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Brief Original Contribution

Case-Control Study of Arsenic in Drinking Water and Kidney Cancer in Uniquely Exposed Northern Chile

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Millions of people worldwide are exposed to arsenic in drinking water. The International Agency for Research on Cancer has concluded that ingested arsenic causes lung, bladder, and skin cancer. However, a similar conclusion was not made for kidney cancer because of a lack of research with individual data on exposure and dose-response. With its unusual geology, high exposures, and good information on past arsenic water concentrations, northern Chile is one of the best places in the world to investigate the carcinogenicity of arsenic. We performed a case-control study in 2007–2010 of 122 kidney cancer cases and 640 population-based controls with individual data on exposure and potential confounders. Cases included 76 renal cell, 24 transitional cell renal pelvis and ureter, and 22 other kidney cancers. For renal pelvis and ureter cancers, the adjusted odds ratios by average arsenic intakes of <400, 400–1,000, and >1,000 μg/day (median water concentrations of 60, 300, and 860 μg/L) were 1.00, 5.71 (95% confidence interval: 1.65, 19.82), and 11.09 (95% confidence interval: 3.60, 34.16) (P_{trend} < 0.001), respectively. Odds ratios were not elevated for renal cell cancer. With these new findings, including evidence of dose-response, we believe there is now sufficient evidence in humans that drinking-water arsenic causes renal pelvis and ureter cancer.

arsenic; case-control; Chile; drinking water; kidney cancer

Abbreviations: CI: confidence interval; RCC, renal cell cancer; TCC, transitional cell carcinoma.

Millions of people worldwide are exposed to arsenic in drinking water, including an estimated 15 million in China, 30 million in India, 30 million in the United States, and 50 million in Bangladesh (1). These exposures have been linked to cardiovascular disease, lung and kidney diseases, reproductive effects, and cancer (2). Although the International Agency for Research on Cancer has concluded that there is sufficient evidence that ingested arsenic causes lung, bladder, and skin cancer, a similar determination has not been made for kidney cancer since "no studies have reported dose-response relationships on the basis of individual exposure data" (3, p. 226). Kidney cancer is the eighth most common cancer in the United States (4), and known risk factors include smoking, obesity, hypertension, and chronic renal disease. Associations with cadmium, trichloroethylene, asbestos, and certain occupations have also been reported (5). We investigated associations between kidney cancer and drinking water arsenic, using detailed individual data on exposure and potential confounders. Finding new associations like this may help raise awareness that millions of people worldwide continue to be exposed and that major efforts are needed to help reduce these exposures.

Two factors make northern Chile one of the best places worldwide to investigate arsenic. First, this is the driest habitable place on earth, so almost all drinking water is obtained from a small number of public water systems. Second, records of arsenic concentrations are available for all these systems, with many dating back >40 years. Because of these

factors, a person's lifetime arsenic exposure can be estimated with good accuracy simply by knowing the cities in which he/she lived. In other highly exposed areas, people obtain water from thousands of small domestic wells with highly variable arsenic concentrations and few historical records, making accurate assessments of past exposure exceedingly difficult. Assessing past exposure is important, since the latency of arsenic-caused cancer is thought to be several decades or more.

MATERIALS AND METHODS

The study area included Regions I and II in northern Chile. In 1958, river water from the Andes mountains containing high arsenic concentrations was diverted to the largest city in the area (Antofagasta) for drinking, causing a 13-year period (1958–1970) with an average arsenic concentration of 860 μg/L. Installation of a treatment plant reduced these concentrations to <10 μg/L today (6). Other cities in these regions have lower arsenic concentrations and offer a good contrast in exposure (Table 1).

Cases were ascertained from all pathologists and radiologists in the study area and included people who 1) had primary kidney or ureter cancer (*International Classification of Diseases, Tenth Revision,* codes C64–C66) diagnosed between October 2007 and December 2010; 2) lived in the study area when diagnosed; 3) were >25 years of age when diagnosed; and 4) could provide interview data or had a relative who could. Most cases (89%) were histologically confirmed, with the remaining diagnosed by computed tomography and clinical findings. Case lists from hospital cancer committees and all death certificates from the study area were used to confirm thorough ascertainment. Bladder and lung cancer cases were also recruited, although only kidney cancer results are reported here. For deceased subjects, the nearest relative (proxy) was interviewed (9.6% of controls and 18.0% of cases). Few people leave the study area for medical care because the other nearest large medical facilities are in Santiago, 675 miles (1,086.31 km) away. Controls without cancer were randomly selected from the Chile Electoral Registry for the study area, frequency matched by gender and 5-year age group (7). The Electoral Registry contains most people ≥18 years of age, including >95% of people over age 50 compared with the national census. Controls matched to all cases (kidney, bladder, and lung) were used here. Ethics approval was obtained from the University of California and Pontificia Universidad Católica de Chile.

After informed consent was obtained, participants were interviewed by using a standardized questionnaire. Participants were asked to provide all residences lived in ≥6 months, all jobs held ≥6 months, and exposure to agents linked to kidney cancer including trichloroethylene and cadmium. Questions regarding tobacco covered the age smoking began, periods quit, total years smoked, and packs smoked per week. Subjects were also asked their typical drinking water intake currently and 20 years ago, including tap water used for coffee and tea. Research has shown that dietary intake can be accurately recalled from the distant past (8). Questions regarding body mass index included height and typical weight currently and 20 and 40 years ago. Subjects were also asked about all medical conditions and medications.

Lifetime arsenic intake was assessed as follows: For each subject, each city or town of residence was linked to a water arsenic measurement so that an arsenic concentration could be assigned to each year of each subject's life. Arsenic measurements from government agencies, research studies, and

Table 1. Historical Concentrations of Arsenic in Drinking Water in Northern Chile by Year (1930–1995 Onward)

Region and City or Town	Population[a]	Average Arsenic Concentration (μg/L) by Years						
		1930–1957	1958–1970	1971–1977	1978–1979	1980–1987	1988–1994	1995 Onward
Region 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
Region 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

[a] Population data are based on the most recent Chile census (21).

other sources were available for >97% of the study area and >90% of all subjects' residences. Until recently, few people drank bottled water or used water filters. Water arsenic concentrations were also available for all large cities in Chile outside the study area, and these were also linked to residences, although almost all involved arsenic concentrations <10 μg/L (9). Residences for which water records were not available were all in areas not known to have high arsenic levels so were assigned a value of zero. Yearly arsenic concentrations for each subject were then multiplied by daily estimates of water intake (L/day) (either current or 20 years ago, whichever was closest to the year involved) to estimate an average daily arsenic intake (μg/day) for each year of each subject's life. Proxy subjects were assigned the median drinking water intake from all nonproxy subjects.

Several indices of exposure were used, including the highest daily average arsenic intake for any contiguous 5-year period and cumulative intake. Cumulative arsenic intake was calculated by multiplying each average daily arsenic intake by 365 days/year and then summing the results of all years. Exposures in the 5 years preceding cancer diagnosis or control ascertainment were not included in these calculations. Exposure categories were based on typical water consumptions and the arsenic water concentrations in the 3 main exposure areas of Arica/Iquique, Calama, and Antofagasta. Because high exposures in Antofagasta ended in 1970, and to account for latency effects (10), some analyses were limited to exposures before 1971. Renal pelvis and ureter cancers were combined because these were all transitional cell carcinomas (TCCs).

Odds ratios were calculated by using unconditional logistic regression. Variables entered into logistic regression models included sex, 10-year age groups, smoking (highest average number of cigarettes smoked) (11), mining work, current body mass index (above or below 30 kg/m^2), and tertiles of socioeconomic status scores. Using smoking as pack-years, body mass index as a continuous variable, or body mass index from 20 or 40 years ago had little impact on results. Socioeconomic status scores were based on ownership of household appliances, car, computer, and use of domestic help. Additional adjustments for hypertension, trichloroethylene, cadmium, asbestos, or solvent exposure (each entered as yes or no based on self-reported exposure) had little effect on results. Analyses were done in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina), and *P* values are 2 tailed.

RESULTS

Of the 148 kidney or ureter cancer cases ascertained from the pathologists and radiologists, 26 (17.6%) could not be located or declined participation. Among 872 controls selected from the Electoral Registry with viable addresses, 232 (26.6%) no longer lived at the address and could not be located, were ineligible due to illness, gave insufficient information, or declined participation. TCC cases, but not renal cell cancer (RCC) cases, were more likely to have hypertension, be of European descent, and have higher arsenic exposures than controls (Tables 2 and 3). Controls were more likely to be male and older than kidney cancer cases, because controls frequency matched to kidney, lung, and bladder cancer cases were used.

Elevated odds ratios and dose-response relationships were seen between kidney and ureter TCCs and various metrics of arsenic intake (Table 4). Adjusted odds ratios by average arsenic intakes of <400, 400–1,000, and >1,000 μg/day were 1.00, 5.71 (95% confidence interval (CI): 1.65, 19.82), and 11.09 (95% CI: 3.60, 34.16) ($P_{trend} < 0.0001$), respectively. The median highest arsenic drinking water concentrations in these 3 categories were 60, 300, and 860 μg/L, respectively. TCC odds ratios were also elevated in analyses of drinking water arsenic concentrations. For example, the adjusted odds ratios for highest known exposure to <100 μg/L, 100–300 μg/L, and >300 μg/L were 1.00, 4.20 (95% CI: 0.77, 22.8), and 16.1 (95% CI: 4.56, 57.0) (not shown). Excluding proxy subjects, ureter cancers, or subjects not of European descent produced similar results (Web Table 1 available at http://aje.oxfordjournals.org/). Associations were not seen for RCCs or other/unclassified cancers.

DISCUSSION

This is the first investigation to identify clear dose-response relationships between arsenic in drinking water and transitional kidney and ureter cancers using individual data on exposure and confounders. Although the number of cases is small, the low *P* values suggest that these findings are not due to chance. Several previous studies, all in highly exposed populations, have also reported associations between arsenic and kidney cancer, but all have been based on ecological designs and limited information on confounders (Web Table 2). This includes the only other study to examine histological subtypes, which also found evidence of higher arsenic-associated risks for TCCs than RCCs (12). The fact that our findings are similar to those of high-exposure ecological studies highlights the consistency of our findings with other research. Some studies have not found links between arsenic and kidney cancer (Web Table 2), but all involved very low exposures (i.e., concentrations <100 μg/L). Because low exposures are likely to be associated with relative risks close to 1.0, low exposure studies are more likely to miss true associations because of insufficient statistical power, confounding, exposure misclassification, or other bias (13).

Our findings changed very little with adjustment for factors linked to kidney cancer, including smoking, body mass index, chronic renal disease, diabetes, urinary tract infections, and hypertension. This is because they were not strongly linked to arsenic exposure in our study. Important confounding from factors such as von Hippel-Lindau disease or phenacetin is also possible but unlikely given their rarity and the low probability they are related to arsenic. Smoking is associated with kidney cancer with generally lower relative risks (e.g., <2.0) for RCCs than TCCs (14, 15). In our study, although the age- and sex-adjusted odds ratio for non-TCC cancers comparing heavier smokers (average, ≥20 cigarettes/day) with never smokers was 0.87 (95% CI: 0.44, 1.72), the corresponding odds ratio for TCCs was 2.24 (95% CI: 0.67, 7.41).

Exposure misclassification is possible in this study, but because exposure was assessed similarly in cases and controls and results did not change with exclusion of proxy subjects,

Table 2. Demographic Characteristics of Controls and Kidney Cancer Cases by Histological Type, Northern Chile, 2007–2010

	Controls		Renal Pelvis and Ureter Cancers (TCCs)				Renal Cell Cancers				Other/Unclassified Cancers				All Kidney Cancers			
	No.	%	No.	%	OR[a]	95% CI	No.	%	OR[a]	95% CI	No.	%	OR[a]	95% CI	No.	%	OR[a]	95% CI
Total	640	100	24	100			76	100			22	100			122	100		
Sex																		
Female	209	33	11	46			34	45			11	50			56	46		
Male	431	67	13	54			42	55			11	50			66	54		
Age group, years																		
≥70	269	42	6	25			18	24			12	55			36	30		
60–69	193	30	8	33			24	32			7	32			39	32		
50–59	132	21	7	29			20	26			1	5			28	23		
<50	46	7	3	13			14	18			2	9			19	15		
Race																		
Other	195	30	2	8	1.00	Referent	23	30	1.00	Referent	4	18	1.00	Referent	29	24	1.00	Referent
European	445	70	22	92	4.82	1.12, 20.7	53	70	1.01	0.60, 1.69	18	82	1.97	0.66, 5.90	93	76	1.40	0.90, 2.20
Smoking																		
Never	242	38	7	29	1.00	Referent	26	34	1.00	Referent	12	55	1.00	Referent	45	37	1.00	Referent
Ever	398	62	17	71	1.48	0.60, 3.61	50	66	1.17	0.71, 1.93	10	45	0.51	0.22, 1.19	77	63	1.04	0.70, 1.55
Socioeconomics (tertiles)																		
Low	231	36	6	25	1.00	Referent	27	36	1.00	Referent	6	27	1.00	Referent	39	32	1.00	Referent
Medium	203	32	8	33	1.52	0.52, 4.45	21	28	0.89	0.49, 1.61	9	41	1.71	0.60, 4.88	38	31	1.11	0.68, 1.80
High	206	32	10	42	1.87	0.67,5.23	28	37	1.16	0.66, 2.04	7	32	1.31	0.43, 3.96	45	37	1.29	0.81, 2.07
Mining work																		
No	498	78	19	79	1.00	Referent	59	78	1.00	Referent	19	86			97	80	1.00	Referent
Yes	142	22	5	21	0.92	0.34, 2.51	17	22	1.01	0.57, 1.79	3	14	0.55	0.16, 1.90	25	20	0.90	0.56, 1.46
Hypertension																		
No	505	79	15	62	1.00	Referent	59	78	1.00	Referent	16	73			90	74	1.00	Referent
Yes	135	21	9	38	2.24	0.96, 5.24	17	22	1.08	0.61, 1.91	6	27	1.40	0.54, 3.65	32	26	1.33	0.85, 2.08
	Mean (SD)		Mean (SD)				Mean (SD)				Mean (SD)				Mean (SD)			
Average cigarettes/day[b]	12.3 (14.1)		16.2 (17.6)				10.0 (13.0)				14.4 (12.0)				11.9 (14.1)			
Body mass index[c]	26.7 (4.3)		26.6 (5.0)				28.2 (4.9)*				26.0 (4.9)				27.5 (5.0)			

Abbreviations; CI, confidence interval; OR, odds ratio; SD, standard deviation; TCC, transitional cell carcinoma.

* $P < 0.05$.

[a] Unadjusted odds ratios and 95% confidence intervals comparing kidney cancer cases with controls. Odds ratios are not reported for age and sex because cases and controls were initially frequency matched on these factors.

[b] Highest average among smokers while smoking.

[c] Body mass index: weight (kg)/height $(m)^2$.

Table 3. Drinking Water and Arsenic Intakes in Controls and Kidney Cancer Cases by Histological Type, Northern Chile, 2007–2010

	Controls, Mean (SD)	Renal Pelvis and Ureter Cancers (TCCs)		Renal Cell Cancers		Other/Unclassified Cancers		All Kidney Cancers	
		Mean (SD)	*P* Value	Mean (SD)	*P* Value	Mean (SD)	*P* Value	Mean (SD)	*P* Value
Drinking water intake, L/day									
Current	1.67 (0.87)	1.58 (0.71)	0.75	1.68 (0.77)	0.75	1.79 (0.47)	0.13	1.67 (0.72)	0.47
20 years ago	1.80 (1.09)	1.74 (0.97)	0.95	1.88 (1.02)	0.29	1.98 (0.61)	0.04	1.87 (0.94)	0.10
Arsenic intake									
Highest 1 year, μg/day	532 (638)	1,046 (631)	<0.0001	495 (669)	0.38	454 (471)	0.93	596 (665)	0.25
Lifetime average, μg/day	145 (162)	315 (192)	<0.0001	139 (155)	0.69	133 (120)	0.96	173 (172)	0.08
Cumulative, mg	9.2 (10.1)	18.1 (10.5)	<0.0001	8.1 (9.5)	0.30	9.2 (8.7)	0.77	10.3 (10.3)	0.24
Highest 1 year before 1971, μg/day	471 (641)	1,013 (658)	<0.0001	471 (689)	0.74	381 (481)	0.92	563 (684)	0.11

Abbreviations: SD, standard deviation; TCC, transitional cell carcinoma.

most of this was likely nondifferential and biased odds ratios toward the null. Arsenic levels were not collected for some residences outside the study area, but the large majority of subjects spent their whole lives in parts of Chile for which we had arsenic records. Arsenic may come from food, air, or work, but analyses have shown that these exposures are likely small compared with the high exposures in Antofagasta (16). Misclassification of water intake is possible, although the odds ratios for TCCs were elevated regardless of whether these data were used. Detection bias is also possible, but major bias

Table 4. Kidney Cancer Odds Ratios by Various Metrics of Arsenic Intake and Histological Subtype, Northern Chile, 2007–2010

Exposure Metric	No. of Controls	Renal Pelvis and Ureter Cancers (TCCs)			Renal Cell Cancers			Other/Unclassified Cancers			All Kidney Cancers		
		No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI
Highest 5-year daily average of arsenic intake, μg/day													
<400	405	5	1.00		53	1.00		13	1.00		71	1.00	
400–1,000	141	8	5.71	1.65, 19.82	10	0.52	0.25, 1.07	7	1.52	0.57, 4.01	25	1.00	0.60, 1.67
>1,000	94	11	11.09	3.60, 34.16	13	1.24	0.64, 2.43	2	0.59	0.13, 2.72	26	1.76	1.05, 2.95
P_{trend}				<0.001			0.72			0.69			0.11
Highest daily arsenic intake before 1971, μg/day													
<400	415	7	1.00		53	1.00		14	1.00		74	1.00	
400–1,000	122	6	3.36	1.02, 11.10	10	0.59	0.29, 1.23	6	1.47	0.53, 4.05	22	1.02	0.60, 1.75
>1,000	103	11	7.13	2.61, 19.44	13	1.06	0.55, 2.06	2	0.53	0.12, 2.43	26	1.53	0.92, 2.55
P_{trend}				<0.001			0.68			0.57			0.18
Cumulative arsenic exposure, mg													
<10	418	7	1.00		58	1.00		15	1.00		80	1.00	
10–25	168	12	5.49	2.02, 14.88	11	0.52	0.26, 1.03	5	0.77	0.27, 2.22	28	0.96	0.59, 1.55
>25	54	5	10.35	2.57, 41.64	7	1.25	0.53, 2.96	2	0.91	0.20, 4.21	14	1.69	0.87, 3.26
P_{trend}				0.008			0.49			0.89			0.06

Abbreviations: CI, confidence interval; OR, odds ratio; TCC, transitional cell carcinoma.

is unlikely because cases were ascertained from all pathologists and radiologists using the same procedures throughout the study area, and hospital cancer committees and death certificates were used to help identify missed cases.

Several factors support the biological plausibility of our findings. The first is that ingested arsenic is a well-established cause of bladder cancer, most of which is also TCC (3). The second is that the kidney is the primary route of arsenic excretion, so almost all ingested arsenic reaches the target organ (17). Third, arsenic is linked to nonmalignant renal toxicity in animals, humans, and human cells, providing evidence that it not only reaches the target site but also causes toxicity there (18–20).

Overall, these findings, with sufficient statistical power, dose-response, appropriate latency, consistency with previous studies, and biological plausibility, provide strong evidence that ingested arsenic causes kidney and ureter transitional cell carcinomas. Identifying this new effect should draw attention to the need to reduce exposures in the millions who continue to drink arsenic-contaminated water worldwide.

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