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Original Contribution

Elevated Lung Cancer in Younger Adults and Low Concentrations of Arsenic in Water

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Arsenic concentrations greater than 100 μg/L in drinking water are a known cause of cancer, but the risks associated with lower concentrations are less well understood. The unusual geology and good information on past exposure found in northern Chile are key advantages for investigating the potential long-term effects of arsenic. We performed a case-control study of lung cancer from 2007 to 2010 in areas of northern Chile that had a wide range of arsenic concentrations in drinking water. Previously, we reported evidence of elevated cancer risks at arsenic concentrations greater than 100 μg/L. In the present study, we restricted analyses to the 92 cases and 288 population-based controls who were exposed to concentrations less than 100 μg/L. After adjustment for age, sex, and smoking behavior, these exposures from 40 or more years ago resulted in odds ratios for lung cancer of 1.00, 1.43 (90% confidence interval: 0.82, 2.52), and 2.01 (90% confidence interval: 1.14, 3.52) for increasing tertiles of arsenic exposure, respectively (*P* for trend = 0.02). Mean arsenic water concentrations in these tertiles were 6.5, 23.0, and 58.6 μg/L. For subjects younger than 65 years of age, the corresponding odds ratios were 1.00, 1.62 (90% confidence interval: 0.67, 3.90), and 3.41 (90% confidence interval: 1.51, 7.70). Adjustments for occupation, fruit and vegetable intake, and socioeconomic status had little impact on the results. These findings provide new evidence that arsenic water concentrations less than 100 μg/L are associated with higher risks of lung cancer.

arsenic; case-control; drinking water; low exposure; lung cancer; northern Chile

Abbreviation: CI, confidence interval.

High concentrations of arsenic in drinking water (e.g., >100 μg/L) are known to cause cancer, but the risks associated with exposure to lower concentrations are unclear (1–3). One difficulty in studying low-level exposures is the prolonged latency of arsenic-caused cancer (2, 4–6). This long latency period means that exposure data must be available for a period of several decades or more in order to identify true overall risks. Another difficulty is that exposure in most arsenic-exposed areas comes from thousands of small private wells, for which historic records are frequently unavailable (7).

Northern Chile is the driest habitable place on earth. There are few water sources, and almost everyone lives in a city and drinks water from municipal supplies. These supplies have had a wide range of arsenic concentrations, and historical records are available from 40 years ago or more (8). These factors mean that a person's lifetime exposure can be reliably estimated simply by knowing the cities in which the person lived.

In 2007–2010, we performed a case-control study in northern Chile and identified high odds ratios for lung, bladder, and kidney cancers (6, 9). These results focused on cities in which arsenic concentrations in drinking water were greater than 800 μg/L. They also involved lifetime average and cumulative exposure metrics, in which short periods of higher exposures can be diluted by longer periods of lower exposure. In the present study, we focused on long-term lower exposures and investigated lung cancer, the most common arsenic-related cause of death (10).

METHODS

The study area comprised 2 neighboring regions (regions I and II), although most arsenic water concentrations less than 100 μg/L occurred in region I. The 2 largest population centers in region I are Arica and Iquique, which have long-term stable arsenic concentrations in the drinking water of 10 μg/L and 60 μg/L, respectively (Web Figure 1, available at http://aje.oxfordjournals.org/) (8). Water supplies in other towns had arsenic concentrations between 1 μg/L and 100 μg/L. Approximately 25% of subjects were born outside of regions I or II in areas with arsenic water concentrations of 6 μg/L or less and moved to those regions after birth.

Participants were a subset of subjects from the larger case-control study (6). Cancer cases were ascertained on a monthly basis from all pathologists, hospitals, and radiologists in the area and included people who: 1) had primary lung cancer diagnosed in 2007–2010; 2) lived in the study area when diagnosed; 3) were older than 25 years of age when diagnosed; and 4) were able to provide interview data or had a close relative who could. Seventy-two percent of cases were histologically confirmed, with the remaining diagnosed radiologically and clinically. Recurrences were detected through medical record review and interviews. Hospital cancer committees and death certificates were used to help confirm ascertainment and diagnosis. Controls without lung, bladder, or kidney cancer were randomly selected from the Chilean Electoral Registry and were frequency-matched by sex and 5-year age group. This registry contained more than 95% of people older than 40 years of age who were recorded in the national census. Further details on study methods have been published elsewhere (6, 9, 11). Analyses here were restricted to subjects from the original study who never had a known arsenic water concentration of 100 μg/L or higher. Ethics approval was obtained in the United States and Chile, and all subjects provided informed consent.

Participants were interviewed in person using a standardized questionnaire that asked about all residences at which they had lived (including place of birth) and all jobs held for 6 months or longer; smoking behaviors; intake of drinking water both currently and 20 years ago; diet; and occupational exposures. For deceased subjects, we interviewed the next of kin, who were not asked about intake of drinking water or diet.

For each subject, each residence was linked to a measured concentration of arsenic in water for that city so that an arsenic concentration could be assigned to each year of each subject's life. Measurements were obtained from municipal water companies (who supply essentially all water in the area), government agencies, and research studies (8, 12–18). Measurements were also available for all large cities in Chile outside the study area, and these were also used. Measurements were available for 90% of residences (84% of person-years). Residences without records were in areas not known to have high arsenic levels, and thus they were assigned a value of 0. Assigning a value of 3 had little impact. Bottled water and filters were rarely used until recently. Yearly arsenic concentrations in water were multiplied by daily estimates of water intake (L/day) (either the current intake or that from 20 years ago, whichever was closest in time), so that a daily intake from drinking water could be estimated for each year (5). Cumulative (μg/L-years) and average concentrations or intakes were calculated as the sum or mean of the subject's yearly values, respectively.

Odds ratios were calculated using unconditional logistic regression. Model variables included sex, age (10-year categories), and smoking (average number of cigarettes/day) (19). Using smoking measured as pack-years in calculations caused little change. Additional models included mining work, body mass index (weight (kg)/height (m^2)), fruit and vegetable intake (daily servings 20 years ago), occupational lung carcinogen exposure (yes or no), race, and socioeconomic status scores (6).

Odds ratios were calculated for tertiles of highest, average, and cumulative exposures. Nonproxy subjects were categorized based on their estimated arsenic intakes. Because data on water intake were not collected from proxy interviewees, proxy subjects were categorized based on their arsenic water concentrations. Using this method, each subject was categorized based on his or her best available data. Models in which arsenic concentration was entered as a continuous variable were also performed. We performed analyses stratified by age and migration status, as well as by whether exposures 5, 20, or 40 years before diagnosis or interview were excluded ("lagged"). Dose-response trends were assessed using the Cochrane-Armitage test, and analyses were done using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Because we had a clear a priori hypothesis that exposure to high levels of arsenic would increase the risk of lung cancer, 90% confidence intervals are reported.

RESULTS

Of the 378 lung cancer cases that were initially ascertained, 68 did not participate because of age and residential eligibility criteria, because they could not be located, or because they declined to participate. Of the 872 initially selected controls with viable addresses, 232 did not participate because they could not be located, were ill, gave insufficient information, or declined to participate. Of the remaining subjects, 92 cases and 288 controls had no known exposure greater than 100 μg/L. Of these, 50 cases (54.3%) and 19 controls (6.6%) had proxy interviews.

Compared with controls, cases were more likely to be heavy smokers (odds ratio = 8.50; 95% confidence interval (CI): 3.78, 19.1), had lower socioeconomic status scores (7.61 vs. 8.64; $P = 0.006$), and had somewhat higher arsenic concentrations in drinking water more than 40 years ago (33.83 μg/L vs. 28.61 μg/L; $P = 0.12$) (Table 1). Proxy cases were similar to nonproxy cases for most characteristics but tended to be heavy smokers (odds ratio = 3.20, 95% CI: 0.91, 11.27) and were older (69.7 vs. 64.8 years, $P = 0.04$) (Web Table 1).

Odds ratios for the arsenic–lung cancer association were all near 1.0 in analyses lagged 5 years (Web Table 2). Adjusted odds ratios by tertile of the highest known exposure 40 or more years ago were 1.00, 1.43 (90% CI: 0.82, 2.52), and 2.01 (90% CI: 1.14, 3.52), respectively, for the lowest to highest tertile (Table 2) (1-sided P for trend = 0.02; mean arsenic water concentrations = 6.5, 23.0, and 58.6 μg/L, respectively).

Table 1. Sociodemographic and Arsenic-Exposure Characteristics in Lung Cancer Cases and Controls, Northern Chile, 2007–2010

Characteristic	Cases			Controls			OR	95% CI	*P* Value[a]
	No.	%	Mean (SD)	No.	%	Mean (SD)			
Sex									
Male	62	67.4		195	67.7		1.00	Referent	
Female	30	32.6		93	32.3		1.01	0.61, 1.67	
Smoking status									
Never smoker	22	23.9		119	41.3		1.00	Referent	
Ever smoker	70	76.1		169	58.7		2.24	1.31, 3.82	
Smoked >10 cigarettes/day[b]	22	23.9		14	4.9		8.50	3.78, 19.1	
Race									
European descent	47	51.1		136	47.2		1.00	Referent	
Other descent	45	48.9		152	52.8		0.86	0.54, 1.37	
Age, years			67.43 (10.99)			66.18 (11.07)			0.41
Socioeconomic status score			7.61 (3.01)			8.64 (2.84)			0.006
Fruit and vegetable intake[c,d]			1.85 (1.11)			1.96 (1.52)			0.83
No. of residences			3.60 (1.99)			3.68 (2.08)			0.86
Drinking water intake, L/day[d]									
Current			1.60 (1.36)			1.66 (1.02)			0.39
20 Years ago			2.07 (1.38)			1.95 (1.33)			0.09
Arsenic intake, μg/day[d]									
Highest–lagged 5 years			92.60 (100.5)			84.89 (81.64)			0.78
Highest–lagged 40 years			63.01 (83.48)			50.82 (71.26)			0.04
Arsenic concentration in water, μg/L									
Highest–lagged 5 years			41.61 (25.25)			41.53 (24.26)			0.82
Highest–lagged 40 years			33.83 (27.82)			28.61 (26.35)			0.12

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.
[a] Two-sided *P* values.
[b] Odds ratio for smoking an average of more than 10 cigarettes per day compared with never smokers.
[c] Self-reported typical number of servings of fruit or vegetables per day 20 years ago.
[d] Only includes data from nonproxy subjects.

Corresponding odds ratios were similar after removing recent migrants: 1.00, 1.57 (90% CI: 0.87, 2.82), and 2.27 (90% CI: 1.27, 4.08), respectively. After excluding proxy subjects, odds ratios were similar but with wider confidence intervals, with odds ratios of 1.00, 1.52 (90% CI: 0.74, 3.12), and 1.90 (90% CI: 0.90, 4.03) (Web Table 3). The odds ratios by tertile of the highest known arsenic water concentration 40 or more years ago were 1.00, 1.27 (90% CI: 0.69, 2.34), and 1.62 (90% CI: 0.93, 2.85) (1-sided *P* for trend = 0.08) (Web Table 4). The odds ratio comparing the upper tertile to the lower tertile of highest known exposure lagged 20 years was 1.58 (90% CI: 0.88, 2.83; *P* for trend = 0.09), but other odds ratios in analyses using 20-year lags were closer to 1.0.

Mean age increased by increasing arsenic exposure tertiles, with values of 61.8, 68.4, and 68.9 years, respectively (Web Table 5). In subjects younger than 65 years of age, odds ratios by increasing tertiles of exposure 40 or more years ago were 1.00, 1.62 (90% CI: 0.67, 3.90), and 3.41 (90% CI: 1.51, 7.70) (1-sided *P* for trend = 0.01) (Table 2). Corresponding odds ratios for subjects 65 years of age or older were near 1.0 (Web Table 6). Odds ratios for each 10-μg/L increase in highest exposure 40 or more years ago were 1.08 (90% CI: 1.00, 1.17) in all subjects and 1.15 (90% CI: 1.02, 1.31) in those younger than 65 years of age. Major differences were not seen by sex or smoking behavior or after adjustments for occupation, socioeconomic status, and fruit and vegetable intake (Web Figure 2).

DISCUSSION

These findings provide evidence that exposure to arsenic concentrations less than 100 μg/L in drinking water increase the risk of lung cancer. The facts that ingested arsenic is an established carcinogen at higher exposures (1), accumulates in the lungs (20, 21), and has been linked to noncancer lung disease (22–25) all support the biologic plausibility of these findings. This is one of the few low exposure–cancer

Table 2. Odds Ratios for Lung Cancer by Tertile of Arsenic Intake 40 or More Years Ago in Nonproxy Subjects and Tertile of Arsenic Concentrations in Water 40 or More Years Ago in Proxy Subjects, Northern Chile 2007–2010

Tertile of Intake (μg/day) in Nonproxy Subjects, by Metric	Arsenic Concentration in Water for Proxys, μg/L	No. of Cases	No. of Controls	Unadjusted		Adjusted[a]	
				OR	90% CI	OR	90% CI
All Subjects							
Highest single year							
<14.5	<10.0	23	103	1.00	Referent	1.00	Referent
14.5–63.6	10.0–59.9	32	98	1.46	0.88, 2.43	1.43	0.82, 2.52
>63.6	>59.9	37	87	1.90	1.16, 3.13	2.01	1.14, 3.52
P for trend[b]					0.02		0.02
Highest 5-year average[c]							
<13.2	<10.0	25	102	1.00	Referent	1.00	Referent
13.2–55.8	10.0–54.0	31	99	1.28	0.78, 2.10	1.27	0.73, 2.20
>55.8	>54.0	36	87	1.69	1.03, 2.76	1.78	1.02, 3.11
P for trend[b]					0.04		0.04
Lifetime average							
<9.0	<6.0	27	103	1.00	Referent	1.00	Referent
9.0–37.2	6.0–22.1	29	95	1.16	0.71, 1.92	1.14	0.67, 1.95
>37.2	>22.1	36	90	1.53	0.94, 2.47	1.56	0.91, 2.67
P for trend[b]					0.07		0.09
Subjects <65 Years of Age							
Highest single year							
<14.5	<10.0	11	66	1.00	Referent	1.00	Referent
14.5–63.6	10–59.9	10	33	1.82	0.82, 4.05	1.62	0.67, 3.90
>63.6	>59.9	17	28	3.64	1.74, 7.61	3.41	1.51, 7.70
P for trend[b]					<0.01		0.01

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, sex, and smoking behavior.
[b] One-sided *P* values.
[c] Highest contiguous 5 years of arsenic exposure.

studies with individual data on past arsenic exposure. Most previous studies have not reported clear associations, although several issues likely limited their ability to identify potential effects (Web Table 7). Two US studies have reported associations but were based on a single short-term exposure metric (i.e., urine or toenail arsenic levels) (26, 27). A separate Chilean study is the only other low exposure–lung cancer study that assessed lifetime exposure (12). That study involved a slightly different study area (regions I, II, and III), different control selection, and different recruitment dates (1994–1996). However, adjusted odds ratios for average arsenic concentrations of 10–29, 30–59, 60–89, and 90–199 μg/L were 0.3 (95% CI: 0.1, 1.2), 1.8 (95% CI: 0.5, 6.9), 4.1 (95% CI: 1.8, 9.6), and 2.7 (95% CI: 1.0, 7.1), respectively, which are fairly similar to those reported here.

Exposure misclassification in the present study could have resulted from missing exposure data, inaccurate recall, lack of intake information from proxy subjects, or exposure to arsenic from nonwater sources. Because exposure was assessed similarly in all subjects, most of this was likely nondifferential and biased the odds ratios towards the null. Also, because exposure data were based mostly on residences and errors in recalling this information are likely minimal, the impact of recall errors is probably small. Errors in recall of water intake could occur, although research has shown that past diet can be fairly accurately recalled (28). Adjustments for occupational arsenic exposure had little impact on results, and arsenic air concentrations are similar in Arica and Iquique (29). Most food in this area comes from outside the region, and arsenic levels in dry foods in Arica and Iquique are similar. Nondifferential misclassification due to arsenic inherent in food would likely bias odds ratios towards 1.0 (17, 29). Some exposure may occur from drinking water used for cooking, but this does not affect our conclusions because this still involves arsenic concentrations in drinking water that are less than 100 μg/L.

Research has shown that proxy respondents can provide reasonably accurate residential and smoking histories (30). The facts that proxy and nonproxy cases were similar (Web Table 1) and that odds ratios were similar when proxy subjects were excluded (Web Table 3) provide evidence that use of proxy subjects caused little bias. We did not record data on cancer histology, and including unrelated histologic types may have biased odds ratios to the null (31).

The highest odds ratios we identified were for exposures 40 or more years ago in subjects who were younger than 65 years of age. This highlights the importance of including past exposures when examining arsenic-cancer relationships. This may also be an indication that early-life exposures are particularly important. In earlier analyses, we used a distinct period of very high exposure (>860 g/L) in region II to examine this issue, and we found that relative risks of lung cancer were very high in people who were only exposed in utero or during childhood (13, 32, 33). Because the lower exposures evaluated in the present study have been ongoing, the effects of latency and age at exposure cannot be separated from our results, and a similar analysis cannot be done here. Regardless, these previous findings are consistent with the results presented here, which could indicate a particular susceptibility caused by exposure in early life (34).

In conclusion, we found associations between lung cancer and relatively low arsenic exposures, with greater odds ratios in younger adults and persons with early-life exposure. We were not able to examine risks for exposure to concentrations below 10 μg/L, which is the current US standard. However, because the relative risks are likely to be low (e.g., <1.5), investigating arsenic-cancer relationships at exposures much below 10 μg/L would require incredibly large sample sizes and highly detailed information on confounding (35, 36). These issues highlight the importance of investigating moderate exposures (e.g., >10 μg/L) and the likely need for extrapolations when setting standards for arsenic concentrations in drinking water.

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