67, 1.09)	0.87 (0.68, 1.11)	0.74 (0.52, 1.05)
>2.12	44,037	0.92 (0.72, 1.17)	0.94 (0.74, 1.20)	0.83 (0.56, 1.23)
Showering and bathing (N = 22,674 participants; 132,212 person-years; 385 breast cancer diagnoses)				
Total THMs (μg/L × min/day)				
≤51.5	44,071	Ref. 1	Ref. 1	Ref. 1
>51.5–125	44,070	1.08 (0.84, 1.37)	1.09 (0.85, 1.40)	1.01 (0.79, 1.31)
>125	44,071	1.12 (0.87, 1.43)	1.12 (0.87, 1.44)	1.00 (0.75, 1.34)
Brominated THMs (μg/L × min/day)				
≤38.1	44,070	Ref. 1	Ref. 1	Ref. 1
>38.1–99.2	44,071	1.02 (0.80, 1.30)	1.02 (0.80, 1.30)	0.98 (0.75, 1.28)
>99.2	44,071	1.15 (0.90, 1.47)	1.15 (0.90, 1.48)	1.18 (0.84, 1.64)
Chloroform (μg/L × min/day)				
≤5.11	44,071	Ref. 1	Ref. 1	Ref. 1
>5.11–18.5	44,070	0.92 (0.72, 1.16)	0.92 (0.73, 1.18)	0.88 (0.68, 1.13)
>18.5	44,071	0.88 (0.69, 1.13)	0.89 (0.69, 1.14)	0.78 (0.59, 1.04)

Brominated THMs include bromodichloromethane, dibromochloromethane, and bromoform.
Total THMs include chloroform, bromodichloromethane, dibromochloromethane, and bromoform.
a Model 1: Extended Cox model with attained age as time-scale, adjusted for education.
b Model 2: Model 1 further adjusted for alcohol consumption, body mass index, dietary healthy score, smoking, physical activity off work, first degree family history of breast cancer, menopausal status, number of children and urbanicity.
c Model 3: Model 2 mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), brominated THMs and nitrate (chloroform model).

nitrogen) in Cape Cod study, 1972–1995 (Brody et al., 2006). The Cape Cod study excluded participants who reported using water filters for a sensitivity analysis but did not consider percentage filtering reductions of parameters concentrations in their exposure assessment. Water consumption habits also differ between studies, with 18 % drinking water from private wells and less than 6 % consuming bottled water in the Iowa Women's Health Study subjects, compared to 33 % of bottled water consumers in the present study. Inoue-Choi et al. (Inoue-Choi et al., 2012) examined nitrate intake assuming an averaged water ingestion of 2 L/day. In the Spanish study (Espejo-Herrera et al., 2016), an average of 1.2 ± 0.7 L of water consumed per day was reported among controls, and waterborne nitrate intake was lower compared to our population (median of 3.8 mg/day vs. 6.9 mg/day in our study). Water intake in our study was similar to the Spanish study (1.0 L/day (IQR: 0.5) for controls) and lower than in other cohorts such as the French cohort NutriNet-Santé (2.3 ± 4.7 L for men and 2.1 ± 2.4 L for women) (Nissensohn et al., 2017). Differences may be partly explained by the way intake was ascertained. For instance, in the NutriNet-Santé cohort, intake was recorded during three days, randomly distributed within a two-week period, including two weekdays and one day of the weekend, and daily mean individual consumption was calculated with a weighting on the type of day (week or weekend).

Three previous studies focused on older (aged 55–60 or more) or menopausal women (Brody et al., 2006; Inoue-Choi et al., 2012; Weyer et al., 2001). There is evidence that menopausal status serves as an important effect modifier for environmental exposures in breast cancer epidemiology. This different susceptibility has been documented across multiple chemicals, including perfluoroalkyl substances (PFAS) (Dou et al., 2024), cadmium (Gallagher and Meliker, 2010), endocrine-disrupting chemicals such as polychlorinated biphenyls (PCBs) (Zhang

et al., 2004), and fine particulate matter ($PM_{2.5}$) (White et al., 2019). Several biological mechanisms may contribute to these observed differences, including post-menopausal changes in hormonal environment, age-related alterations in detoxification pathways, cumulative lifetime exposure effects, changes in tissue composition and cellular repair mechanisms, and age-associated modifications in immune function. More specifically, in the case of nitrate, menopausal changes in cytochrome P450 (CYP) enzyme function may play a critical role. Nitrosamines, carcinogens formed from nitrate, require metabolic activation by specific CYP enzymes to exert their carcinogenic effects (IARC, 2010). These enzymes have been detected in various tissues, including breast tissue (Leung et al., 2013). Research indicates that tobacco-specific nitrosamines undergo differential metabolism by CYP enzymes (particularly CYP2E1 and CYP3A) and catechol-O-methyltransferase (COMT) in breast tissue, with metabolic patterns varying based on menopausal status (Gankhuyag et al., 2017; Williams and Phillips, 2000). This enzymatic variation could help explain the observed differences in nitrate-associated breast cancer risk between pre- and postmenopausal women. Also, breast cancer often has a lengthy latency period, occurring more frequently after the age of 55 (Trichopoulos et al., 1972). However, an increasing trend of breast cancer incidence was observed in young women in France since the past decade (Hassaine et al., 2022). Despite having younger women in our study, we still found overall significant associations between waterborne nitrate ingestion and breast cancer. Even if the interaction was non-significant, after stratification by menopausal status, statistically significant (and higher) associations were only observed among post-menopausal women. This may be partly due to misclassification among premenopausal women since we used age at censorship as a rough proxy to define menopausal status.

In Espejo-Herrera et al., long-term waterborne ingested nitrate was associated with breast cancer risk among post-menopausal women with high consumption of red meat or processed meat. Odds ratio (OR) (95 % CI) for red meat intake ≥20 g/day was 1.64 (1.08, 2.49), interaction p-value = 0.17 (Espejo-Herrera et al., 2016). This effect modification is biologically plausible since red meat contains amines, amides, and heme iron, that are precursors of endogenous nitrosation. In our study, however, we did not find evidence of such effect modification, and associations were indeed larger among participants eating less red meat (once a week or less). Likewise, vitamin C and other antioxidants such as vitamin E and polyphenols inhibit the endogenous formation of NOCs and DNA adducts (Mach et al., 2020; Mirvish, 1996). When taken between 2 h before and 1 h after administration of nitrate and amino acids, vitamin C inhibited the formation of NOCs (Mirvish et al., 1995). Accordingly, in a recent study on waterborne nitrate ingestion and prostate cancer, high intake of fiber, fruit/vegetables or vitamin C lowered the risk between waterborne ingested nitrate and prostate cancer (Donat-Vargas et al., 2023). However, in the present study we observed an unexpected higher association among those with higher fruit and vegetable consumption. In the Iowa Women Health Study, higher risk was associated with increased waterborne nitrate levels among women with high folate intake (>400 μg/day) (Inoue-Choi et al., 2012). As folate are abundant in many high nitrate vegetables such as lettuce, these results are consistent with ours, although precise diet intake including nitrate could not be estimated based on the cohort questionnaire. Individuals with elevated vegetable consumption might experience higher overall nitrate intake (Menard et al., 2008),

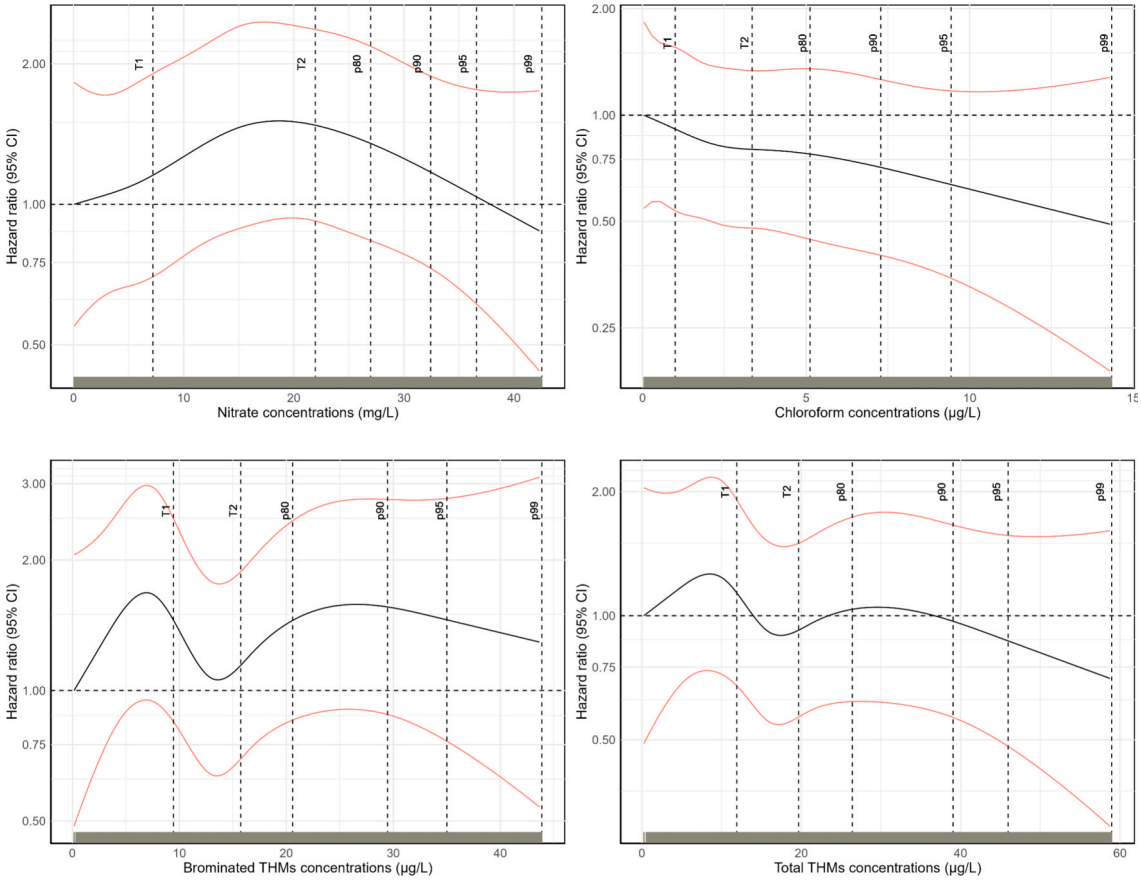

Fig. 2. Exposure-response relationship between residential levels and risk of breast cancer estimated using restricted cubic splines (with three degrees of freedom). Hazard ratios and confidence intervals estimated by extended Cox model with attained age as underlying time-scale and time-dependent variables, adjusted for education, alcohol consumption, body mass index, dietary healthy score, smoking, physical activity off work, first degree family history of breast cancer, menopausal status, number of children, urbanicity, and mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), brominated THMs and nitrate (chloroform model).

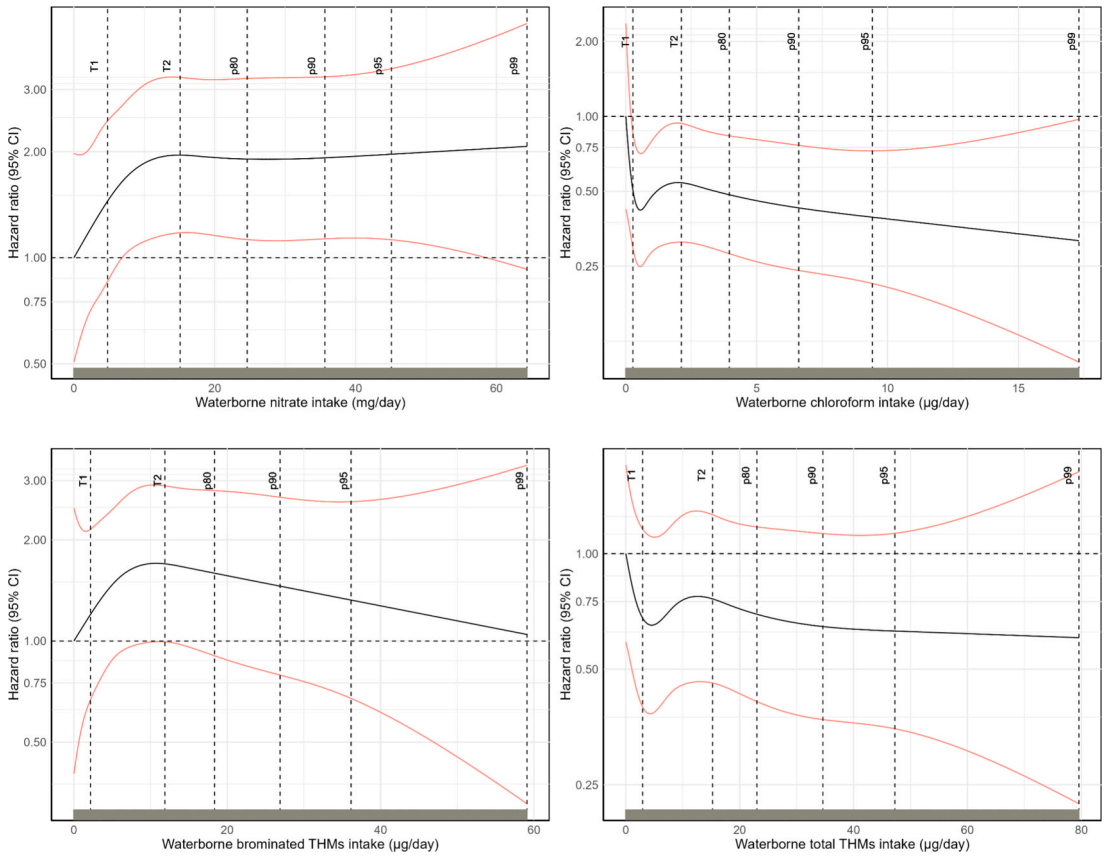

Fig. 3. Exposure-response relationship between exposure by ingestion and risk of breast cancer estimated using restricted cubic splines (with three degrees of freedom). Hazard ratios and confidence intervals estimated by extended Cox model with attained age as underlying time-scale and time-dependent variables, adjusted for education, alcohol consumption, body mass index, dietary healthy score, smoking, physical activity off work, first degree family history of breast cancer, menopausal status, number of children, urbanicity, and mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), brominated THMs and nitrate (chloroform model).

particularly if they consume conventionally grown products utilizing nitrate-based fertilizers (Hosseini et al., 2023), and could exceed the Acceptable Daily Intake (3.7 mg/kg of body weight e.g. 222.0 mg/day for a 60-kg person) defined by expert committees on food additives (JFAO, 2003). The presence of protective antioxidants may not suffice to counteract a high total nitrate intake from both water and food sources. Also, washing and cooking habits of vegetables are important (Ebrahimi et al., 2020; Shamloo et al., 2018) as they can reduce nitrate intake. Since they are not taken into account in the different studies, it may lead to exposure misclassification. In addition, stratification in our study was based on food consumption at inclusion and lack of previous information could also potentially lead to misclassification. Stratified analyses by smoking status were consistent between our study and the Spanish one, and also with the expected patterns since tobacco contains NOCs precursors (Edwards et al., 2017).

The few studies evaluating DBP exposure and breast cancer have methodological constrains such as ecological design, lack of confounder adjustment or information on water use. A large study in Finland found an increased breast cancer risk (RR = 1.11 (1.01, 1.22)) with drinking water mutagenicity among women supplied by chlorinated surface water (Koivusalo et al., 1997). Only two studies focused on breast cancer and THMs as DBP surrogates (Font-Ribera et al., 2018; Marcus et al., 1998). In an ecological study conducted in the USA (Marcus et al., 1998), total THM exposure with a mean level of 53.4 µg/L (range: 1.6–95.4) was not associated with breast cancer. In a study conducted in Spain (Font-Ribera et al., 2018), adult-lifetime residential chloroform was associated with breast cancer (OR = 1.47 (1.05, 2.06) for the highest quartile (>24 µg/L) compared to the lowest (<8µg/L); p-trend = 0.024). No association was detected for residential Br-THMs or total THMs. Residential total THM levels in our study were much lower than in previous studies. Specifically, median residential chloroform level in our study was 9 times lower than in the study conducted in Spain (Font-Ribera et al., 2018) (2.1 µg/L vs. 18.8 µg/L). While we did not find an association between residential THM species and breast cancer, Br-THMs exposure through showering and bathing led a suggestive association with breast cancer, especially when we did not adjust on nitrates. This result is supported by the fact that brominated DBPs are more genotoxic and cytotoxic than chlorinated ones (Richardson et al., 2007). They also are rodent carcinogens and two out of three (bromoform and chlorodibromomethane) caused mammary gland fibroadenomas in female rats (National Toxicology Program, 1989, 1987, 1985). Only the Spanish study also considered individual showering and bathing habits. However, despite having a similar range of Br-THMs exposure through showering and bathing, they found results opposed to ours, with a protective exposure–response relationship. This discrepancy shows that further investigation into this matter is warranted. We found an unexpected inverse association with waterborne ingested total THMs, and excluding participants consuming bottled water led to null or positive associations, although not statistically significant. Residual confounding by unmeasured factors, such as other drinking-water contaminants, cannot be ruled out. Indeed, drinking-water arsenic for instance was associated with breast cancer risk in some studies (Baastrup et al., 2008; Hinwood et al., 1999) and is more often found in groundwater than surface water, which are usually less chlorinated (Helte et al., 2025). While drinking-water exposure to PFAS was not associated with overall breast cancer (Barry et al., 2013; Li et al., 2022), it may have a role depending on menopausal status or breast cancer subtype (Chang et al., 2024; Shahi et al., 2025). The use of bottled water was a bit higher

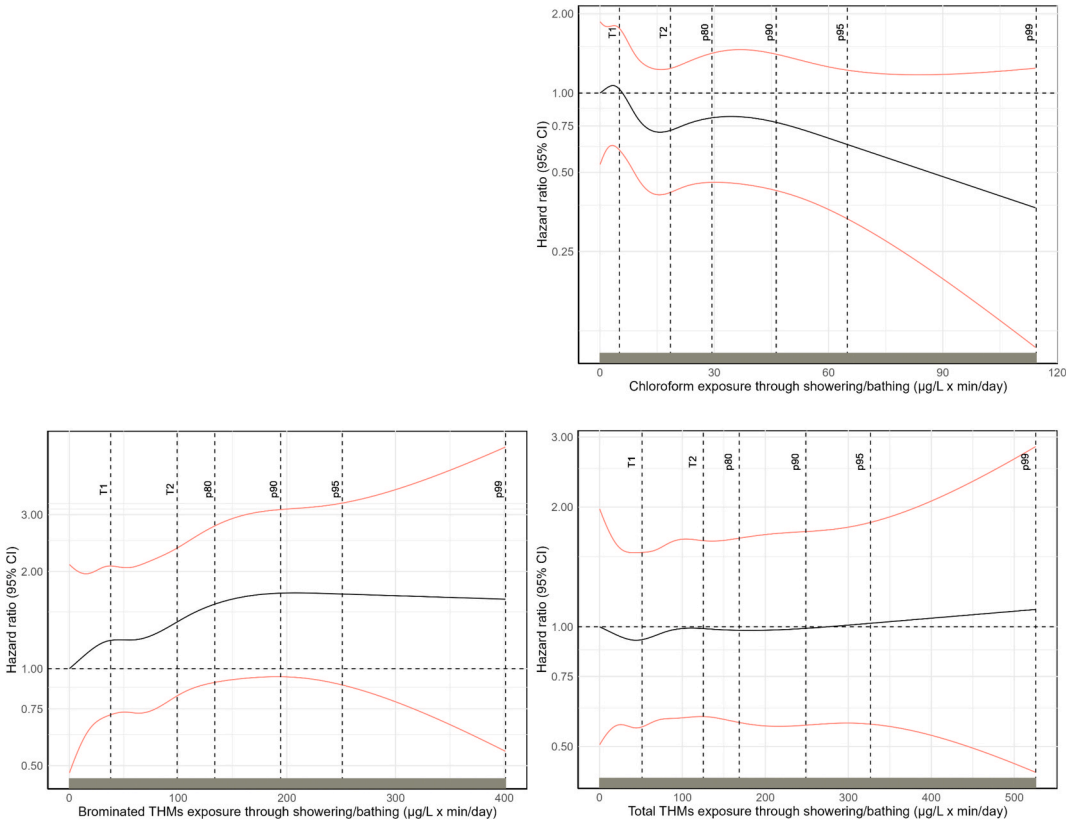

Fig. 4. Exposure-response relationship between exposure through shower and bath and risk of breast cancer estimated using restricted cubic splines (with three degrees of freedom). Hazard ratios and confidence intervals estimated by extended Cox model with attained age as underlying time-scale and time-dependent variables, adjusted for education, alcohol consumption, body mass index, dietary healthy score, smoking, physical activity off work, first degree family history of breast cancer, menopausal status, number of children, urbanicity, and mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), brominated THMs and nitrate (chloroform model).

compared to Spain (33 % vs. 21 %), yet our results without bottled water consumers are closer to the ones of the Spanish study than the ones including them. This might be due to a different composition of bottled water depending on the countries.

Stratification by urbanicity only showed signification associations between ingested nitrate and breast cancer risk among participants who mostly lived in urban areas. Number of cases were limited in non-urban strata. These differences may also be partly explained by urbanicity-specific measurement error.

Exposure measurement error is expected to be higher for THMs compared to nitrate, given more measurements available for nitrate and predictive models performed better (overall median R^2 was 0.85 for nitrate vs. 0.68 for total THMs) (Lafontaine et al., 2024). In total, 35 % of annual nitrate estimates assigned to study subjects corresponded to actual concentrations, compared to 16 % of total THMs estimates. High exposure peaks were smoothed as we used annual concentrations and did not evaluate seasonal trends. However, shorter exposure periods are not etiologically relevant in the cancer framework. Exposure misclassification may be higher in less densely populated areas with fewer and more poorly geocoded surveillance areas, as a single point represented an entire area. However, our results remained consistent while excluding participants with less than 70 % of yearly concentrations assigned from well geocoded surveillance areas, despite losing the significance due to a loss of power. Other sources of measurement error include the absence of information on waterborne ingestion outside the residence. Although we collected type of water consumed outside the residence, the exposure assessment was residence-based as we did not have occupational history nor information on use of filters to assess exposure at the workplace.

Breast cancer subtypes could not have been evaluated in our study. Subtypes include estrogen receptor positive (ER+)/luminol, progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and triple-negative (TNBC). While HER2+ accounts for approximately 15–25 % of breast cancers worldwide (Orrantia-Borunda et al., 2022), a French nationwide population study estimated prevalence of breast cancer subtypes: 80.2 % for ER+, TNBC (9.5 %), and HER2+ (10.3 %) (Dumas et al., 2022). However, these percentages differed depending on the age at breast cancer diagnosis. TNBC and ER + subtypes attained 23.3–29.7 % and 46.9 %-56.8 % of cases respectively for <40-years old women at diagnosis, and 10.3–12.4 % and 74.2 %–77.8 % of cases respectively for women aged 40–59 at diagnosis. Therefore, based on the age of women in our population, we may assume that ER+ subtype is the predominant breast cancer subtype in our analyses. However, with no further information, we cannot conclude on potential breast cancer subtype-specific associations, which would have strengthened our results.

Another limitation of the study is the inability to evaluate early-life exposures. This specific window of exposure may be critical for breast cancer (Bonner et al., 2005; Lillycrop and Burdge, 2014; Terry et al., 2019). However, this limitation is common to many other studies in countries where certain water contaminants were not monitored through time. Furthermore, water consumption/use habits during early life may be difficult to obtain to construct exposures with specific pathways and subject to recall bias. The period covered by the SISE-Eaux database prevented us from extending the exposure period, which could have reduced potential exposure misclassification, especially for older participants. While we had waterborne contaminants concentrations for 2000–2020, since we used a 5-year lag for exposures and inclusion started in 2012, median exposure period was 11 and 13 years for cases and non-cases respectively, which is lower than other studies (from 18

Table 4
Hazard ratio (HR) and 95% confidence interval (CI) of breast cancer associated with average residential exposure and waterborne ingested nitrate and trihalomethanes (THMs) over the exposure period stratified by menopausal status* at censorship.

Exposure	Person-years	HR (95 % CI)	Person-years	HR (95 % CI)	Interaction p-value
Residential levels	Pre-menopausal* (n = 10,800; 129 cases)		Post-menopausal* (n = 15,869; 308 cases)		
Nitrate (mg/L)					
≤7.21	16,572	Ref. 1	34,694	Ref. 1	0.26
>7.21–22.0	20,439	1.33 (0.85, 2.08)	30,790	1.28 (0.95, 1.73)	
>22.0	18,871	1.00 (0.62, 1.62)	32,376	1.27 (0.95, 1.70)	
TTHMs (μg/L)					
≤11.9	18,322	Ref. 1	32,926	Ref. 1	0.03
>11.9–19.7	19,633	0.58 (0.35, 0.95)	31,614	0.95 (0.70, 1.28)	
>19.7	17,927	0.95 (0.62, 1.46)	33,320	0.85 (0.63, 1.15)	
Brominated THMs (μg/L)					
≤9.46	18,052	Ref. 1	33,196	Ref. 1	0.46
>9.46–15.7	19,701	0.70 (0.43, 1.15)	31,592	0.79 (0.58, 1.08)	
>15.7	18,129	0.97 (0.60, 1.56)	33,072	0.96 (0.70, 1.32)	
Chloroform (μg/L)					
≤1.00	17,692	Ref. 1	33,590	Ref. 1	0.31
>1.00–3.35	20,216	0.78 (0.50, 1.23)	30,997	0.88 (0.67, 1.17)	
>3.35	17,974	0.88 (0.56, 1.39)	33,273	0.76 (0.56, 1.03)	
Waterborne ingested	**Pre-menopausal***(n=10,568; 113 cases)		Post-menopausal* (n=12,096; 274 cases)		
Nitrate (mg/day)					
≤4.80	16,949	Ref. 1	34,819	Ref. 1	0.73
>4.80–15.1	13,944	1.19 (0.69, 2.05)	22,363	1.48 (1.05, 2.09)	
>15.1	17,075	1.54 (0.87, 2.72)	26,962	1.53 (1.05, 2.25)	
TTHMs (μg/day)					
≤2.95	13,760	Ref. 1	30,278	Ref. 1	0.27
>2.95–15.2	17,555	0.91 (0.53, 1.54)	26,482	0.68 (0.48, 0.97)	
>15.2	16,653	0.63 (0.34, 1.18)	27,384	0.78 (0.54, 1.14)	
Brominated THMs (μg/day)					
≤2.16	13,850	Ref. 1	30,188	Ref. 1	0.66
>2.16–11.9	17,200	1.20 (0.61, 2.34)	26,837	0.88 (0.56, 1.39)	
>11.9	16,918	0.94 (0.40, 2.22)	27,119	0.82 (0.47, 1.44)	
Chloroform (μg/day)					
≤0.27	13,964	Ref. 1	30,074	Ref. 1	0.74
>0.27–2.12	17,198	0.79 (0.42, 1.49)	26,839	0.74 (0.49, 1.13)	
>2.12	16,806	0.77 (0.38, 1.56)	27,231	0.87 (0.55, 1.40)	

Brominated THMs includes bromodichloromethane, dibromochloromethane, and bromoform.
Total THMs (TTHMs) includes chloroform, bromodichloromethane, dibromochloromethane, and bromoform.
HR (95 %CI) estimated by extended Cox models with attained age as time-scale adjusted for education, alcohol consumption, body mass index, dietary healthy score, smoking, physical activity off work, first degree family history of breast cancer, menopausal status, number of children, urbanicity, and mutually adjusted for the other corresponding components, i.e., total THMs (nitrate model), nitrate (THMs model), chloroform and nitrate (brominated THMs model), brominated THMs and nitrate (chloroform model).
*A 51 years old cut-off was used for age at censorship as a proxy of menopausal status.

years of age to 2 years before the study interview for Espejo-Herrera et al. (Espejo-Herrera et al., 2016) and a 33-year period for Inoue-Choi et al. (Inoue-Choi et al., 2012) for instance). Our lag choice was a compromise between considering cancer latency while covering a sufficient and meaningful exposure period. Defining an adequate latency period for cancer is difficult and often arbitrary (Abecasis et al., 2020) and we acknowledge that ours may be short to fully capture associations between chronic exposure to nitrate and trihalomethanes and breast cancer risk. However, exploring a 10-year lag, even if the resulting reduced exposure window may be less relevant, led to similar findings. Finally, a potential selection bias cannot be ruled out, since women in our study population were more educated and slightly older than women in the overall cohort. However, we assume that it is not exposure-dependent and would be a non-differential bias, if any.

To our knowledge, this is the first study evaluating breast cancer risk and exposure both to waterborne nitrate and THMs, thus providing a more realistic exposure scenario compared to single-pollutant analyses. Despite the inherent challenges of using routine monitoring data, this study establishes a precedent by utilizing nationwide centralized water quality data at the surveillance area level linked to a large, ongoing prospective cohort. Key strengths of this study include the longitudinal approach: we used a methodology for a complex population as CONSTANCES participants moved several times during the exposure period, while several studies focused on permanent residents (Brody et al., 2006) or subjects who had utilized the same water supply for over a decade (Weyer et al., 2001). Detailed individual information collected repeatedly throughout the follow-up period allowed the assessment of several potential confounders and effect modifiers, the latest being often unexplored (Benmarhnia et al., 2018). We took into account water habits in our analyses as well as co-exposure to two widespread water contaminants. While having a large sample size, number of cancer cases were limited due to the youthfulness of our population and a relatively short follow-up. Yet, we managed to enlighten associations between drinking water contaminants and breast cancer for nitrate concentrations below the WHO guidelines (World Health Organization, 2022).

5. Conclusions

Findings suggest that long-term waterborne ingested nitrate could be a risk factor of breast cancer, even at levels under the current regulation. Exposure to Br-THMs through showers and baths showed an exposure–response relationship with breast cancer that never reached statistical significance. Further studies are warranted to draw firm conclusions.

CRediT authorship contribution statement

Antoine Lafontaine: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Carolina Donat-Vargas:** Writing – original draft, Formal analysis. **Emeline Lequy:** Writing – review & editing, Methodology,

Conceptualization. **Sewon Lee:** Writing – review & editing, Formal analysis. **Philippe Glorennec:** Writing – review & editing, Resources. **Barbara Le Bot:** Writing – review & editing, Resources. **Marcel Goldberg:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Marie Zins:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Benedicte Jacquemin:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Cristina M. Villanueva:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109853.

Data availability

The authors do not have permission to share data.

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