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RESEARCH

Arsenic in drinking water and breast cancer: a case–control study from a high exposure area in Northern Chile

Estela Blanco[1,2] · Johanna Acevedo[3,4] · Liliana Pérez[2] · Marian Herrera[2] · Viviana Durán[5] · Teresa Barlaro[6] · Rodrigo Meza[7] · Juan Carlos Roa[8] · Roxana Parra[9] · Hugo Benitez[9] · Molly E. Schwalb[10] · Craig Steinmaus[11] · Catterina Ferreccio[2,12]

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Abstract

Purpose Exposure to arsenic in drinking water is a cause of lung, bladder, and skin cancer, however the relation between arsenic and breast cancer is unclear. Northern Chile had high levels of arsenic in drinking water (up to 900 µg/l) between 1950 and 1970, facilitating the study of outcomes with long latency. We conducted a breast cancer case–control study in Northern Chile (2014–2018) and analyzed 505 incident breast cancer cases and 409 population-based female controls with data collected on lifetime exposure to arsenic and potential confounders.

Methods We identified cases in collaboration with cancer committees, hospitals, and medical facilities in the study area. Controls were recruited from the Chile Voter Registry. Logistic regression was used to assess the relationship between arsenic exposure and breast cancer adjusting for education and age. We evaluated cumulative, lifetime average and highest single year exposure with tertiles and quartiles and population weighted controls based on age and region of residence.

Results Exposure levels were high in both cases and controls, with median (interquartile range) values of: 52 (15–84) and 42 (10–106) µg/L for average lifetime concentration, respectively. Adjusted odds ratios (OR) for tertile of cumulative exposure to arsenic concentrations in water (< 1.17, 1.17–5.16, and ≥ 5.17 mg) were 1.00, 0.85 [95% confidence interval (CI), 0.60–1.18], and 1.10 (0.79–1.55). Results were similar for lifetime average and single-highest year exposure metrics.

Conclusion We did not find evidence of increased odds of higher arsenic exposure among incident breast cancer cases compared to female population controls.

Keywords Arsenic · Case–control study · Breast cáncer · Drinking wáter · Chile

Introduction

Arsenic is a natural element, present in the earth's crust, and, in its inorganic form, is extremely toxic [1]. Of all the potential sources of arsenic, exposure via groundwater represents the greatest threat to public health, due to the magnitude of the affected populations [2]. Arsenic is an established cause of lung, bladder, and skin cancer [2], and has been linked to cardiovascular disease [3], diabetes [4], reproductive effects [5], and other adverse health outcomes [6, 7]. However, its relationship with breast cancer is less clear.

Breast cancer is the most common cancer occurring in women [8]. In 2022, over 2.29 million new cases of breast cancer were diagnosed worldwide [9] and, in Chile, it is a leading cause of death among women > 40 years [9]. Breast cancer is complex, and the label encompasses several different diseases, based on the cell-type affected. As such, risk and protective factors are complicated by type, but there is consensus that early menarche (< 12 years), late natural menopause (> 55 years), nulliparity, first pregnancy > 30 years, alcohol use and body mass index relate to increased risk [10]. Given the prevalence of disease worldwide, clarifying the role of potential risk factors, particularly modifiable risk factors like environmental pollutants, is important.

Since the most recent review of the scientific evidence related to the carcinogenic risk of arsenic conducted by the International Agency for Research on Cancer (IARC) in 2012, new evidence is available from areas with levels below [11, 12] and above [13, 14] the 10 µg/L recommended by the World Health Organization (WHO). A recent review on arsenic exposure and breast cancer risk [15] found mixed results. Comparisons between studies is difficult, as exposure

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measurement varies widely. Thus, differences in results may reflect the period of arsenic exposure assessed (chronic versus acute exposures or past versus current exposures). Furthermore, limited exposure assessment and narrow exposure ranges may have also affected the ability of some previous studies to identify valid effects.

The North of Chile is an ideal place to study exposure to arsenic. Several water systems in this area had very high concentrations of naturally occurring arsenic until treatment plants were installed in the 1970's. Most of the population obtains drinking water from public water systems for which historical information on arsenic concentrations is available. As part of a case–control study of lung, bladder, prostate, and breast cancer in northern Chile, we examined the association between levels of arsenic in drinking water and incident breast cancer.

Methods

We recruited incident cases of breast cancer from the Arica y Parinacota, Tarapacá, and Antofagasta regions of Northern Chile. Recruitment personnel maintained close contact with oncology departments in hospitals of the four major cities (Arica, Iquique, Antofagasta, and Calama). Study staff were in constant contact with pathologists and radiologists and received case referrals directly from cancer committees in the area. All new cancer cases are reviewed by a regional hospital-based cancer committee to decide therapeutic management for all patients seeking care in the public sector. Few people leave the area for medical care since full surgical, radiotherapy, and oncology services are available in the region, and the next closest city with this level of care is Santiago, which is between 1,000 and 2,000 km away. Thus, the chance of an incident case being diagnosed or treated in the study area without being approached for participation was low.

We included breast cancer cases who: were first diagnosed between October 2014 and May 2018, resided in the study area at the time of diagnosis, were at least 18 years of age at diagnosis, and had a medical diagnosis of breast cancer (clinical radiologic, cytologic or histologic). Histologic confirmation was standard practice for all cases of suspected cancer in Chile. After contacting the diagnosing physician, a study nurse called or visited new cancer cases at their homes or hospital rooms to discuss the study. For all cases, nurses gathered medical information from physicians, the radiological and pathology laboratories, and medical records.

Enrollment of controls occurred independently of enrollment of cases. Controls were randomly selected from the Chilean Voter Register available for the regions of interest. In Chile, voting was required by law until early 2012, thus all persons who were over the age of 18 before January 31, 2012, would have been represented on the registry if they were registered to vote in one of the three study regions. The last year for which Registry data was made available to the study personnel was 2010, which included people enrolled up to late 2009. The registry includes names, addresses, birth dates, and sex of voters. The expected number of cancer cases in the study area by sex and 5-year age groups was estimated based on the incidence of lung, bladder, breast, and prostate cancer in the study area in the five years prior to study recruitment. Controls were then randomly selected from the Voter Registry for the study area frequency matching individuals with the expected age- and sex-distribution of the four cancer types. To reduce risk of overmatching by the exposure, controls were randomly recruited from throughout the same three regions in Northern Chile from which the cancer cases were ascertained. Eligibility criteria for controls included being at least 18 years of age and never having been diagnosed with cancer. In the current study, we focus on female controls only.

Potential controls were mailed a letter describing the study and asking the potential control to phone the study coordinator. The letter also explained that if they were unable to call, a nurse would visit their home to discuss the study. Repeated visits were made at different times of the day and week until contact was made, or it was established that the person no longer lived at the residence. If a person did not want to participate, could not be found (no contact after 10 visits), or moved outside the area, another eligible person was selected from the registry. Eligible and willing controls were scheduled for an interview at a convenient time and location.

To calculate participation rates, detailed records were kept of contacts made, refusals, and ineligible and missing subjects. For subjects who were deceased, next of kin were contacted and invited to participate in the study using a separate questionnaire covering a more limited range of topics that they might reasonably be expected to know. For the current analysis, we focused on only those female cases and controls that were listed on the voter registry and who were living at the same address in 2009 (the last year for which registry data was available) as they were living at study recruitment, to ensure comparability of the samples. Comparisons between cases on and not on the voter registry can be found in the Supplementary Material (Supplementary Table 1–2). All participants provided signed informed consent before answering questionnaires. The study was reviewed and approved by the Institutional Review Board of the Pontificia Universidad Católica of Chile (ID: 15–037) and the Northern Region Ethical Committee of the Public Health System.

Exposure assessment

Lifetime arsenic intake was assessed as follows: participants were asked to list each town or city they had lived in for at least 6 months of their life. We linked reported residences to water arsenic measurements obtained from government agencies and research studies, as previously described [16]. While participants were asked the source of their drinking water at each residence, the vast majority reported municipal drinking water as their main source, some reported "other sources" and only a very small proportion reporting drinking bottled water. Thus, an arsenic concentration was assigned to each year of life for all participants based on reported residence. We successfully matched participant reported residences with an arsenic concentration for 97% of residences. The few residences for which water records were not available were in areas not known to have high arsenic levels and were assigned a value of 1 µg/L. We calculated several exposure metrics, related to exposure concentrations and intake. Lifetime cumulative exposure was obtained by summing yearly arsenic concentrations (mg). Other metrics included average exposure (lifetime cumulative/age at evaluation, µg/L) and highest exposure (µg/L) to arsenic concentrations in any single year. Given the long latency period of arsenic-related cancers [17–19], we excluded exposures from the five years preceding study participation for all exposure metrics.

Covariate assessment

All participants responded to a standardized questionnaire administered by study staff. In addition to providing all residences lived in ≥ 6 months and demographic information (e.g., age, education level, occupation), participants were asked about common risk factors for various types of cancers: smoking and alcohol consumption (current and previous habits), age at menarche and menopause, use of hormone replacement therapy, children, and breastfeeding habits, among others. Questions regarding body mass index included height and typical weight currently and in the last 10 years ago. Participants were also asked about medical conditions and medications.

Analysis

Continuous variables were described with medians and interquartile ranges (IQR) and, for categorical variables, with frequencies. Exposure metrics were categorized into tertiles. We estimated the odds of being in each exposure tertile among incident breast cancer cases versus female population controls using logistic regression, considering different exposure metrics: lifetime average, cumulative exposure, and highest single year exposure to arsenic in drinking water, adjusting for potential confounders (age and education level).

To help account for differences in participation rates (Supplmentary Table 3) or recent residential mobility among controls across regions or random errors in control selection, sample weights for controls were developed using the 2009 Census and incorporated into odds ratio calculations. Sample weights were developed by first calculating the age distribution in the regions by 10-year age group. Next, we calculated the expected number of controls by multiplying the proportion in each region by the total number of controls recruited in that age range. Weights were calculated by dividing the expected number of participants by the enrolled controls for each age and region. All cases were given a weight of 1.0 since recruitment rates among cases was high in all regions. A weighted database was then created in R using the function "svydesign" in the library "survey" and ORs were then calculated incorporating weights as part of the design. We provided results of unweighted logistic regression models in supplementary material (Supplemental Tables 4-. To further explore dose–response trends, we replicated the primary analyses using quartiles of exposure. Furthermore, we estimated new models including early menarche, late menopause, nulliparity, breastfeeding, use of oral contraceptives, alcohol use, and overweight/obesity status, which are known risk factors for breast cancer [10], but are not necessarily true confounders of the relationship of arsenic and breast cancer. All analyses were conducted using R software [20].

Results

A total of 823 potential breast cancer cases were identified through the ascertainment process and 782 were contacted to participate in the study. Of these, 699 (85%) agreed to participate; 505 (72%) were listed in the Voter Registry and at the same address at the time of recruitment since 2009. For controls, we attempted to contact a total of 691 possible female controls. Of these 560 (81%) agreed to participate; 409 (73%) were living at the address listed for them in the Voter Registry (Fig. 1). Given the sample size and tertile- or quartile-based exposure classification, the study had 80% power to detect an odds ratio of approximately 1.5 or greater, assuming a two-sided alpha of 0.05.

Breast cancer cases and female population controls had similar median ages (62 [IQR 53–71] and 62 [51–72] years, respectively), level of education (over half completed at least high school), prevalence of overweight (around 70%), and other risk factors associated with breast cancer (Table 1). Cases had higher median levels of lifetime cumulative (3.37 [IQR 0.81–8.07] and 2.06 [0.66–6.40] mg, respectively), lifetime average exposure (52 [15–84] and 42 [10–106]

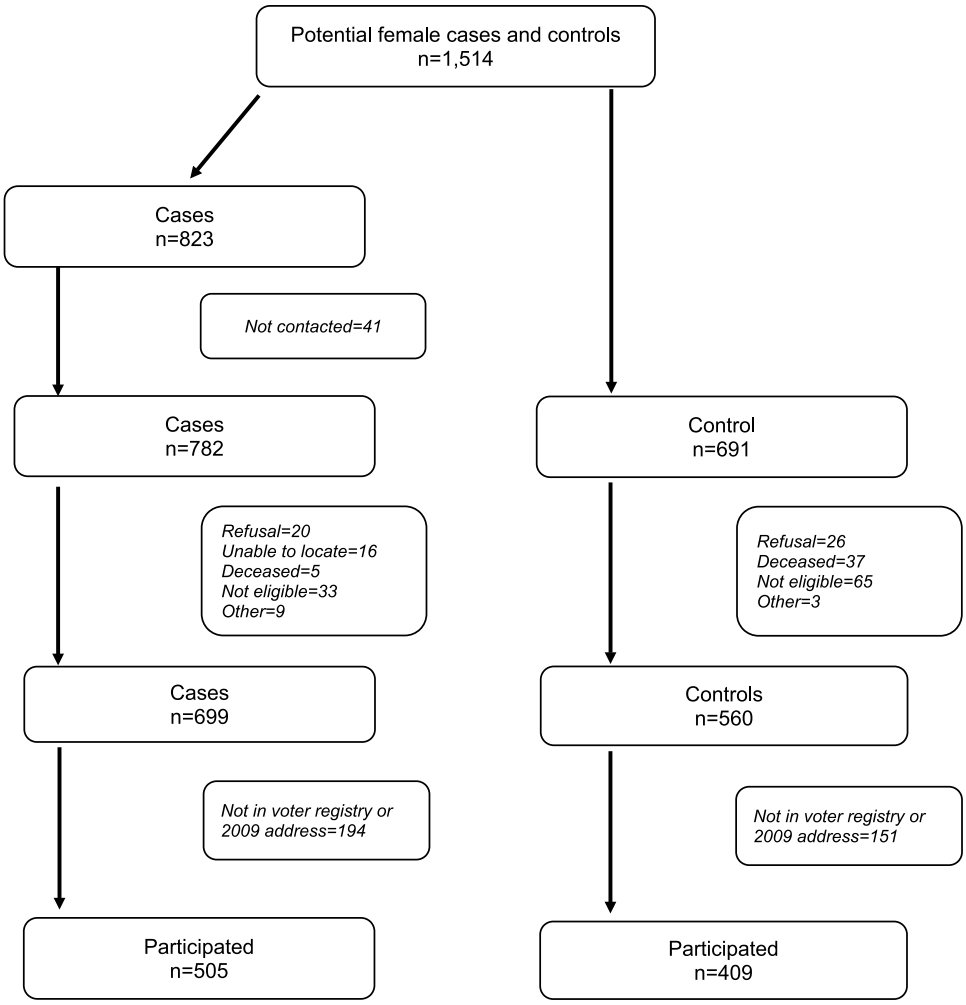

Fig. 1 Participant flow chart for breast cancer and population female controls from Northern Chile, 2014–2018

µg/L, respectively), and highest single-year exposure to arsenic (150 [60–860] and 70 (40–555] µg/L, respectively) (Table 1).

In population-weighted logistic regression models, we did not observe higher odds of being in the highest tertile category of any of the exposure metrics evaluated among incident breast cancer cases compared to population controls (Table 2). Adjusted odds ratios (OR) for tertile of cumulate exposure (< 1.17, 1.17–5.16, and ≥ 5.17 mg) were 1.00, 0.85 [95% confidence interval (CI), 0.60–1.18], and 1.10 (0.79–1.55). ORs for highest single year exposure to arsenic concentrations in water (< 60, 60–297, and ≥ 298 µg/L) were 1.00, 0.65 (95% CI: 0.45–0.94), and 1.06 (0.76–1.48), respectively. ORs were < 1 and increased with tertile of exposure for lifetime average, although confidence intervals for the highest tertile contained the null value (Table 2).

In models adjusted for additional known risk factors for breast cancer, we observed similar results, no differential odds of being in the highest tertile category of any of the exposure metrics evaluated among incident breast cancer cases compared to population controls (Table 2, Fully Adjusted Models). Further, after changing the exposure groups to reflect quartiles, rather than tertiles, we observed similar effects. That is, no differential odds of exposure to the highest quartile of arsenic among cases versus control (Table 3). For cumulative exposure, ORs (< 0.71, 0.71–2.73, 2.74–7.26, and ≥ 7.27 mg) were 1.00, 0.61 (0.41–0.89), 0.90 (0.61–1.32) and 1.03 (0.70–1.51) for the minimally adjusted model and 1.00, 0.77 (0.47–1.27), 0.89 (0.55–1.42), and 0.97 (0.62–1.53) in the fully adjusted model.

Results of unweighted logistic regression models using tertile and quartile of exposure are provided in Supplementary Table 4 and 5, respectively. In sum, in the unweighted logistic regression models, ORs were > 1 for all exposure metrics evaluated and increased with exposure group, however all confidence intervals contained the null value in fully adjusted models.

Table 1 Descriptive statistics of cases of breast cancer and female population controls, Northern Chile, 2014–2018

	Cases n = 505	Controls n = 409
Age[1]	62 (53–71)	62 (51–72)
Age group		
< 40	2 (< 1)	29 (7)
40–49.9	76 (15)	61 (15)
50–59.9	145 (28)	92 (22)
60–69.9	138 (27)	107 (26)
70–79.9	93 (18)	82 (20)
≥ 80	51 (10)	38 (9)
Highest level of education		
< no/little education	111 (22)	100 (24)
< high school	145 (28)	102 (25)
High school	119 (23)	114 (27)
> High school	128 (25)	92 (22)
Menarche < 12 years	58 (12)	59 (14)
Had children	453 (91)	377 (93)
First child > 30 years	43 (10)	37 (10)
Ever breastfed	399 (79)	342 (83)
Age at menopause[1,2]	48 (44–50)	49 (45–50)
Menopause > 55 years[1,2]	7 (2)	13 (5)
Weekly alcohol[1]	0 (0–0.2)	0 (0–0.5)
BMI[1]	27 (24–31)	27 (24–32)
Overweight/obesity[3]	325 (70)	281 (72)
Hormone replacement	81 (16)	53 (13)
Arsenic exposure[1]		
Lifetime cumulative, mg	3.37 (0.81–8.07)	2.06 (0.66–6.40)
Lifetime average, µg/L	52 (15–84)	42 (10–106)
Highest single year, µg/L	150 (60–860)	70 (40–555)
Born before 1970	455 (90)	337 (82)

Values are n (%) unless indicated

[1]Median (interquartile range)

[2]Among those who reported having natural menopause

[3]Considering average weight in the last 10 years

Discussion

In our case–control study conducted in the North of Chile, an area in which the population was exposed to extremely high levels of arsenic prior to 1970 via municipal water sources, we did not find evidence that arsenic acts as a risk factor for breast cancer. Even at extremely high exposure levels (concentrations of > 600 µg/L in a single year), levels not commonly observed in drinking water, we did not observe consistent evidence of increased risk of higher exposure among cases of breast cancer.

Northern Chile provides a natural experiment for investigating variations in cancer risk associated with arsenic exposure. Arsenic is found naturally in the few water sources available in this arid desert area, which was not filtered out of municipal water sources until 1971. Records from as early as 1930 show that arsenic measured in the municipal water of 3 large northern cities (Antofagasta, Tocopilla, and Calama) prior to the 1950's was: 90, 250, and 150 µg/L, respectively [21]. Antofagasta, the largest city in Northern Chile, is the most extreme example of the quasi-experimental nature of the exposure. Beginning in the 1950 s, the population began to grow, in part because of the increased mining activities. Increased population and the use of water sources by the mining operations forced the municipal authorities to change the water source to one with even higher levels of arsenic (860 µg/L). Thus, between 1958 and 1970, the entire population of Antofagasta was exposed to extremely high levels of arsenic, which abruptly decreased to 110 in 1971, when a treatment plant was installed to filter arsenic from drinking water, and further decreased in the decades that followed [21]. All cities in the north of Chile currently maintain levels of arsenic below recommended levels in municipal sources (10 µg/L), however, some small towns, many without water treatment plants, frequently exceed recommended levels [22]. Arsenic is known to cause several types of cancers [2] and given the long latency it is important to study potential risk exposure not at diagnosis, but rather at the triggering point of cell damage. Because municipal records of historical arsenic levels are available in Chile, we were able to easily create accurate exposure histories after obtaining information from residences from all participants.

Although arsenic is a well-established cause of lung, bladder, and skin cancer [2], its relationship to breast cancer is unclear. Previous studies showed a latency of 40–50 years for lung and bladder cancers caused by arsenic, with most cancers being diagnosed years after high exposures stopped [17, 18]. Most other studies have either found no associations or increased risk of breast cancer [13, 23, 24]. Differences in study design, exposure levels, exposure assessment in the relevant period, and information on exposure duration make comparisons difficult. For example, the exposure levels in our study are much different from those in other areas. In a study conducted in Denmark, the median value for the "high" exposure group was 2.1, with a maximum of 25.3 µg/L [24]. Another study conducted in Mexico reported that exposure ranged between < 1 to 303, with between 80 and 90% of women exposed to levels < 35 µg/L [23]. In Northern Chile, arsenic in drinking water was extremely high in the period before 1970 (i.e., > 800 ug/L), [16]. Both cases and controls in our study had high lifetime average exposures (> 42 µg/L) with a large portion having had exposures > 60 ug/L in at least 1 year.

A previous study in Northern Chile found an association between arsenic exposures > 800 ug/L and reduced breast cancer mortality [14]. Strong evidence was provided that the results were biologically plausible and not due to bias or

Table 2 Effect of exposure to arsenic in water (*tertiles*) and breast cancer, population weighted logistic regression

Exposure[1]	Exposure Level	Cases n = 505	Controls n = 409	Minimally Adjusted OR[2] (95% CI)	Fully Adjusted OR[3] (95% CI)
Cumulative	< 1.17	155	126	1.00 (Ref)	1.00 (Ref)
exposure	1.17–5.16	165	156	0.85 (0.60–1.18)	0.81 (0.53–1.24)
(mg)	≥ 5.17	185	127	1.10 (0.79–1.55)	0.95 (0.64–1.40)
Lifetime	< 21	159	112	1.00 (Ref)	1.00 (Ref)
average	21–93	158	168	0.66 (0.47–0.93)	0.84 (0.55–1.28)
(µg/L)	≥ 93.1	188	129	0.99 (0.71–1.38)	0.85 (0.57–1.25)
Highest single year (µg/L)	< 60	124	92	1.00 (Ref)	1.00 (Ref)
	60–297	140	158	0.65 (0.45–0.94)	0.76 (0.45–1.19)
	≥ 298	241	160	1.06 (0.76–1.48)	0.95 (0.64–1.43)

[1]Does not consider 5 years prior to evaluation

[2]Adjusted for education and age

[3]Adjusted for education, age, early menarche, late menopause, ever had children, ever breastfed, alcohol frequency, and BMI

Table 3 Effect of exposure to arsenic in water (*quartiles*) and breast cancer, population weighted logistic regression

Exposure[1]	Exposure Level	Cases n = 503	Controls n = 408	Minimally Adjusted OR[2] (95% CI)	Fully Adjusted OR[3] (95% CI)
Cumulative	< 0.71	118	111	1.00 (Ref)	1.00 (Ref)
exposure	0.71–2.73	108	119	0.61 (0.41–0.89)	0.77 (0.47–1.27)
(mg)	2.74–7.26	137	91	0.90 (0.61–1.32)	0.89 (0.55–1.42)
	≥ 7.27	140	87	1.03 (0.70–1.51)	0.97 (0.62–1.53)
Lifetime	< 13	119	84	1.00 (Ref)	1.00 (Ref)
average (µg/L)	13–47	108	122	0.63 (0.43–0.93)	0.74 (0.46–1.20)
	48–114	132	109	0.84 (0.57–1.24)	0.84 (0.52–1.36)
	≥ 115	146	94	1.05 (0.72–1.53)	0.98 (0.62–1.53)
Highest single	< 40	116	86	1.00 (Ref)	1.00 (Ref)
year (µg/L)	40–109	106	117	0.65 (0.44–0.97)	0.72 (0.44–1.17)
	110–635	108	102	0.77 (0.52–1.14)	0.79 (0.48–1.28)
	≥ 636	175	103	1.19 (0.82–1.72)	1.04 (0.67–1.62)

[1]Does not consider 5 years prior to evaluation

[2]Adjusted for education and age

[3]Adjusted for education, age, early menarche, late menopause, ever had children, ever breastfed, alcohol frequency, and BMI

confounding. There are several major differences between this previous study and ours. First, our study investigated cancer incidence rather than cancer mortality. While further research is needed on this topic, it may be that arsenic has different effects at different stages of the cancer process. Another important difference is that the mortality study assessed effects beginning in the 1950's and up to 2010. Reductions in mortality began a few years after the high exposures started (around 1958) and began returning to baseline levels relatively soon after the high exposures stopped (around 1970). In contrast, most of the cases in our study were diagnosed many years after the higher exposures stopped. Overall, because of these differences, the relevance of the previous mortality study to our findings is unknown.

We did not specify the cellular type of breast cancer nor did we have genotype information to explore gene-arsenic interaction, which has been shown to influence the arsenic-breast cancer relationship [25]. We also did not evaluate arsenic methylation capacity, which may be related to risk breast cancer [26], and did not have consistently collected information on other important clinical and biological distinctions (e.g., ductal carcinoma in situ, estrogen and progesterone receptor status). A case–control study of kidney cancer associated with arsenic intake did not identify a clear dose–response relationship when grouping all kidney cancers together, but did when focusing on renal pelvis and ureter cancers separately [27]. Breast cancer is complex and is made up of different histological types with differences in

prognosis and treatment based on the cell type affected. It is likely that in our sample of incident cases of breast cancer from Northern Chile there were a mix of different breast cancer types. Unfortunately, information on cell type is not routinely available and thus, we were unable to conduct a more sensitive analysis. Future research should explore the possibility of a differential effect of arsenic based on genetic differences, methylation capacity, and breast cancer type.

We evaluated the possibility that our results were affected by biases or confounding. We collected information on several important risk factors for breast cancer, and analyses involving different adjustments gave similar results. Another potential source of error is selection bias. For control selection, we relied on the Voter Registry. Because voting was required by law for all persons over the age of 18 until early 2012, the Registry is estimated to include approximately 90% of all adults in our study area. The last year we had registry data was 2009. As such, some people in the Registry likely moved out of the area by the time our subject ascertainment began in 2015. Thus, the controls that participated in our study were only those people who were listed in the Voter Registry and who lived at their current address from at least 2009. To help prevent selection bias, we also limited our breast cancer cases to those cases who were in the same Voter Registry and who lived in the same address since 2009. This restriction of cases to the same source used to ascertain controls likely helped limit any bias caused using a somewhat older Voter Registry. To account for differences observed in the distribution of controls, we created population weights by region and age and incorporated weights into the analysis [28]. Specifically, our unweighted analysis reflected that we had a disproportionate number of controls, especially those of advanced age, from lower arsenic areas. This likely explains why we observed consistently higher ORs that were > 1 in unweighted models. With regards to case ascertainment, the research team had over 20 years of experience with cancer case ascertainment in the area [18, 29] and the same procedures were used in high and low arsenic areas. Overall, although selection bias cannot be ruled out, we do not expect that limitations in finding of cases or controls represents any major systematic bias. Exposure misclassification is possible, but unlikely. We matched residence with arsenic concentrations reported from government sources for nearly all cities reported. Given the retrospective design of our case–control study, measuring arsenic biomarkers in urine was not applicable. However, prospective studies or those examining more acute effects of arsenic may be better positioned to characterize dose–response relationships using biomarkers rather than exposure proxies. This approach could also be beneficial in cases where participants, as was true for a portion of our sample, report obtaining drinking water from non-municipal sources. In the preent study, the vast majority of participants reported that their water was supplied by the local municipality, however, some did report that drinking water was obtained elsewhere.'Other sources'could have referred to water from a truck or a private well, which are rare in the area [14]. It is likely these other sources would have contained arsenic levels similar to those in municipally supplied drinking water during the periods of highest exposure, as arsenic was not being filtered at that time [21]. While persons, can be exposed to arsenic via other sources besides water, they have been shown to be of little importance given the high levels in drinking water pre-1970s [21]. Occupational exposure to arsenic in copper smelting is not relevant in the current study since this job type is almost exclusively limited to men.

In conclusion, we did not observe evidence of increased odds of higher exposure to arsenic among incident cases of breast cancer compared to female population controls even at extremely high levels of exposure among women in Northern Chile. We found no evidence for confounding or selection bias, but these issues cannot be ruled out. Arsenic is a known carcinogenic agent for lung, bladder and skin cancer [2]; our study provides evidence that it might not be for breast cancer.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-025-07765-9.

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Author contributions All authors contributed to the study conception and design and read and approved the final manuscript. Data collection was performed by Johanna Acevedo, Liliana Pérez, Viviana Durán, Teresa Barlaro, Rodrigo Meza, Roxana Parra, and Hugo Benitez. Marian Herrera assisted with data preparation. Craig Steinmaus and Catterina Ferreccio supervised all activities. The first draft of the manuscript was written by Estela Blanco and all authors commented on previous versions of the manuscript.

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Data availability The datasets generated during and/or analysed during the current study are not publicly available due to requirements from

the Ethics Committee, but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The study was reviewed and approved by the Institutional Review Board of the Pontificia Universidad Católica of Chile (ID: 15-037) and the Northern Region Ethical Committee of the Public Health System.

Patient consent All participants (cases, controls and next of kin proxies) provided signed informed consent before answering questionnaires.

References

1. Khanjani N, Jafarnejad AB, Tavakkoli L (2017) Arsenic and breast cancer: a systematic review of epidemiologic studies. Rev Environ Health 32(3):267–277. https://doi.org/10.1515/reveh-2016-0068
2. International Agency for Research on Cancer (2012) IARC Monographs: Arsenic, Metals, Fibres, and Dusts. IARC Monogr. Eval. Carcinog. Risks Hum., vol. 100C, no. Arsenic, metals, fibres, and dusts.
3. Yuan Y et al (2007) Acute myocardial infarction mortality in comparison with lung and bladder cancer mortality in arsenic-exposed region II of Chile from 1950 to 2000. Am J Epidemiol 166(12):1381–1391. https://doi.org/10.1093/aje/kwm238
4. Castriota F et al (2018) Obesity and increased susceptibility to arsenic-related type 2 diabetes in Northern Chile. Environ Res. https://doi.org/10.1016/j.envres.2018.07.022
5. Hopenhayn C et al (2003) Arsenic exposure from drinking water and birth weight. Epidemiology 14(5):593–602. https://doi.org/10.1097/01.ede.0000072104.65240.69
6. Hall EM et al (2017) Hypertension among adults exposed to drinking water arsenic in Northern Chile. Environ Res. https://doi.org/10.1016/j.envres.2016.11.016
7. Smith AH, Marshall G, Yuan Y, Liaw J, Ferreccio C, Steinmaus C (2011) Evidence from chile that arsenic in drinking water may increase mortality from pulmonary tuberculosis. Am J Epidemiol 173(4):414–420. https://doi.org/10.1093/aje/kwq383
8. Worldwide cancer data | World Cancer Research Fund International. WCRF International. Accessed: Nov. 21, 2022. [Online]. Available: https://www.wcrf.org/cancer-trends/worldwide-cancer-data/
9. Global Cancer Observatory: Cancer Today (version 1.1). International agency for research on cancer. Accessed: Apr. 14, 2025. [Online]. Available: Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today
10. "Breast cancer statistics | World Cancer Research Fund International," WCRF International. Accessed: Nov. 21, 2022. [Online]. Available: https://www.wcrf.org/cancer-trends/breast-cancer-statistics/
11. García-Esquinas E et al (2013) Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol Biomarkers Prev 22(11):1944–1953. https://doi.org/10.1158/1055-9965.EPI-13-0234-T
12. Marciniak W et al (2020) Blood arsenic levels and the risk of familial breast cancer in Poland. Int J Cancer 146(10):2721–2727. https://doi.org/10.1002/ijc.32595
13. Aballay LR, Del Pilar Díaz M, Francisca FM, Muñoz SE (2012) Cancer incidence and pattern of arsenic concentration in drinking water wells in Córdoba, Argentina. Int J Environ Health Res 22(3):220–231. https://doi.org/10.1080/09603123.2011.628792
14. Smith AH et al (2014) Rapid reduction in breast cancer mortality with inorganic arsenic in drinking water. EBioMedicine 1(1):58–63. https://doi.org/10.1016/j.ebiom.2014.10.005
15. Pullella K, Kotsopoulos J (2020) Arsenic exposure and breast cancer risk: A re-evaluation of the literature. Nutrients 12(11):1–17. https://doi.org/10.3390/nu12113305
16. Ferreccio C et al (2013) Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. Epidemiology. https://doi.org/10.1097/EDE.0b013e31829e3e03
17. Yuan Y et al (2010) Kidney cancer mortality: fifty-year latency patterns related to arsenic exposure. Epidemiology. https://doi.org/10.1097/EDE.0b013e3181c21e46
18. Steinmaus CM et al (2013) Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. Cancer Epidemiol Biomarkers Prev 22(4):623–630. https://doi.org/10.1158/1055-9965.EPI-12-1190
19. Marshall G et al (2007) Fifty-Year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst 99(12):920–928. https://doi.org/10.1093/jnci/djm004
20. Rs. Team (2016) RStudio: Integrated Development for R. RStudio, Inc., Boston, MA.
21. Ferreccio C, Sancha AM (2006) Arsenic exposure and its impact on health in Chile. J Health Popul Nutr 24(2):164–175. https://doi.org/10.3329/jhpn.v24i2.728
22. Diaz O et al (2015) Estimation of arsenic intake from drinking water and food (raw and cooked) in a rural village of northern chile. urine as a biomarker of recent exposure. Int J Environ Res Public Health 12(5):5614–5633. https://doi.org/10.3390/ijerph120505614
23. López-Carrillo L, Hernández-Ramírez RU, Gandolfi AJ, Ornelas-Aguirre JM, Torres-Sánchez L, Cebrian ME (2014) Arsenic methylation capacity is associated with breast cancer in Northern Mexico. Toxicol Appl Pharmacol 280(1):53–59. https://doi.org/10.1016/j.taap.2014.07.013
24. Baastrup R et al (2008) Arsenic in drinking-water and risk for cancer in Denmark. Environ Health Perspect 116(2):231–237. https://doi.org/10.1289/ehp.10623
25. Gamboa-Loira B, Cebrián ME, Salinas-Rodríguez A, López-Carrillo L (2017) Genetic susceptibility to breast cancer risk associated with inorganic arsenic exposure". Environ Toxicol Pharmacol. https://doi.org/10.1016/j.etap.2017.08.032
26. López-Carrillo L, Gamboa-Loira B, Gandolfi AJ, Cebrián ME (2019) Inorganic arsenic methylation capacity and breast cancer by immunohistochemical subtypes in northern Mexican women. Environ Res 184(October):2020. https://doi.org/10.1016/j.envres.2020.109361
27. Ferreccio C et al (2013) Case-control study of arsenic in drinking water and kidney cancer in uniquely exposed Northern Chile. Am J Epidemiol 178(5):813–818. https://doi.org/10.1093/aje/kwt059
28. C. Instituto Nacional de Estadísticas, "Resultados CENSO 2017." Accessed: Jan. 10, 2021. [Online]. Available: http://resultados.censo2017.cl/
29. Ferreccio C, González C, Milosavjlevic V, Marshall G, Sancha AM, Smith AH (2000) Lung cancer and arsenic concentrations in drinking water in Chile. epidemiology 11(6):673–679. https://doi.org/10.1097/00001648-200011000-00010

Authors and Affiliations

Estela Blanco[1,2] · Johanna Acevedo[3,4] · Liliana Pérez[2] · Marian Herrera[2] · Viviana Durán[5] · Teresa Barlaro[6] · Rodrigo Meza[7] · Juan Carlos Roa[8] · Roxana Parra[9] · Hugo Benitez[9] · Molly E. Schwalb[10] · Craig Steinmaus[11] · Catterina Ferreccio[2,12]

✉ Catterina Ferreccio
cferreccio@ispch.cl

Estela Blanco
estela.blanco@uc.cl

Johanna Acevedo
johannaacevedo@udd.cl

Liliana Pérez
lili.p.rodriguez@gmail.com

Marian Herrera
herrerariquelme.m@gmail.com

Viviana Durán
viduhe@hotmail.com

Rodrigo Meza
biopsiacalama@gmail.com

Juan Carlos Roa
viduhe@hotmail.com

Roxana Parra
chanitaparra@yahoo.com

Hugo Benitez
hugocesarpatologo@gmail.com

Molly E. Schwalb
molly.schwalb@oehha.ca.gov

Craig Steinmaus
craigs@berkeley.edu

[1] College UC, Pontificia Universidad Católica de Chile, Santiago, Chile

[2] Escuela de Salud Pública, Pontificia Universidad Católica de Chile, Santiago, Chile

[3] Centro de Epidemiología y Políticas de Salud, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

[4] Centro Para La Prevención y Control del Cáncer (CECAN), Santiago, Chile

[5] Department of Pathology, Hospital Juan Noé, Arica, Chile

[6] Department of Pathology, Hospital Ernesto Torres Galdames de Iquique, Iquique, Chile

[7] Department of Pathology, Hospital Carlos Cisternas de Calama, Calama, Chile

[8] Department of Pathology, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[9] Department of Pathology, Hospital Leonardo Guzmán de Antofagasta, Antofagasta, Chile

[10] Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA, USA

[11] Arsenic Research Group, School of Public Health, University of California, Berkeley, CA, USA

[12] Instituto de Salud Pública de Chile, Marathón 1000, Ñuñoa Santiago, Chile