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Drinking water arsenic in northern Chile: high cancer risks 40 years after exposure cessation

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Abstract

Background—Millions of people worldwide are exposed to arsenic-contaminated water. In the largest city in northern Chile (Antofagasta) >250,000 people were exposed to high arsenic drinking water concentrations from 1958 until 1970 when a water treatment plant was installed. Because of its unique geology, limited water sources, and good historical records, lifetime exposure and long-term latency patterns can be assessed in this area with better accuracy than in other arsenic-exposed areas worldwide.

Methods—We performed a population-based case-control study in northern Chile from October 2007 to December 2010 involving 232 lung and 306 bladder cancer cases and 640 age- and gender-matched controls, with detailed information on past exposure and potential confounders, including smoking and occupation.

Results—Bladder cancer odds ratios for quartiles of average arsenic concentrations in water before 1971 (<11, 11–90, 91–335, and >335 μg/L) were 1.00, 1.36 (95% confidence interval, 0.78 to 2.37), 3.87 (2.25 to 6.64), and 6.50 (3.69 to 11.43), respectively. Corresponding lung cancer odds ratios were 1.00, 1.27 (0.81 to 1.98), 2.00 (1.24 to 3.24), and 4.32 (2.60 to 7.17). Bladder and lung cancer odds ratios in those highly exposed in Antofagasta during 1958–70 but not thereafter were 6.88 (3.84 to 12.32) and 4.35 (2.57 to 7.36), respectively.

Conclusions—The lung and bladder cancer risks that we found up to 40 years after high exposures have ended are very high.

Impact—Our findings suggest that prevention, treatment, and other mortality reduction efforts in arsenic-exposed countries will be needed for decades after exposure cessation.

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Conflicts of Interest: The authors declare that there are no financial or personal conflicts of interest regarding the materials discussed in the manuscript.

Introduction

Millions of people worldwide are exposed to naturally-occurring arsenic in their drinking water, including an estimated 50 million in Bangladesh, 30 million in India, 15 million in China, and millions more in the U.S., Europe, and South and Central America (1). Epidemiologic studies from Taiwan, Japan, Argentina, Chile, and elsewhere have identified associations between arsenic in drinking water and cancer, and the International Agency for Research on Cancer has classified ingested arsenic as cause of lung, bladder, and skin cancer in humans (2, 3). Recent research suggests that the cancer and mortality risks from these exposures are very high (4). One study in Bangladesh reported that exposure to arsenic water concentrations >150 μg/L may cause a 68% increase in overall mortality (5). The World Health Organization and others are making major efforts to reduce arsenic exposures in developing countries and elsewhere. However, these may not be the only strategies needed to reduce arsenic-associated health risks. If the latency period (the period from exposure to the time of disease diagnosis) of arsenic-caused disease is long, efforts to reduce mortality and morbidity, including cancer screening, reducing important co-exposures, treatment and hospice resource planning, and public awareness, may be needed for many years after high exposures are stopped. Information on the rate at which cancer risks fall after exposures are stopped is only available for a few agents. For tobacco smoke, cancer risks begin to decline within a few years after smoking cessation and approach the risks in non-smokers within a few decades (6). However, arsenic may be different: some evidence from highly exposed regions in Taiwan and Chile have suggested that the latency of arsenic-caused cancers may be much longer than this (7, 8). To date, however, this evidence is based only on ecologic studies without individual information on exposure levels, migration, important confounders, or the exact timing when high exposures were stopped.

An unusual arsenic exposure scenario in northern Chile provides several key advantages for investigating the long-term risks of arsenic-caused cancer. In the late 1950s, river water from the nearby Andes Mountains containing high concentrations of naturally-occurring arsenic was diverted to the largest city in the area (Antofagasta) for drinking (9). This resulted in a 13-year period (1958–70) with an average arsenic concentration of 860 μg/L in the city's water supply. Installation of a treatment plant reduced these concentrations to <10 μg/L today (Figure 1). This exposure scenario, with its well-documented high exposure to a well-known and potent carcinogen, large numbers of people exposed, and a distinct end to the high exposure period, is unusual in environmental epidemiology and offers a rare opportunity to study the long-term latency patterns of a widespread carcinogen like arsenic.

Another unique feature of northern Chile is that it is the driest inhabited place on earth. Because there are so few water sources, almost everyone in this area lives in one of the cities or towns and drinks water from one of the few large public water supplies. In addition, historical records of arsenic concentrations are available for each of these large supplies, with many records dating back 40 years or more. This combination of factors means that a person's lifetime arsenic exposure in this area can be estimated with good accuracy simply by knowing the cities or towns in which that person has lived. In all other known highly exposed areas worldwide, many people obtain water from thousands of small domestic wells with highly variable arsenic concentrations and few historic records, and many people may use different water sources at home, school, and work (10). If the latency period between exposure and disease is several decades or more, subjects and each of their various water sources must be followed for many years, making it exceedingly difficult and costly to accurately assess people's true lifetime exposure. Northern Chile is different. Because of its small number of water sources, lack of alternative water supplies, and good historical records, retrospective estimates of lifetime exposure can be generated that are more accurate than those from all other large, highly exposed areas worldwide.

In this study, we use the unique features of northern Chile to examine the long-term latency patterns of arsenic-related lung and bladder cancer. Lung cancer appears to be the most common cause of arsenic-related death, and relative risks for bladder cancer are higher than those for all other internal arsenic-related cancers (11). Our goal is to provide accurate information on the long-term health burdens of arsenic exposure in order to inform both policy-makers and the public on the long-term risks and needs for medical interventions in arsenic-exposed areas.

Materials and Methods

Study area and participant selection

The study area comprises two contiguous regions (Regions I, II) in northern Chile with a total population of 922,579 (12). The major cities in these Regions, including Antofagasta, and the arsenic concentrations in their public water supplies are shown in Table 1. Cases included people who: 1. Had primary lung or bladder cancer first diagnosed between October 2007 and December 2010; 2. Lived in the study area at the time of diagnosis; 3. Were over age 25 years at the time of diagnosis; and 4. Were able to provide interview data or had a close relative who could. Cases were ascertained from all pathologists, hospitals, and radiologists in the study area. Relatively few long-term residents leave the study area for all of their medical care, since the nearest large medical facilities are in Santiago, 675 miles away. The large majority of cases were histologically confirmed (98% for bladder cancer and 72% for lung cancer), with the remaining diagnoses based on a combination of radiologic (computed tomography) and physician's clinical findings. Controls without lung or bladder cancer who otherwise met these same criteria were randomly selected from the Chilean Electoral Registry for the study area for the years 2007–2009, frequency matched to cases by gender and five-year age group. Enrollment in the Electoral Registry was mandatory during the 1970s and many people have remained on it since that time. Our analysis of the registries used for this study showed that they contained >95% of people over age 50 years when compared to the Chile national census.

The names of 370 lung and 289 bladder cancer cases were obtained from local pathologists, radiologists, or hospitals. Of these, 46 lung and 23 bladder cancer cases were ineligible based on age and residential criteria. Of the remaining, 4 lung (1.2%) and 12 (4.5%) bladder cancer cases (or their next of kin) could not be located, had moved outside the study area, or provided insufficient residential information. Of the remaining, 14 lung (4.4%) and 22 (8.7%) bladder cancer cases or their next of kin declined participation. The large majority of cases were interviewed within 4–5 months of diagnosis, and 39.6% and 17.7% of lung and bladder cancer cases had died prior to interview. Among 872 controls randomly selected from the Electoral Registry with viable addresses, 78 (8.9%) no longer lived at the address and could not be located, were ineligible due to illness, or gave insufficient information. Of the remaining 794 people, 154 (19.4%) declined to participate. Controls who did not participate were younger (63.7 vs. 66.0 years, respectively) and more likely to be male (72.5 vs. 67.3%) than those who did, but overall inclusion rates among controls were similar among major exposure areas: 75.5% in highly exposed Antofagasta, 71.3% in moderately exposed Iquique and Calama, and 74.5% in low exposure Arica.

Participant interviews

After obtaining informed consent, all participants were interviewed in person using a standardized questionnaire. For deceased subjects, we interviewed the nearest relative (proxy). The proportions of proxy interviews were 8.7% for controls, 20.3% for bladder cancer, and 46.4% for lung cancer. Participants were asked to provide all residences at which they (or the subject for proxy interviews) lived for six months or longer. They were

also asked to describe all jobs held for six months or longer and exposure to specific chemicals linked to lung or bladder cancer, including silica, asbestos, and arsenic. Particular attention was paid to mining work, since this is a common occupation in northern Chile. Questions regarding tobacco smoke covered age when smoking began, periods quit, total years smoked, number of cigarettes smoked per day, and childhood or adult secondhand smoke exposure. Subjects were also asked their typical amount of drinking water intake currently (or one year before cancer diagnosis) and 20 years ago, including tap water used for coffee, tea, and other beverages. When asked to recall past drinking water intake, subjects were reminded of where they lived and worked and other major events in their lives at the time. Previous research has shown that intake of dietary variables, including coffee and tea, can be accurately recalled from the distant past (13).

Exposure indices based on arsenic water concentration

Arsenic exposure was based on either arsenic water concentrations, or on estimated arsenic intakes. For analyses based on arsenic water concentrations, each city or town of residence in Chile in which each subject lived was linked to a water arsenic measurement for that city or town so that an arsenic concentration could be assigned to each year of each subject's life within Chile. The drinking water arsenic concentrations for each city or town in the study area were collected from government agencies, research studies, and the water suppliers themselves, and were available for >97% of all drinking water in the study area (14–20). Arsenic measurements were also available for all large cities and towns in Chile outside the study area, although almost all of these were <10 μg/L (11). Until recently, few people drank bottled water or used water filters. The yearly arsenic concentrations were then used to develop several different exposure indices for each subject, including the highest exposure for any one year, the highest exposure averaged over any contiguous 5-, 20-, or 40-year period, cumulative exposure (calculated by summing the yearly concentrations or intakes), and average lifetime exposure (cumulative exposure divided by the age at cancer diagnosis or study enrollment). Subjects were then categorized based on the quartiles of each index in all subjects.

Exposure indices based on estimated arsenic intake

For analyses of arsenic intakes, each subject's daily arsenic intake from water in μg/day was estimated by multiplying each subject's yearly arsenic concentration in μg/L (as calculated above) by their self-reported daily water intake (L/day) (either current or 20 years ago, whichever was closest to the year of residence). Proxy subjects were assigned the median drinking water intake volume from all non-proxy subjects. Daily arsenic intake estimates were then used to calculate each subject's average daily intake over their lifetime or for various periods (e.g., all intakes prior to 1971). Cumulative intake for each subject was calculated by multiplying the subject's average daily intakes for each year by 365 days/year and then summing the results across all years. To account for possible latency effects, arsenic exposures or intakes in the five years preceding cancer diagnosis (for cases) or ascertainment (for controls) were not included in exposure calculations. Using a 10- or 15-year period had little impact on results.

Statistical analysis

Odds ratios were calculated using unconditional logistic regression, separately for lung and bladder cancer but combining all controls. Because the latency of arsenic-related cancer appears to be at least several decades and because the very high exposures in Antofagasta ended in 1970, separate analyses were done using only those exposures before 1971. To investigate latency with even greater detail, further analyses were done comparing subjects who lived in Antofagasta during the high exposure period, but who did not live in a high

exposure city (e.g., Calama or San Pedro) afterwards, to subjects who never had water concentrations >10 μg/L.

Potential confounding variables entered into logistic regression models included sex, age (ten-year groups), smoking (highest average number of cigarettes smoked per day) (21), mining work, race, body-mass index (BMI), and tertiles of socioeconomic status (SES) scores. Following advice from experienced local researchers, SES scores were based on 12 items, including ownership of household appliances (e.g., refrigerator, microwave), car, computer, and use of domestic help. Analyses adjusting for exposure to childhood or adult secondhand smoke or occupational carcinogens (each entered as 'yes' or 'no' based on self-reported exposure) were restricted to non-proxy respondents. Analyses were conducted in SAS version 9.2 (SAS Institute Inc., Cary NC) and all p-values are two-sided. Analysis of trends in odds ratios across quartiles of arsenic exposure were assessed using the Cochrane-Armitage test for linear trend.

Results

Subjects' demographic characteristics are shown in Table 2. Although the distribution of gender, age, SES, and mining work were similar, bladder and lung cancer cases were more likely to be of European descent, ever-smokers, and exposed to higher arsenic concentrations in water than controls (also see Supplementary Table 1). Table 3 shows the bladder and lung cancer odds ratios by various metrics of arsenic exposure. In analyses of average arsenic water concentrations before the end of high exposure period in 1970, adjusted bladder cancer odds ratios from the lowest to highest quartile of exposure were 1.00, 1.36 (95% confidence interval (CI), 0.78–2.37), 3.87 (2.25–6.64), and 6.50 (3.69–11.43), respectively. Corresponding odds ratios for lung cancer were 1.00, 1.27 (0.81–1.98), 2.00 (1.24–3.24), and 4.32 (2.60–7.17). In general, odds ratios were higher when only exposures prior to 1971 were considered and when arsenic intakes, rather than just concentrations, were evaluated (Table 3). The p-trend values for all analyses in Table 3 were <0.001. In the analysis examining subjects who lived in Antofagasta during the high exposure period 1958–70 but were not highly exposed afterwards, the odds ratios were 6.88 (3.84–12.32) and 4.35 (2.57–7.36) for bladder and lung cancer, respectively.

Bladder cancer odds ratios comparing the upper and lower tertiles of average arsenic concentration prior to 1971 were higher in women (OR=23.67, CI=4.14–135.3) than in men (OR=5.35, CI 2.84–10.06) (Figure 2 and Supplementary Table 2). And, odds ratios changed only slightly when proxy respondents and non-histologically confirmed cases were excluded. Additional adjustments for exposure to secondhand smoke or other known lung carcinogens like asbestos or silica only had small effects on odds ratios (not shown in Tables).

Discussion

Overall, clear evidence of dose-response relationships were identified between increasing arsenic exposure and increasing odds ratios for lung and bladder cancer. These new findings are important for several reasons. First, this is the largest study to date with data on cancer incidence, rather than mortality, and individual rather than ecologic data on lifetime arsenic exposure and confounders. The relatively large number of cases and wide range of exposures provides dose-response estimates with good precision. Also, because the study area has a limited number of water supplies and detailed records of arsenic concentrations dating back many years, and because information was collected on major potential confounders, the relative risk estimates generated here are likely more accurate than those previously reported from other highly exposed areas worldwide.

This is the first study to provide clear evidence that substantially increased risks of arsenic-related cancer remain almost 40 years after cessation of high exposure. The lung and bladder cancer odds ratios in people from Antofagasta who were last highly exposed in 1970, an average of 38 years before their cancers were diagnosed, were about four to seven times higher than those in people with low exposure. Although many studies of carcinogens other than arsenic have examined latency patterns from the time exposures first began, few have examined patterns after exposure cessation. For tobacco smoking, most studies show that lung cancer relative risks fall below 2.0 within 10 to 30 years of smoking cessation (4). The only exposure for which high cancer risks are known to continue for decades after exposure cessation is asbestos-caused mesothelioma. In a case-control study involving 1041 cases, Lacourt *et al.* reported odds ratios of 6.4 (3.2–12.9) for mesothelioma 30 years after exposure cessation (22), but mesothelioma is a much rarer cancer than those we studied in Chile. Overall our findings are unprecedented given the large relative risk estimates, the long period of time after high exposures were stopped, and that they involved two very common cancers. The mechanism by which arsenic may increase long-term cancer risks is unknown, but arsenic has been linked to several epigenetic effects, such as global DNA and gene specific hypo- and hyper-methylation, and it is possible these effects are permanent and lead to long-term increased cancer risks (23).

The findings presented here have some direct public health relevance to exposed populations in India, Bangladesh, Taiwan, China, Chile, Europe, the U.S. and elsewhere. The extraordinarily long latency means that the incidence of arsenic-related cancer in these areas is likely to remain very high for many years after arsenic exposures have ended. This very long latency period not only highlights the importance of eliminating exposures as soon as possible, it also underscores the potentially important role public health interventions may have for many years after exposures have stopped. Possible long-term interventions include cancer screening, public awareness campaigns, or long-term treatment or hospice resource planning. For example, research has shown that agents like tobacco smoke, poor nutrition, and certain occupational exposures can markedly increase the risks of arsenic-related disease (17, 24, 25). Public awareness campaigns aimed at reducing these important co-exposures or improving nutrition might help reduce long-term arsenic-related morbidity and mortality. Also, routine screening with low-dose lung computed tomography has been shown to reduce mortality in heavy smokers (26), raising the possibility that similar screening might also be effective in people with high arsenic exposure. Overall, given the tens of millions of people exposed worldwide and the very high and persistent cancer risks seen here, reducing exposures as soon as possible, as well as early planning for long-term interventions, could have major impacts on the burdens of arsenic-related disease for many years to come.

Another important aspect of this study is that it helps confirm several key findings previously reported from northern Chile. This includes novel findings regarding arsenic-lung cancer dose-response relationships, synergy with smoking, and early life exposure effects (17, 27, 28). The fact that the bladder and lung cancer results of this study, with individual data on exposure and confounders, are similar to the results of this previous research supports the validity of these earlier findings.

Some exposure misclassification is likely in this study. But because arsenic exposure in this area can be determined primarily by the cities or towns in which the subjects lived, and errors in recalling this information is expected to be minimal, the impact of this bias is likely small. Proxy interviews were more common among cases than controls, and less accurate recall among proxies than living subjects could have produced some differential exposure misclassification. However, previous studies have shown that proxy respondents can provide reasonably accurate residential histories (29). In addition, odds ratios for both bladder and lung cancer were very similar, regardless of whether proxy subjects were included or

excluded, suggesting that the inclusion of proxy respondents caused little bias. Arsenic levels were not collected for residences outside Chile, but the large majority of subjects spent their whole lives in Chile and none lived in those other countries with known high exposure. Errors may also occur in assessing past drinking water intake. However, odds ratios were similar whether or not these data were used. Arsenic may also come from food, air, or work, but a previous analysis has shown that these exposures are relatively low (e.g., <2% of total arsenic intake) compared to arsenic intake from water during the high exposure period in Antofagasta (30). Also, adjustments for mining or self-reported arsenic exposure at work had little effect on results. Similarly, exposure misclassification could occur if drinking water exposures outside the residence were missed; however, this is not a major concern in northern Chile, since each city and town has essentially only one water supply and few people commuted elsewhere for work or school. Confounding from factors not adjusted for (e.g., diet, radon) is also possible, but there is no evidence that these were strongly enough related to both cancer and arsenic to cause the high odds ratios identified (31).

In conclusion, this study provides evidence of four-fold increases in lung cancer and almost seven-fold increases in bladder cancer 35–40 years after high arsenic exposures ended. These findings could help public health agencies in planning long-term strategies and obtaining the resources needed to reduce the long-term impacts of arsenic-related disease. Importantly, the fact that odds ratios are still fairly high suggests that it may be many more years before these increased risks fall to zero. Further research in Antofagasta, with its distinct period of high exposure many years in the past and good data on historical exposure, would help determine the number of years or decades these risks are likely to remain high.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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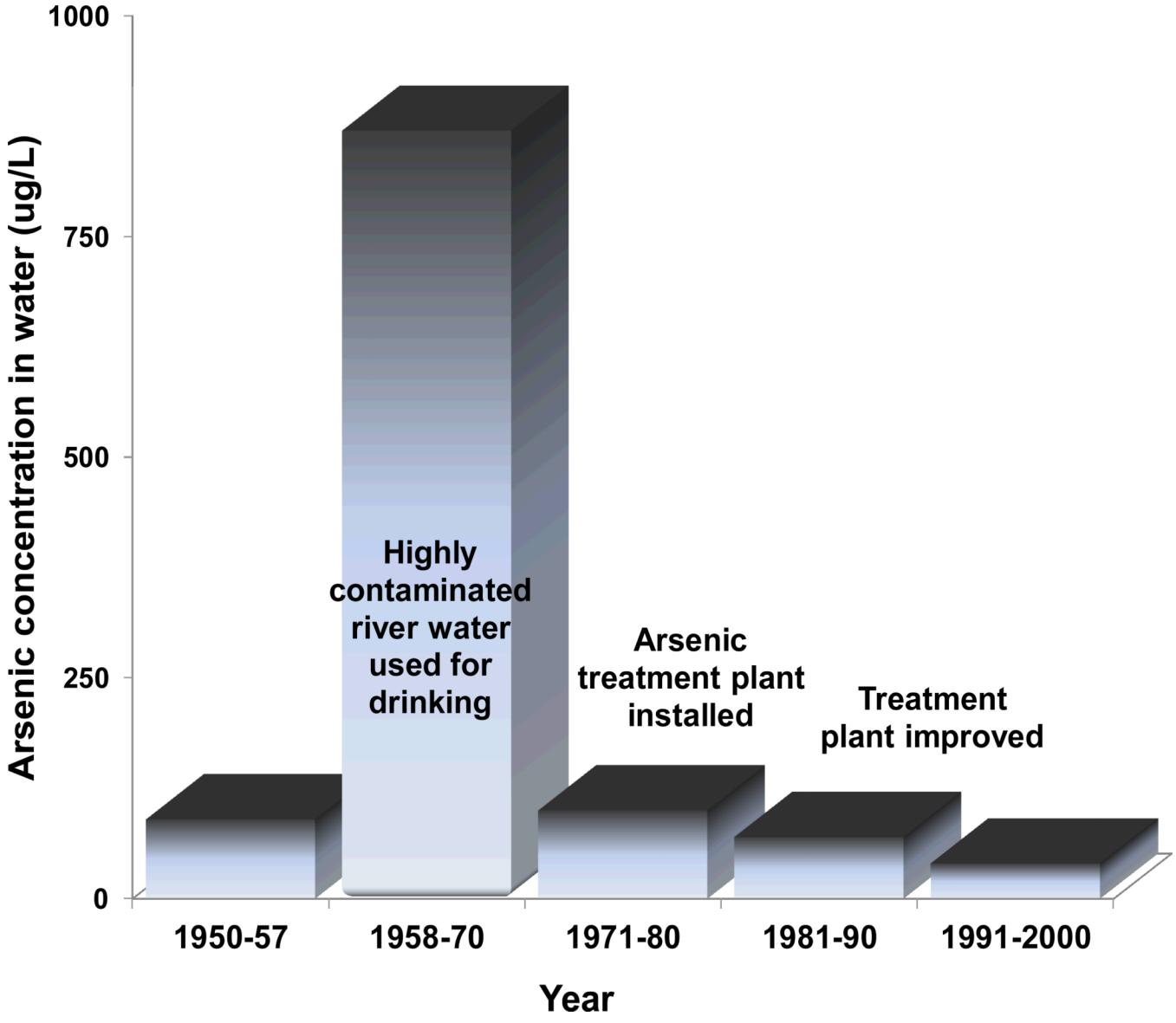

Figure 1.
Arsenic concentrations in the drinking water in Antofagasta, northern Chile

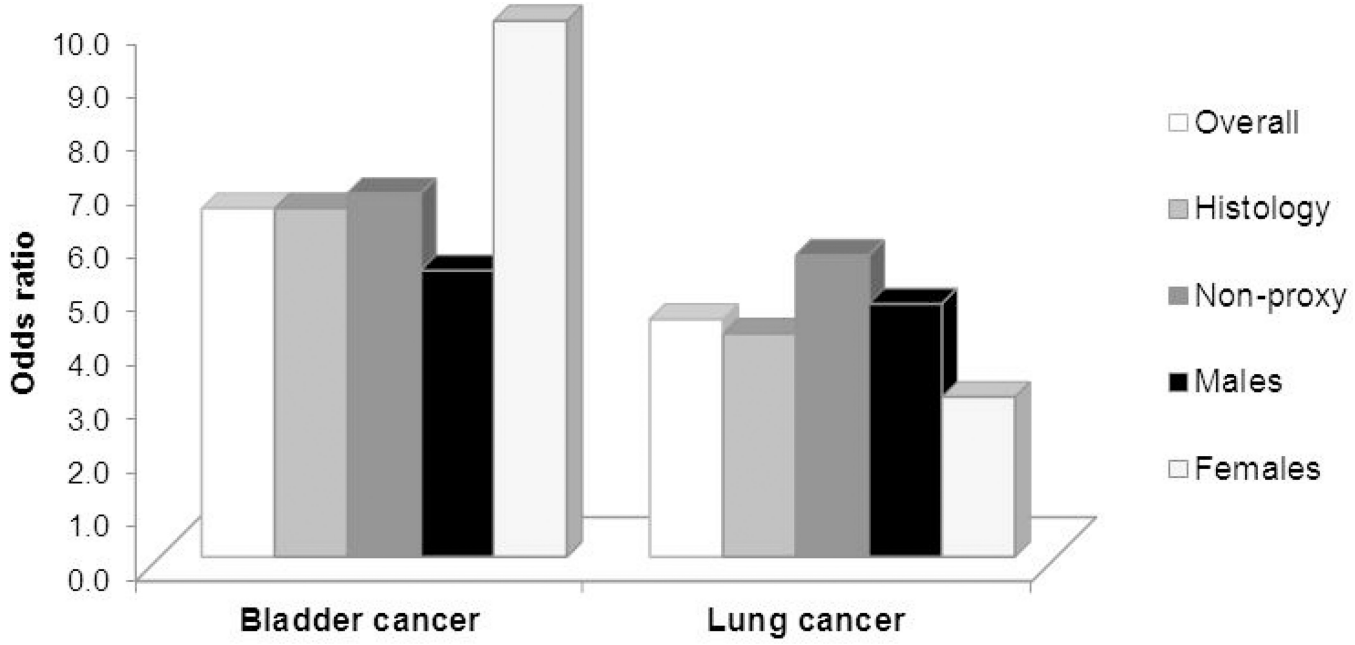

Figure 2.

Bladder and lung cancer odds ratios* including only cases with histologic confirmation, in non-proxy subjects, and in males and females comparing subjects in the upper to lower quartiles of average lifetime arsenic concentration prior to 1971.

*Odds ratios are adjusted for age, sex, smoking, mining work, race, body-mass index, and socioeconomic status. For display purposes, the bladder cancer odds ratio in females of 23.6 (95% CI, 4.14 to 135.3) is truncated.

Table 1

Historical arsenic concentrations in drinking water in the study area by year

			Average Arsenic Concentration (μg/L)						
			Years						
Region	**City or Town**	**Population***	**1930–57**	**1958–70**	**1971–77**	**1978–79**	**1980–87**	**1988–94**	**1995+**
I	Arica	168,594	10	10	10	10	10	10	9
	Putre	1,799	1	1	1	1	1	1	1
	Iquique	196,941	60	60	60	60	60	60	10
	Huara	2,365	30	30	30	30	30	30	30
	Pica	5,622	10	10	10	10	10	10	10
	Pozo Almonte	9,855	40	40	40	40	40	40	40
II	Tocopilla	21,827	250	250	636	110	110	40	10
	Maria Elena	6,852	250	250	636	110	110	39	39
	Calama	125,946	150	150	287	110	110	40	38
	San Pedro	4,522	600	600	600	600	600	600	600
	Antofagasta	270,184	90	860	110	110	70	40	10
	Mejillones	7,660	90	860	110	110	70	37	10
	Taltal	10,101	60	60	60	60	60	60	60
	Recent migrants	82,312	<10	<10	<10	<10	<10	<10	<10

*Population data are based on the most recent Chile census (10)

Table 2

Demographic characteristics of controls and bladder and lung cancer cases

	Controls		Bladder cancer				Lung cancer			
	N	(%)	N	(%)	OR*	(95% CI)	N	(%)	OR*	(95% CI)
Total	640	(100)	232	(100)			306	(100)		
Sex										
Female	209	(32.7)	62	(26.7)			91	(29.7)		
Male	431	(67.3)	170	(73.3)			215	(70.3)		
Age (years)										
70+	269	(42.0)	94	(40.5)			112	(36.6)		
60–69	193	(30.2)	76	(32.8)			111	(36.3)		
50–59	132	(20.6)	39	(16.8)			69	(22.5)		
40–49	39	(6.1)	23	(9.9)			10	(3.3)		
30–39	7	(1.1)	0	(0)			4	(1.3)		
Race										
Other	195	(30.5)	35	(15.1)	1.00		70	(22.9)	1.00	
European	445	(69.5)	197	(84.9)	2.47	(1.67 to 3.64)	236	(77.1)	1.48	(1.08 to 2.02)
Mining work										
No	498	(77.8)	173	(74.6)	1.00		241	(78.8)	1.00	
Yes	142	(22.2)	59	(25.4)	1.20	(0.84 to 1.70)	65	(21.2)	0.95	(0.68 to 1.32)
Body-mass index >30 kg/m^2										
No	518	(80.9)	191	(82.3)	1.00		269	(87.9)	1.00	
Yes	122	(19.1)	41	(17.7)	0.91	(0.62 to 1.35)	37	(12.1)	0.58	(0.39 to 0.87)
Smoking										
Never	242	(37.8)	65	(28.0)	1.00		59	(19.3)	1.00	
Ever	398	(62.2)	167	(72.0)	1.56	(1.13 to 2.17)	247	(80.7)	2.55	(1.85 to 3.51)
Socioeconomic status (tertiles)										
Low	231	(36.1)	73	(31.5)	1.00		126	(41.2)	1.00	
Medium	203	(31.7)	66	(28.4)	1.03	(0.70 to 1.51)	103	(33.7)	0.93	(0.67 to 1.28)
High	206	(32.2)	93	(40.1)	1.43	(1.00 to 2.04)	77	(25.2)	0.69	(0.49 to 0.96)
Water arsenic (μg/L) (highest one year)†										

	Controls		Bladder cancer				Lung cancer			
	N	(%)	N	(%)	OR*	(95% CI)	N	(%)	OR*	(95% CI)
0–59	138	(21.6)	23	(9.9)	1.00		48	(15.7)	1.00	
60–199	193	(30.2)	27	(11.6)	0.84	(0.46 to 1.52)	52	(17.0)	0.77	(0.49 to 1.21)
200–799	144	(22.5)	60	(25.9)	2.50	(1.48 to 4.22)	69	(22.6)	1.38	(0.89 to 2.13)
≥ 800	165	(25.8)	122	(52.6)	4.44	(2.75 to 7.15)	137	(44.8)	2.39	(1.61 to 3.54)
Drinking water intake (L/day)‡										
Current	1.66	(±0.91)	2.04	(±1.14)	p<0.001		1.84 ±1.02		p=0.04	
20 years ago	1.80	(±1.14)	1.97	(±1.22)	p=0.03		1.94 ±1.05		p=0.02	

*Unadjusted odds ratios (OR) comparing bladder or lung cancer cases to controls. Odds ratios are not reported for age and sex since subjects were frequency matched on these factors.

†These category cut-off points were chosen so each category includes the highest arsenic water concentration of each of the four largest cities in the study area: Arica (0–59 μg/L), Iquique 60–199 μg/L), Calama (200–799 μg/L), and Antofagasta ≥ 800 μg/L.

‡Means, standard deviations, and p-values comparing bladder or lung cancer cases to controls.

Table 3

Bladder and lung cancer odds ratios (OR) in relation to various metrics of arsenic exposure

Arsenic metric	Arsenic level[†]	Subjects			Bladder cancer		Lung cancer	
		Control	Bladder	Lung	OR[*]	(95% CI)	OR[*]	(95% CI)
Arsenic water concentrations								
Lifetime average: all years (μg/L)	<26	202	33	61	1.00		1.00	
	26–79	189	33	61	0.92	(0.52 to 1.61)	0.98	(0.62 to 1.53)
	80–197	142	71	85	2.62	(1.53 to 4.50)	1.70	(1.05 to 2.75)
	>197	107	95	99	6.00	(3.38 to 10.64)	3.18	(1.90 to 5.30)
Lifetime average: before 1971 (μg/L)	<11	199	28	51	1.00		1.00	
	11–90	192	37	66	1.36	(0.78 to 2.37)	1.27	(0.81 to 1.98)
	91–335	138	78	80	3.87	(2.25 to 6.64)	2.00	(1.24 to 3.24)
	>335	107	89	105	6.50	(3.69 to 11.43)	4.32	(2.60 to 7.17)
Cumulative: all years (μg/L-years)	<1,578	198	34	60	1.00		1.00	
	1,578–4,876	192	33	61	0.86	(0.49 to 1.52)	0.95	(0.61 to 1.50)
	4,877–12,841	132	78	89	2.97	(1.76 to 5.02)	1.89	(1.19 to 3.02)
	>12,841	118	87	96	5.27	(2.86 to 9.70)	2.90	(1.69 to 4.97)
Cumulative: before 1971 (μg/L-years)	<372	204	34	51	1.00		1.00	
	372–2,464	190	32	64	1.03	(0.59 to 1.80)	1.29	(0.82 to 2.02)
	2,465–10,319	131	78	87	3.40	(2.05 to 5.65)	2.40	(1.51 to 3.81)
	>10,319	111	88	100	6.33	(3.54 to 11.32)	4.82	(2.79 to 8.34)
Arsenic intake[‡]								
Lifetime daily average: all years (μg/day)	<41	197	32	64	1.00		1.00	
	41–136	194	39	56	1.08	(0.62 to 1.87)	0.87	(0.55 to 1.36)
	137–307	154	64	76	3.06	(1.75 to 5.35)	1.24	(0.78 to 1.98)
	>307	95	97	110	5.85	(3.41 to 10.05)	3.16	(1.98 to 5.03)
Lifetime daily average: before 1971 (μg/day)	<21	199	31	53	1.00		1.00	
	21–159	193	35	64	1.21	(0.69 to 2.11)	1.19	(0.76 to 1.85)
	160–525	154	70	73	3.15	(1.84 to 5.38)	1.63	(1.01 to 2.65)
	>525	90	96	112	6.76	(3.97 to 11.51)	4.89	(2.99 to 7.99)
Cumulative: all years (μg)	<2,438	195	31	64	1.00		1.00	

Arsenic metric	Arsenic level†	Subjects			Bladder cancer		Lung cancer	
		Control	Bladder	Lung	OR*	(95% CI)	OR*	(95% CI)
	2,438–8,214	194	42	58	1.14	(0.65 to 1.99)	0.84	(0.54 to 1.32)
	8,215–19,093	158	58	77	2.58	(1.46 to 4.56)	1.29	(0.81 to 2.06)
	>19,093	93	101	107	7.90	(4.45 to 14.01)	3.25	(2.00 to 5.29)
Cumulative: before 1971 (μg)	<576	205	35	53	1.00		1.00	
	576–4,429	187	34	63	1.11	(0.64 to 1.94)	1.21	(0.77 to 1.89)
	4,430–14,347	145	71	78	2.99	(1.80 to 4.97)	1.92	(1.22 to 3.03)
	>14,347	99	92	108	6.82	(3.92 to 11.87)	4.86	(2.92 to 8.09)
Other								
Antofagasta 1958–1970	No	199	28	51	1.00		1.00	
	Yes	102	84	99	6.88	(3.84 to 12.32)	4.35	(2.57 to 7.36)

*Odds ratios (OR) are adjusted for age, sex, smoking, mining work, race, body-mass index, and socioeconomic status. The p-values for linear trends in odds ratios across exposure categories are < 0.001 for all analyses in this Table.

†Exposure categories are based on quartiles in all subjects.

‡Includes data on arsenic concentrations in water and drinking water intake.