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Case-Control Study of Bladder Cancer and Drinking Water Arsenic in the Western United States

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Numerous epidemiologic investigations have identified links between high concentrations of arsenic in drinking water and cancer, although the risks at lower exposures are largely unknown. This paper presents the results of a case-control study of arsenic ingestion and bladder cancer in seven counties in the western United States. These counties contain the largest populations historically exposed to drinking water arsenic at concentrations near 100 μg/liter. All incident cases diagnosed from 1994 to 2000 were recruited. Individual data on water sources, water consumption patterns, smoking, and other factors were collected for 181 cases and 328 controls. Overall, no increased risks were identified for arsenic intakes greater than 80 μg/day (odds ratio = 0.94, 95% confidence interval: 0.56, 1.57; linear trend, $p = 0.48$). These risks are below predictions based on high dose studies from Taiwan. When the analysis was focused on exposures 40 or more years ago, an odds ratio of 3.67 (95% confidence interval: 1.43, 9.42; linear trend, $p < 0.01$) was identified for intakes greater than 80 μg/day (median intake, 177 μg/day) in smokers. These data provide some evidence that smokers who ingest arsenic at concentrations near 200 μg/day may be at increased risk of bladder cancer.

arsenic; bladder neoplasms; smoking; water supply

Abbreviations: CI, confidence interval; HCFA, Health Care Financing Administration.

Since 1980, the International Agency for Research on Cancer has considered arsenic carcinogenic to humans (1). The earliest reports linking arsenic to cancer involved associations between lung cancer and inhaled arsenic in miners and associations between skin cancer and ingestion of arsenic-based medicines (2). Tseng et al. in 1968 (3), as well as Tseng in 1977 (4), reported an increased prevalence of skin cancer in Taiwanese populations exposed to arsenic in their drinking water. Since then, a number of epidemiologic studies in Taiwan and other countries have reported links between drinking water arsenic and cancers of the skin and several internal organs (5). These have included cancers of the bladder, kidneys, and lung, with the highest relative risks found for cancer of the bladder (6–12). Ingested arsenic exposures can result from industrial contamination or arsenic in medicines or foods. However, the most common exposure is consumption of groundwater containing naturally occurring arsenic.

Several populations in the United States have been exposed to arsenic-contaminated drinking water at levels near 100 μg/liter (13). However, since there is little information on the cancer risks at these levels, risk estimates for these exposures have involved extrapolations from the results of studies from highly exposed populations in Taiwan (5, 14–16). Such extrapolations have suggested that the cancer risk from drinking water containing arsenic at 50 μg/liter may be as high as one in 100 (5, 16, 17). Many different models have been used in these extrapolations, and differences in the models have led to large disparities in estimated risks (14). These disparities have fueled controversy and uncertainty in the low dose risk estimation process, highlighting the importance of actual studies at low exposures. According to the 1999 National Research Council Subcommittee on Arsenic in Drinking Water, "Additional epidemiologic evaluations are needed to characterize the dose-response relationship for arsenic-associated cancer and noncancer endpoints, especially at low doses. Such studies

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are of critical importance for improving the scientific validity of risk assessment" (5, p. 3). The purpose of the present study was to investigate bladder cancer risk using a case-control study design in a population exposed to low to moderate arsenic levels in drinking water.

MATERIALS AND METHODS

The study area consisted of six counties in western Nevada and Kings County in California. The cities of Hanford, California, and Fallon, Nevada, which comprise 21 percent of the current population of the study area (18), have historically been the two largest populations in the United States exposed to drinking water arsenic near 100 μg/liter. Other parts of the study area have substantially lower arsenic levels, thus offering a marked contrast in exposure.

Cases were subjects aged 20–85 years, with primary bladder cancer first diagnosed between 1994 and 2000, who lived in the study area at the time of diagnosis. Lists of subjects meeting these criteria were provided by the Nevada Cancer Registry and the Cancer Registry of Central California. Completeness of case ascertainment for the Nevada Cancer Registry has been estimated at 94.5 percent for the years 1995 and 1996 (19). Completeness for the Cancer Registry of Central California has been estimated at 95 percent (20). In Nevada, rapid case ascertainment, involving hospitals and physicians, was used to ascertain cases for the last 3 years of the study period. All pathology laboratories and associated hospitals in the study area and in Reno, Nevada, the nearby referral area, participated in rapid case ascertainment.

Controls were frequency matched to cases by 5-year age group and gender. Controls with a history of bladder cancer were excluded. Random digit dialing was used to gather controls under the age of 65 years (21). Controls over 65 years of age were randomly selected using Health Care Financing Administration (HCFA) rolls or random digit dialing.

Participants were interviewed over the telephone using a standardized questionnaire. For participants who were deceased, attempts were made to interview the nearest relative. Interviewers were blinded to the case-control status of the subject. Participants were asked to provide the address or location of all residences they had lived at for 6 months or longer over their lifetime. For each residence, participants were asked about sources of their drinking water (private well, community supply, bottled water, or other) and water filter use. Participants were asked their typical intake of drinking water and beverages, such as coffee and soups, made with tap water 1 year prior to the interview or prior to any recent illness, 20 years ago, and 40 years ago. Participants were also asked to provide the amount of tap water and fluid consumption separately for home, work, and away from home or work.

Participants were asked to describe all jobs they had held for 6 months or longer. Jobs were classified as low risk and possible risk, based on the degree of evidence linking specific jobs to elevated bladder cancer risks (22–27). Smoking questions covered age when smoking began, age of cessation, total years smoked, and typical number of packs smoked per week.

To determine arsenic exposure for each subject, we linked each residence within the study area to a water arsenic measurement for that residence. By doing so, an arsenic concentration could be assigned to each year of a subject's life within the study area. Arsenic exposures for residences outside the study area were assigned a value of zero. The average daily arsenic intake (μg/day) for a given year was then calculated by multiplying the arsenic concentration (μg/liter) for that year by the daily water intake (liters/day) estimated from responses to questions on water consumption. Estimates of daily water consumption for each year were ascribed from intake data for the nearest time period available. For example, information on drinking water intake from 20 years ago was used to estimate water intake for years 10–30 prior to diagnosis or ascertainment. The use of bottled water and water treated with a filter known to remove arsenic was assigned an arsenic level of zero.

Arsenic measurements for all community-supplied drinking water within the study area were provided by the Nevada State Health Division and the California Department of Health Services. We obtained over 7,000 arsenic measurements for community and domestic wells within our study area. For all large community water sources, records dated back 15 years or more. Records were available for both Hanford and Fallon documenting arsenic levels near 100 μg/liter since the 1940s. Over the last 10 years, the arsenic levels in Hanford have dropped to below 50 μg/liter because of the development of new wells. In Fallon, levels remain near 100 μg/liter, although a treatment plant is currently being built. Most of the remaining public water supplies in the study area contain less than 10 μg of arsenic per liter, although a few small cities have public water supplies with arsenic levels between 10 and 50 μg/liter. Most private wells in the study area contain arsenic below 10 μg/liter, although levels in private wells near Fallon and Hanford vary dramatically, from 0 to over 1,000 μg/liter.

When historical records were unavailable, more recent measurements were used. In an analysis using nationwide data, arsenic levels in a particular well have been shown to be relatively stable over time (13). In a separate analysis performed as part of our investigation, a Pearson correlation coefficient of 0.84 (95 percent confidence interval (CI): 0.74, 0.90) was obtained when we compared recent and past arsenic measurements taken at least 10 years apart from 69 wells in the study area.

Some arsenic measurements for private wells were obtained from the Nevada State Health Division. When records were not available, the residence was visited, and a water sample was collected. If a well could not be located, proxy estimates were used. These were calculated as the mean arsenic level on file at the Nevada State Health Division for all wells of similar depth within the same township/range/section as the unlocated well. Estimates were made only if at least five other wells existed within the same section, and the range between the highest and lowest arsenic level was less than 20 μg/liter. Researchers were blind to the case-control status when calculating proxy estimates. For

residences where arsenic measurements could not be located or estimated, arsenic levels were assigned a value of zero.

Odds ratios were calculated using unconditional multiple logistic regression. Several indices of arsenic exposure were assessed. These were as follows: 1) the highest average daily arsenic intake for any one year, 2) the highest daily average arsenic intake averaged over any contiguous 5 years, 3) the highest daily average arsenic intake averaged over any contiguous 20 years, and 4) total lifetime cumulative exposure, calculated by multiplying the daily average arsenic intake for each year of a subject's life by 365 to produce yearly intakes and then summing yearly intakes to produce total lifetime exposures. Stratification of the first three indices was based on a priori hypotheses regarding the current and past US drinking water standards. Stratification levels were set so that subjects exposed below the new US standard of 10 μg/liter would generally end up in the lowest exposure category, while subjects exposed above the current standard of 50 μg/liter would end up in the highest exposure category, assuming an average drinking water intake of 2 liters per day. Cumulative exposures were divided into tertiles. Other stratification levels were also assessed. Each exposure index was assessed with exposure lags of 5 years, 20 years, and 40 years from diagnosis. A time window analysis was performed in which the average arsenic intake in 10-year windows was the measure of exposure (28). Tests for linear trends were performed by the Cochran-Armitage test using category means.

Potential confounding variables entered into the logistic regression models included sex, age, smoking (categorized as never smokers, former smokers, current smokers averaging less than one pack per day, current smokers averaging one pack per day or more), highest education, occupation associated with elevated rates of bladder cancer, and income. In addition, adjustment for smoking was performed using pack-years or average cigarettes smoked per day in seven categories: never smokers, tertiles in former smokers, and tertiles in current smokers.

RESULTS

A total of 265 bladder cancer cases were identified during the study period. Fifteen of these had primary residences outside the study area at the time of diagnosis. Of the 250 who remained, 181 (72 percent) were interviewed, 30 (12 percent) declined participation, 30 (12 percent) could not be located, and 10 (4 percent) were not interviewed because of language issues or illness. Of the 328 controls enrolled in the study, 80 were obtained using random digit dialing, and 248 were enrolled using HCFA data. Of the 380 HCFA subjects we attempted to contact, 12 had primary residences outside the study area. Of the 368 who remained, 248 (67 percent) were interviewed, 64 (17 percent) declined participation, 36 (10 percent) could not be located, and 20 (5 percent) were not interviewed because of language issues or illness. During random digit dialing, of the phone numbers identified as residential, 84 percent were within the study area and provided a household census. Of those who met the age and gender criteria for the study, 83 percent agreed to participate.

Information on age, gender, and last known residence was available on nonparticipants. We compared the percentages of participants and nonparticipants whose last known residences were in areas with public water supplies containing more than 40 μg of arsenic per liter. Nonparticipants included those whom we were unable to locate and those who declined participation. For controls, 20 percent and 21 percent of participants and nonparticipants, respectively, lived in exposed areas. For cases, 20 percent of participants and 26 percent of nonparticipants lived in exposed areas.

A total of 181 cases and 328 controls were enrolled in the study (table 1). Cases and controls were of similar age, race, and gender distribution. Cases were more likely to be in the lower income bracket, less educated, and current smokers. Next-of-kin interviews were used for 35 cases (19 percent) and 20 controls (6 percent).

Table 2 shows the sources of drinking water and arsenic exposure data for the study participants. Overall, participants spent approximately one third of their lives within the study area. Average tap water consumption, sources of drinking water, and the percentage of proxy estimates were similar among cases and controls. Arsenic exposure was unknown for approximately 11 percent of the total person-years that participants lived in the study area, mostly because of unknown private well data. Participants used water from 240 private wells within the study area. Of these, records were available for or samples were taken from 101 (42 percent), proxy measurements were used for 64 (27 percent), and arsenic levels were unknown in 75 (31 percent). Table 2 also shows the percentages of cases and controls drinking water containing arsenic at various concentrations. These percentages are for the highest single year arsenic concentration to which the participants were exposed.

Table 3 shows odds ratios of bladder cancer for the four arsenic exposure indices. All odds ratios are near 1.0 when exposure lags of 5 and 20 years are used. When exposures are lagged 40 years, odds ratios above 1.0 are seen for arsenic intakes greater than 80 μg/day, although none of the confidence intervals excludes the null value. For smokers with highest 1-year exposures greater than 80 μg/day, an adjusted odds ratio of 3.67 (95 percent CI: 1.43, 9.42; linear trend, $p < 0.01$) was identified for exposures lagged 40 years (table 4). The median intake in each of the three exposure categories in this analysis was 0, 20, and 177 μg/day. The unadjusted odds ratio for this category was 3.52 (95 percent CI: 1.42, 8.73). One-sided p values for linear dose-response trends were less than 0.05 in all analyses of exposures lagged 40 years in smokers. Linear trend p values in all other analyses were greater than 0.05. For nonsmokers, odds ratios below 1.0 were found in the highest exposure categories. However, these were based on very few cases.

Analyses adjusting for smoking based on pack-years and average number of cigarettes smoked per day generally resulted in small increases in the odds ratios. For example, with six categories of pack-years of smoking history, the odds ratio in all subjects for highest 1-year exposures greater than 80 μg/day lagged 40 years was 1.80 (95 percent CI: 0.89, 3.66). In smokers, the corresponding odds ratio was 4.23 (95 percent CI: 1.58, 11.36).

TABLE 1. Demographic characteristics of bladder cancer cases and controls, western Nevada and central California, enrolled 1994–2000

	Cases (n = 181)		Controls (n = 328)		Crude OR*	95% CI*
	No.	%	No.	%		
Gender						
Females	34	18.8	76	23.2	1.00	
Males	147	81.2	252	76.8	1.30	0.83, 2.05
Income						
<$20,000 per year	59	32.6	70	21.3	1.00	
$20,000–80,000 per year	105	58.0	202	61.6	0.64	0.42, 1.00
>$80,000 per year	10	5.5	42	12.8	0.32	0.14, 0.70
Don't know or refused	7	3.9	14	4.3	0.54	0.19, 1.57
Race						
Caucasian	174	96.1	311	94.8	1.00	
Hispanic	2	1.1	6	1.8	0.60	0.12, 2.93
Other	5	2.8	11	3.4	0.81	0.28, 2.37
Smoking history						
Never	29	16.0	119	36.3	1.00	
Former	76	42.0	139	42.4	2.24	1.37, 3.67
Current: less than 1 ppd*	16	8.8	22	6.7	2.98	1.39, 6.39
Current: 1 ppd or greater	60	33.2	48	14.6	5.13	2.94, 8.94
Occupation						
Low risk	128	70.7	236	72.0	1.00	
Possible elevated risk	22	12.2	34	10.4	1.19	0.67, 2.12
Unknown risk	31	17.1	58	17.7	0.99	0.61, 1.60
	Mean	SD*	Mean	SD*	p value	
Age (years)	69.8	9.6	70.3	9.6	0.54	
Education (years)	12.1	3.0	12.9	2.7	<0.01	

* OR, odds ratio; CI, confidence interval; ppd, packs of cigarettes per day; SD, standard deviation.

Analyses using different stratification cutoff points produced similar results. For example, adjusted odds ratios for exposures greater than 100 μg/day lagged 40 years were 1.85 (95 percent CI: 0.88, 3.92) for all participants and 4.54 (95 percent CI: 1.53, 13.45) for smokers.

Table 5 presents the results of the time-window analysis. In the overall analysis, no clear elevations in relative risk were seen. However, in the analysis confined to smokers, elevated odds ratios were seen for exposures 51–60 years prior to diagnosis (odds ratio = 4.99, 95 percent CI: 1.31, 18.9) and for 61–70 years prior to diagnosis (odds ratio = 10.1, 95 percent CI: 1.17, 87.1).

DISCUSSION

Overall, no clear association was identified between bladder cancer risk and the exposures found in our study area. Interestingly, the overall risks were below those predicted using data from highly exposed populations in Taiwan (5, 14, 16, 17). This study, however, provides some evidence of elevated relative risks for bladder cancer in smokers exposed to drinking water arsenic at levels near 200 μg/day.

Numerous studies have reported increased risks of bladder cancer with arsenic ingestion, although most have involved exposures higher than those reported here (6–9, 11, 12, 29–31). The results of studies in populations with lower exposures have been mixed. A cohort mortality study in Utah, where exposures ranged from 14 to 166 μg/liter, showed reduced risks of bladder cancer mortality in people with cumulative exposures greater than 5,000 ppb-years (standardized mortality ratio = 0.44 in males and 0.22 in females) (32). These findings were based on three male and two female bladder cancer deaths, and they did not include data on water intake or smoking (33). A cohort mortality study in Taiwan found evidence of increased bladder cancer risks from consuming arsenic-containing water at levels greater than 640 μg/liter, but no increases were seen at lower levels (34). This study also did not include individual data on arsenic intake or level of smoking. In a more recent cohort study in Taiwan, relative risks of 8.2 (95 percent CI: 0.7, 99.1) and 15.1 (95 percent CI: 1.7, 139.9) for bladder cancer were reported for those exposed to arsenic levels of 50–100

TABLE 2. Data used to assess arsenic intake from bladder cancer cases and controls, western Nevada and central California, enrolled 1994–2000

	Cases	Controls
Average tap-water intake (liters/day)		
Current	2.20	2.19
20 years ago	2.79	2.71
40 years ago	2.65	2.43
Person-years inside study area (%)		
Lifetime	33.2	35.8
40 years preceding diagnosis	60.0	64.3
Sources of arsenic data (%)*		
Community water records	63.3	61.3
Bottled water	4.3	6.3
Private well		
Available records or measurements	14.7	11.6
Proxy measurement	5.9	7.6
Other water source	0.1	2.0
Unknowns		
Community records unavailable	0.4	0.2
Private well records unavailable	9.9	10.4
Water source unknown	1.4	0.5
Arsenic concentration (%)†		
5-year lag		
0–19 μg/liter	70.7	72.6
20–79 μg/liter	16.6	13.1
80–120 μg/liter	9.9	13.4
>120 μg/liter	2.8	0.9
20-year lag		
0–19 μg/liter	81.2	83.5
20–79 μg/liter	8.3	3.0
80–120 μg/liter	9.4	12.8
>120 μg/liter	1.1	0.6
40-year lag		
0–19 μg/liter	88.4	91.8
20–79 μg/liter	6.1	0.6
80–120 μg/liter	5.0	7.0
>120 μg/liter	0.6	0.6

* Total person-time drinking water from each source divided by total person-time in the study area.

† Percentage of cases and controls drinking water containing arsenic at various concentrations. The categories represent the highest single-year arsenic concentration to which the subjects were exposed, and they incorporate filter and bottled water use.

μg/liter and greater than 100 μg/liter, respectively (35). This study had two cases in the 50- to 100-μg/liter category, and the range of exposures in the highest exposure category (100–3,590 μg/liter) was substantially greater than the range in our study.

In this study, arsenic-associated cancer risks were analyzed for several different subgroups. When evaluating multiple outcomes such as this, one needs to consider the issue of multiple comparisons and the likelihood that positive associations may be due to chance. The positive outcomes identified in this study are consistent with findings from other studies. There is a growing amount of evidence supporting the hypothesis that arsenic and cigarette smoke act synergistically in causing cancer. In two studies involving very low arsenic exposures, elevated risks of bladder cancer associated with arsenic intake were identified only in smokers. In a case-control study in Utah, Bates et al. (28) found an odds ratio of 3.31 (95 percent CI: 1.1, 10.3) in smokers and of 0.53 (95 percent CI: 0.1, 1.9) in nonsmokers for those with cumulative arsenic exposures greater than 53 mg. In a case-control study in Finland, Kurttio et al. (36) reported odds ratios of 10.3 (95 percent CI: 1.16, 92.6) in smokers and of 0.87 (95 percent CI: 0.25, 3.02) in nonsmokers for arsenic exposures greater than 0.5 μg/liter. Two studies have also identified synergistic relations between smoking and ingested arsenic in lung cancer (6, 37). For example, in a lung cancer case-control study in Chile, odds ratios of 8.0 in never smokers and of 32.0 in smokers were reported for arsenic exposures above 200 μg/liter (37). A synergistic relation has also been identified with smoking in several studies of inhaled arsenic and lung cancer (38).

The results presented here suggest that the latency of arsenic-caused cancer may be greater than 40 years. Other chemical carcinogens appear to have latency or induction periods of at least several decades, although the data on ingested arsenic are mixed (39). In a time-window analysis of arsenic-exposed populations in Utah, Bates et al. (28) reported increased risk in smokers in the 30- to 40-year period, but they did not find increased risks in other periods, including the 40- to 50-year period. The Finish cohort study of bladder cancer found relative risks of 2.44 (95 percent CI: 1.11, 5.37) for arsenic exposures 3–9 years prior to diagnosis and of 1.51 (95 percent CI: 0.67, 3.38) for exposures 10 years and earlier (36). Both of these studies were based on exposures substantially lower than those reported in this study. In a cohort study of bladder cancer and Fowler's solution (potassium arsenite), three of the five cancer deaths in the study occurred within the first 10 years of exposure, and two occurred more than 20 years after the first exposure (11). Case series of arsenic ingestion and skin cancer report a wide range of latencies, although most of these are 20 years or more (40–44).

One aspect of this study warranting comment is that it did not incorporate arsenic exposures from outside the study area. However, the likelihood that participants received substantial exposures in other areas appears small. In the US Geological Survey's data set of potable groundwater supplies, arsenic levels above 50 μg/liter were found in only 79 of the 5,306 (1.5 percent) domestic well samples and 18 of the 1,982 (0.9 percent) public water samples (45). In a report by the US Environmental Protection Agency that includes both ground- and surface water, it was estimated that only 0.36 percent of the nation's community water systems contain arsenic levels greater than 50 μg/liter (46). The US Geological Survey has estimated that the median arsenic concentration in all potable groundwater resources in the United States is approximately 1.0 μg/liter (13). Ascribing

TABLE 3. Adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, with highest 1-year, 5-year, and 20-year average and cumulative exposures, western Nevada and central California, enrolled 1994–2000*

	5-year lag				20-year lag				40-year lag			
	No. of cases	No. of controls	OR†	95% CI†	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Highest 1-year average												
<10 μg/day	83	156	1.00		127	230	1.00		155	283	1.00	
10–80 μg/day	61	105	1.04	0.67, 1.61	28	53	0.92	0.54, 1.59	7	21	0.83	0.33, 2.12
>80 μg/day	37	67	0.94	0.56, 1.57	26	45	1.07	0.61, 1.87	19	24	1.78	0.89, 3.56
Highest 5-year average												
<10 μg/day	93	173	1.00		130	239	1.00		156	285	1.00	
10–80 μg/day	52	94	0.95	0.60, 1.50	25	48	0.96	0.54, 1.68	8	20	0.92	0.37, 2.26
>80 μg/day	36	61	0.99	0.59, 1.67	26	41	1.27	0.72, 2.25	17	23	1.74	0.85, 3.58
Highest 20-year average												
<10 μg/day	121	211	1.00		139	258	1.00		160	294	1.00	
10–80 μg/day	35	74	0.74	0.45, 1.21	23	34	1.24	0.68, 2.28	10	16	1.28	0.53, 3.11
>80 μg/day	25	43	1.02	0.57, 1.82	19	36	1.05	0.56, 1.98	11	18	1.70	0.73, 3.96
Cumulative exposure												
<6.4 mg	66	101	1.00		123	212	1.00		153	282	1.00	
6.4–82.8 mg	57	111	0.77	0.48, 1.24	17	46	0.59	0.31, 1.13	9	13	1.63	0.64, 4.13
>82.8 mg	58	116	0.73	0.45, 1.17	41	70	1.02	0.64, 1.65	19	33	1.40	0.73, 2.70

* Adjusted for age, gender, occupation, smoking history (<1 pack per day (ppd), ≥1 ppd, former smoker, never smoker), income, education, and race.

† OR, odds ratio; CI, confidence interval.

TABLE 4. Adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer among smokers and nonsmokers, western Nevada and central California, enrolled 1994–2000*

	Ever smokers								Never smokers							
	5-year lag				40-year lag				5-year lag				40-year lag			
	No. of cases	No. of controls	OR†	95% CI†	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Highest 1-year average																
<10 μg/day	71	103	1.00		131	190	1.00		12	53	1.00		24	92	1.00	
10–80 μg/day	48	67	0.97	0.59, 1.61	4	11	0.54	0.16, 1.80	13	37	1.40	0.53, 3.69	3	10	1.51	0.33, 6.99
>80 μg/day	33	38	1.14	0.64, 2.04	17	7	3.67	1.43, 9.42	4	29	0.45	0.13, 1.64	2	17	0.31	0.06, 1.66
Highest 5-year average																
<10 μg/day	77	117	1.00		132	190	1.00		16	56	1.00		24	94	1.00	
10–80 μg/day	43	56	1.06	0.63, 1.78	5	12	0.59	0.19, 1.78	9	37	0.77	0.29, 2.08	3	8	2.94	0.56, 15.49
>80 μg/day	32	35	1.26	0.70, 2.25	15	6	3.87	1.41, 10.60	4	26	0.41	0.12, 1.44	2	17	0.32	0.06, 1.72
Highest 20-year average																
<10 μg/day	101	141	1.00		134	197	1.00		20	70	1.00		26	96	1.00	
10–80 μg/day	30	44	0.86	0.50, 1.48	9	7	1.97	0.65, 5.38	5	29	0.54	0.17, 1.69	1	9	0.48	0.05, 4.39
>80 μg/day	21	23	1.24	0.63, 2.43	9	4	4.01	1.16, 13.9	4	20	0.51	0.14, 1.83	2	14	0.40	0.07, 2.24
Cumulative exposure																
<6.4 mg	58	63	1.00		130	189	1.00		8	38	1.00		23	92	1.00	
6.4–82.8 mg	46	79	0.69	0.40, 1.18	6	8	1.06	0.34, 3.33	11	32	1.55	0.51, 4.72	3	5	2.65	0.49, 14.24
>82.8 mg	48	66	0.76	0.44, 1.30	16	11	2.25	0.97, 5.20	10	49	0.83	0.28, 2.49	3	22	0.50	0.12, 2.05

* Adjusted for age, gender, occupation, income, education, and race.

† OR, odds ratio; CI, confidence interval.

TABLE 5. Adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, time window analysis, western Nevada and central California, enrolled 1994–2000*

	Exposure intervals prior to diagnosis															
	10–20 years				21–30 years				31–40 years				41–50 years			
	No. of cases	No. of controls	OR†	95% CI†	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
All																
<10 μg/day	106	172	1.00		131	233	1.00		145	270	1.00		160	290	1.00	
10–80 μg/day	37	89	0.65	0.40, 1.06	22	49	0.76	0.43, 1.37	16	25	1.26	0.63, 2.55	9	13	1.54	0.61, 3.91
>80 μg/day	38	67	0.76	0.46, 1.26	28	46	1.00	0.58, 1.73	20	33	1.19	0.63, 2.26	12	25	1.12	0.52, 2.44
Smokers																
<10 μg/day	90	112	1.00		112	150	1.00		124	175	1.00		136	191	1.00	
10–80 μg/day	29	53	0.67	0.38, 1.16	17	28	0.75	0.38, 1.48	12	15	1.09	0.48, 2.50	6	9	0.91	0.30, 2.74
>80 μg/day	33	43	0.86	0.49, 1.49	23	30	0.94	0.51, 1.75	16	18	1.25	0.59, 2.66	10	8	1.84	0.68, 4.99
	51–60 years				61–70 years				71–80 years							
	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR‡	95% CI	No. of cases	No. of controls	OR‡	95% CI				
All																
<10 μg/day	166	299	1.00		172	311	1.00		178	319	1.00					
10–80 μg/day	3	13	0.73	0.19, 2.71	1	5	0.59	0.06, 5.41	1	2	2.35	0.20, 28.2				
>80 μg/day	12	16	1.86	0.80, 4.33	8	12	1.86	0.69, 4.91	2	7	0.74	0.14, 3.86				
Smokers																
<10 μg/day	141	200	1.00		146	204	1.00		151	207	1.00					
10–80 μg/day	1	5	0.33	0.04, 2.98	0	3			0	0						
>80 μg/day	10	3	4.99	1.31, 18.9	6	1	10.1	1.17, 87.1	1	1	1.93	0.11, 33.9				

* Adjusted for age, gender, occupation, smoking history (<1 pack per day (ppd), ≥1 ppd, former smoker, never smoker), income, education, and race.
† OR, odds ratio; CI, confidence interval.
‡ Odds ratio not calculated in some categories because of zero cells.

this number for exposures outside the study area had no impact on our results.

The major advantage of this study is that the assessment of arsenic exposure is based on not only drinking water arsenic concentrations but also the volume of water consumption, the use of bottled water, and the use of water filters that remove arsenic. The importance of this is highlighted by the data presented in table 2, showing that the maximum concentration to which participants were exposed was similar among cases and controls. In addition, adjusted odds ratios calculated without the use of water consumption data resulted in odds ratios that were lower than the elevated odds ratios presented in tables 3–5. For example, the adjusted odds ratios for highest 1-year exposures greater than 40 μg/liter compared with 5 μg/liter or less, lagged 40 years, were 1.13 (95 percent CI: 0.52, 2.50) for all participants and 2.45 (95 percent CI: 0.83, 7.23) for smokers. Studies with less detailed data may be more likely to incorrectly classify arsenic intake and therefore could be more likely to miss true causal associations.

Errors in assessing arsenic intake may have arisen from errors in measuring drinking water intake or from errors in assigning arsenic concentrations to drinking water sources. We were able to link drinking water sources to data on arsenic concentrations for almost 90 percent of the total time the participants lived in the study area. This percentage was similar for both cases and controls. Most other aspects of exposure assessment were also similar for both cases and controls, including the volume of tap water consumed, the percentage of proxy well measurements used, the median arsenic value assigned using proxy measurements, and the percentage of participants' lives spent outside the study area. These data suggest that most errors in assessing exposure were nondifferential and therefore not likely to have been responsible for the positive associations identified in this paper.

Cases and controls differed in several characteristics. The higher percentage of controls in the upper income brackets is likely related to the increased participation rates among those in higher socioeconomic brackets (47–50). Other studies have shown little or no association between socioeconomic status and bladder cancer, suggesting that this variable is not likely to act as a substantial confounder (51). The crude odds ratios for the upper income categories increased only slightly when adjusted for smoking, age, gender, and arsenic exposure.

A greater percentage of next-of-kin interviews was performed for cases compared with controls. This may have led to a greater rate of misclassification among cases. Correcting for this misclassification would result in odds

ratios that are higher than those reported here (52). For example, if 5 percent of the exposed cases were actually unexposed, and 5 percent of the unexposed cases were actually exposed, the crude odds ratio for smokers with highest 1-year exposures greater than 80 μg/day lagged 40 years would increase from 3.52 to 4.99.

Cases and controls also differed in the percentage of nonparticipants with last known residences in arsenic-exposed areas. The percentage of nonparticipants from exposed areas was 5 percent higher among cases than controls. In analyses based on recent exposures, this difference would probably mean that more exposed cases were missed, biasing the odds ratio toward the null. The impact on analyses of exposures from the distant past is unknown.

In conclusion, the results of this study suggest that smokers who drink water containing arsenic at concentrations near 200 μg/day may be at increased risk of bladder cancer compared with smokers at lower arsenic exposures. This study also adds to evidence suggesting a long latency between arsenic exposure and bladder cancer diagnosis, although further confirmatory work is needed.

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