

Childhood Cancer Incidence and Arsenic Exposure in Drinking Water in Nevada

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ABSTRACT. Inorganic arsenic exposure through drinking water causes cancer in adults; however, the carcinogenic potential in children remains unknown. A recent leukemia cluster in Churchill County, Nevada, where arsenic levels in water supplies are relatively high, has prompted concern. The authors investigated the incidence of childhood cancer between 1979 and 1999 in all 17 Nevada counties, grouped by low (i.e., < 10 µg/l), medium (10–25 µg/l), and high (35–90 µg/l) population-weighted arsenic levels in public drinking water supplies. The standardized incidence ratios (SIRs) for all childhood cancers combined were 1.00 (95% confidence interval [CI] = 0.94, 1.06), 0.72 (95% CI = 0.43, 1.12), and 1.25 (95% CI = 0.91, 1.69) for low-, medium-, and high-exposure counties, respectively. There was no relationship between arsenic levels in water and childhood leukemia (SIRs = 1.02, 0.61, and 0.86, respectively [95% CIs = 0.90, 1.15; 0.12, 1.79; and 0.37, 1.70, respectively]). For all childhood cancers, excluding leukemias, the SIRs were 0.99 (95% CI = 0.92, 1.07), 0.82 (95% CI = 0.42, 1.22), and 1.37 (0.92, 1.83), respectively. The excess in 5- to 9-yr-old children and 10- to 14-yr-old children was in bone cancers, and the excess in 15- to 19-yr-old young adults was primarily in lymphomas. The findings in this study are reassuring in that leukemia risks were not increased at the concentrations of arsenic in water found in this study. Nonetheless, the results raise the possibility that there are increased risks for non-leukemic childhood cancers that require confirmation in other studies, particularly those in which higher exposures are addressed.

<Key words: ALL, arsenic, childhood cancer, cluster, drinking water>

CHRONIC EXPOSURE to inorganic arsenic, particularly in drinking water, causes a wide range of adverse health effects, including internal cancers—particularly lung and bladder cancers.¹ Most epidemiologic cancer studies of populations that ingest arsenic-contaminated water in Taiwan, Argentina, and Chile^{2–6} have reported risks to adults only. Arsenic-associated risks for childhood cancers have seldom been studied. In a study that included only a small number of subjects, Wulff et al.⁷ examined cancer incidence in children born in a smelting community between 1961 and 1990. Thirteen cases of childhood cancer were identified among children

born in the vicinity of the smelter, compared with 6.7 expected (standardized incidence ratio [SIR] = 1.95; 95% confidence interval [CI] = 0.88, 3.00). Among individuals who were born away from the smelter, the observed number of cases ($n = 42$) was similar to the number expected ($n = 41.8$). Perhaps that study involved multiple exposures associated with mining.

In another population-based case-control study, Infante-Rivard et al.⁸ also evaluated the relationship between exposure to arsenic in drinking water and childhood lymphoblastic leukemia. A slightly increased risk of leukemia was associated with very low levels of ar-

senic in drinking water (odds ratio [OR] = 1.39), but the 95% CI (0.70, 2.76) indicated that the findings could have resulted from chance.

Recently, a cluster of 15 childhood leukemia cases in Churchill County, Nevada, prompted concern.⁹ Historically, Churchill County has had high levels of arsenic in public drinking water sources.¹⁰⁻¹² One hypothesis for the leukemia cluster was that arsenic in drinking water might have caused the cancer increase.

We designed the current ecological study to test the hypothesis that chronic ingestion of inorganic arsenic in drinking water might cause increases in childhood cancer—particularly leukemia. If the recently detected leukemia cluster in Churchill County was, in fact, caused by arsenic, increased risks should have been apparent when we reviewed historical childhood cancer data, inasmuch as high exposures have occurred in this county for many years.

Method

Study area. The study population included all children and young adults between 0 and 19 yr of age who lived in Nevada between 1979 and 1999. According to the 1990 census,^{13,14} the Nevada population was estimated at 1,201,833, of whom 327,947 (27.3%) were 0–19 yr of age. Nevada is divided into 17 counties that vary widely demographically. Clark County is densely populated, and in 1990 it contained 61.7% of Nevada's total population. Other counties (e.g., Lincoln, White Pine) are relatively less inhabited than Clark County. Although county population numbers vary widely, each county contains a similar proportion of children between the ages of 0 and 19 yr.

Exposure data. Arsenic in drinking water has long been of concern in Nevada, particularly in Churchill and Lyon counties.^{9,10} In this study, we used data that were collected for a study of arsenic in drinking water and mortality from vascular disease in the United States.¹⁵ Arsenic levels for public water systems in Nevada were obtained from health departments in the state.¹⁵ We computed the mean arsenic level for each county by weighting the mean arsenic level for each water system and dividing it by the total county population served by the system. Arsenic measurements below detection limits were ≤ 1 $\mu\text{g/l}$. We grouped Churchill and Lyon counties as high-exposure counties inasmuch as 89% of Churchill County residents and 35% of Lyon County residents drank water that contained 100 $\mu\text{g/l}$ and 82 $\mu\text{g/l}$, respectively, of arsenic. Both counties also had high arsenic concentrations in their ground water, and some private wells had arsenic concentrations that exceeded 500 $\mu\text{g/l}$.¹² We grouped Esmerelda, Lander, Lincoln, and Nye counties in a "medium-exposure" category, because the public water supplies contained arsenic concentrations that were lower than the maximum contaminant level of 50 $\mu\text{g/l}$, but the concentrations were higher than 10 $\mu\text{g/l}$ (i.e., the drinking water guideline concentration proposed by the World Health Organization¹⁶). We grouped the remaining counties by arsenic exposure

inasmuch as the majority of their populations were served with water supplies that contained less than 10 μg arsenic/l.

Cancer incidence and population data. Nevada cancer incidence statistics for the years 1979–1999 were obtained from the Nevada State Cancer Registry. In a report issued by the registry in February 2001, investigators calculated that the percentage of estimated cases reported before 1999 averaged more than 90% for most years (i.e., 93.4%–95.6%); in 1999, the percentage was the most incomplete at 85.2%.¹³ Population figures for Nevada and for each of its 17 counties were obtained from the 1990 census,¹⁴ which was gleaned at the midpoint of the study period.

Statistical analysis. SIRs for all cancers, leukemias, and all other cancers (excluding leukemias) were calculated for each county. We based the expected numbers for each county on incidence rates for all of Nevada for 1979–1999, by 5-yr age groups (i.e., from 0–4 yr, 5–9 yr, 10–14 yr, and 15–19 yr). The 95% CI for the SIR was calculated on the basis of Byar's approximation.¹⁷

Results

The distribution by county of children aged 0–19 yr, average arsenic levels, and exposure ranks for each county are presented in Table 1.

In Table 2, the SIRs are presented for all childhood cancers by county and for each exposure group. There

Table 1.—Seventeen Nevada Counties Ranked by Mean Arsenic Level in Drinking Water

County	Population: 0–19 yr olds*	Level of arsenic ($\mu\text{g/l}$)†	Rank
<i>High-exposure group</i>			
Churchill	5,525	91.5	1
Lyon	5,845	35.9	2
<i>Medium-exposure group</i>			
Esmerelda	356	24.6	3
Lander	2,288	15.6	4
Lincoln	1,349	11.1	5
Nye	4,758	10.0	6
<i>Low-exposure group</i>			
Elko	11,706	7.8	7
Pershing	1,427	6.4	8
Douglas	7,574	3.4	9
Story	622	3.0	10
Clark	201,094	1.6	11
Mineral	2,037	1.3	12
Eureka	452	0.9	13
Washoe	65,989	0.8	14
Humboldt	7,550	0.2	15
Carson City	9,961	0.1	16
White Pine	2,761	0.0	17

*Population rates by county for the State of Nevada were gleaned from the 1990 U.S. Census, www.census.gov.¹⁴

†See reference no. 15 herein.

Table 2.—Age-Adjusted Standardized Incidence Ratios (SIRs) for All Childhood Cancers, by County, for 0–19-yr-old Children and Young Adults in Nevada State, 1979–1999

County	All cancers		SIR	95% CI
	Observed	Expected		
<i>High-exposure group</i>				
Churchill	19	16.7	1.14	
Lyon	24	17.6	1.37	
Subtotal	43	34.3	1.25	0.91, 1.69
<i>Medium-exposure group</i>				
Esmerelda	1	1.1	0.93	
Lander	5	6.9	0.73	
Lincoln	1	4.2	0.24	
Nye	12	14.4	0.84	
Subtotal	19	26.5	0.72	0.43, 1.12
<i>Low-exposure group</i>				
Elko	16	35.4	0.45	
Pershing	2	4.3	0.46	
Douglas	23	22.7	1.01	
Storey	1	1.8	0.55	
Clark	608	616.0	0.99	
Mineral	6	6.3	0.96	
Eureka	0	1.4	0.00	
Washoe	229	203.0	1.13	
Humboldt	13	12.6	1.03	
Carson City	38	30.5	1.25	
White Pine	5	8.3	0.61	
Subtotal	941	942.2	1.00	0.94, 1.06
Total	1,003	1,003.0	1.00	0.94, 1.06

Note: CI = confidence interval.

was considerable variation in SIRs across individual counties within each exposure group. This variation resulted mainly from the small size of most county populations and from the corresponding small number of cancer cases. The combined SIR (1.25) was slightly higher in the high-exposure group than in the low- and medium-exposure groups, but the confidence interval was wide (95% CI = 0.91, 1.69). In Table 3, SIRs are presented for leukemias and for all cancers, excluding leukemias. The SIRs revealed no increased exposure-related risk in the high-exposure counties (SIR = 0.86; 95% CI = 0.37, 1.70). When we examined other childhood cancers and excluded the leukemias from the analysis, there was some limited evidence of increased risks in the high-exposure counties (SIR = 1.37; 95% CI = 0.96, 1.91).

In Table 4, the types of nonleukemia childhood cancers found in the high-exposure counties are presented. The major types of nonleukemia cancers were those of the brain and central nervous system, lymphomas, and cancers of the bones and joints. The overall distribution of cancer types in Churchill and Lyon counties was similar to that found in all of Nevada (Table 4). Although the numbers are small and the confidence intervals wide, the SIRs increased after 4 yr of age. Overall, the SIR of 1.37 resulted from the children aged 5–19 yr. The SIR for children aged 5–14 yr result-

ed primarily from bone cancers. The SIR for young adults who were 15–19 yr of age was 1.64 (95% CI = 0.89, 2.75), which resulted primarily from the increased incidence of lymphomas, followed by soft tissue and testicular cancers.

Discussion

We designed this study to test the hypothesis that ingestion of arsenic in drinking water is associated with a detectable increase in childhood cancer. This topic has never been studied in any of the many arsenic endemic areas of the world and, therefore, merits further study. Moreover, a recent cluster of 15 cases of childhood leukemia in Churchill County—an area of Nevada with historically high levels of arsenic in drinking water—has prompted concern. During the period of study (i.e., 1979–1999), only 2 cases of leukemia were observed. (The 15 cases of childhood leukemia occurred between 2000 and 2001 and had not yet been entered into the database.) Therefore, if arsenic were the cause of the cluster, then a historically elevated increase in leukemia would have been apparent. A recent report by Infante-Rivard et al.,⁸ raised the possibility that arsenic levels in excess of 5 µg/l might be associated with childhood leukemia. The reported risk, however, was very low (OR = 1.37), and the 95% CI was wide (0.7, 2.7); there appeared to be little evidence in support of such a conclusion. We found no such evidence at much higher concentrations of arsenic in drinking water (~ 90 µg/l). Arsenic exposure in adults has never been associated with leukemia.

The results of this study revealed a small excess incidence of nonleukemia childhood cancer when we combined Churchill and Lyon counties and compared them with the rest of Nevada (SIR = 1.37; 95% CI = 0.96, 1.91). Childhood cancer incidence, when examined by age category, was higher in children 5+ yr of age than in 0- to 4-yr-old children. The excesses in 5- to 9-yr-old children and in 10- to 14-yr-old children were observed primarily in bone cancers, whereas the excesses in 15- to 19-yr-old young adults was observed in lymphomas, soft-tissue cancer, and testicular cancer. Whether the data indicate a true increase in childhood nonleukemia cancer risk cannot be determined because the populations in the high-exposure counties were small. However, the fact that the cancer SIR was higher in Lyon County than in Churchill County argues against any such association. Therefore, the results of this study, in light of the small numbers and relatively low environmental exposures to arsenic, should be interpreted cautiously.

This study was ecologic in nature. Although criticized frequently, such studies are actually quite favorable for the study of health effects from drinking water contaminants. Given that most individuals drink water from public sources, the lack of individual exposure data most likely would not cause a misclassification of exposure. Moreover, any effect of exposure misclassification, such as that caused by use of bottled water, would tend to be more likely to dilute the effect and

Table 3.—Age-Adjusted Standardized Incidence Ratios (SIRs) for All Leukemias, and All Cancers Excluding Leukemias, by County, for 0–19-yr-old Children and Young Adults in Nevada State, 1979–1999

County	Leukemia				All cancer (leukemia excluded)			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
<i>High-exposure group</i>								
Churchill	2	4.5	0.44		17	12.4	1.37	
Lyon	6	4.8	1.25		18	13.1	1.37	
Total	8	9.3	0.86	0.37, 1.70	35	25.5	1.37	0.96, 1.91
<i>Medium-exposure group</i>								
Esmeralda	0	0.3	0.00		1	0.8	1.25	
Lander	1	1.9	0.53		4	5.1	0.78	
Lincoln	1	1.0	1.0		0	3.0	0.00	
Nye	1	3.9	0.26		11	10.7	1.03	
Total	3	4.9	0.61	0.12, 1.79	16	19.6	0.82	0.47, 1.33
<i>Low-exposure group</i>								
Elko	7	9.6	0.73		9	26.2	0.34	
Pershing	0	1.2	0.00		2	3.2	0.63	
Douglas	6	6.2	0.97		17	17.1	1.00	
Storey	0	0.5	0.00		1	1.4	0.71	
Clark	186	164.6	1.13		422	450.7	0.94	
Mineral	2	1.6	1.25		4	4.6	0.87	
Eureka	0	0.4	0.00		0	1.0	0.00	
Washoe	46	53.9	0.85		183	147.9	1.24	
Humboldt	1	3.4	0.29		12	9.4	1.28	
Carson City	8	8.1	0.99		30	22.3	1.35	
White Pine	1	2.2	0.45		4	6.2	0.65	
Total	257	251.7	1.02	0.90, 1.15	684	689.9	0.99	0.92, 1.07

Note: CI = confidence interval.

Table 4.—Nonleukemia Childhood Cancers, by Age Category, Observed in the High-Exposure Group, Compared with Those Expected in Nevada, 1979–1999

Cancer type	0–4 yr age group		5–9 yr age group		10–14 yr age group		15–19 yr age group		Churchill and Lyon counties		Nevada state	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Total*	%	Total*	%
Brain/CNS	2	2.1	3	1.9	1	1.4	2	1.0	8	22.9	186	25.3
Lymphomas	0	0.4	1	0.7	0	1.4	5	2.1	6	17.1	131	17.8
Bone	0	0.0	2	0.4	3	0.7	0	1.0	5	14.3	65	8.8
Soft tissue	0	0.8	0	0.1	1	0.3	2	0.5	3	8.6	50	6.8
Kidney	3	1.1	0	0.1	0	0.1	0	0.0	3	8.6	40	5.4
Testes	0	0.3	0	0.0	0	0.0	2	0.7	2	5.7	29	3.9
Endocrine system	1	0.5	0	0.2	0	0.4	2	1.2	3	8.6	71	9.7
Liver	0	0.5	0	0.0	1	0.1	0	0.1	1	2.9	20	2.7
Nasopharynx	0	0.0	0	0.1	1	0.1	0	0.0	1	2.9	7	1.0
Prostate	0	0.0	0	0.0	1	0.0	0	0.0	1	2.9	1	0.1
Small intestine	0	0.0	0	0.0	0	0.0	1	0.0	1	2.9	2	0.1
Retroperitoneum and peritoneum	1	0.2	0	0.0	0	0.0	0	0.1	1	2.9	10	1.4
Others	0	1.2	0	0.3	0	0.6	0	2.0	0	4.2	124	16.9
Total	7	7.2	6	3.9	8	5.3	14	8.5	35	100.0	735	100.0
SIR	0.97		1.53		1.50		1.64		1.37			
95% CI	0.39, 1.99		0.56, 3.33		0.65, 2.96		0.89, 2.75		0.96, 1.91			

Notes: Obs. = observed, Exp. = expected, CNS = central nervous system, SIR = standardized incidence ratio, and CI = confidence interval.
*Total number of nonleukemia cancers.

lead to underestimation of the associations found. The effects of misclassification caused by migration are also minimized in childhood cancer studies because childhood cancer has a much briefer latency than adult cancers.

Relatively little is known about the causes of childhood cancer, and relatively few etiologic studies have been published, compared with studies of adult-onset cancers. Therefore, relatively little is known about possible confounding factors, including those associated with drinking water. The earliest studies focused on in utero diagnostic radiation exposure and risk of childhood leukemia.^{18,19} Other possible causes of childhood leukemia include exposure to environmental chemicals,^{20,21} electromagnetic fields,^{22,23} and viral infections.^{24,25} Nonetheless, in only a few studies have researchers identified strong relationships between childhood environmental exposures and childhood cancer development. If the associations seen in this study were to be confounded, we would have to correlate a causal factor for childhood cancer at a county level with the population-weighted average level of arsenic in the public water supply.

Arsenic is a known human carcinogen in adults, yet its carcinogenicity in children remains uninvestigated. It is a multisite carcinogen, and it causes tumors in the lung, skin, urinary bladder, and most likely in other sites, in adults.¹ As with many other metals, no clear mechanism of carcinogenesis has been observed. For many metals, aberrant cell proliferation, including alterations in apoptosis, is one hypothetical model. Arsenite also appears to disturb normal cell cycle progression and disrupts the mitotic spindle in normal diploid human peripheral fibroblasts and lymphocytes.^{26,27} Arsenite also induces both aneuploidy and chromosome breakage in vivo in human lymphocytes and exfoliated epithelial cells.^{28,29} This combination of cell cycle disruption and genetic damage could increase the likelihood of genetic instability, and of cancer developing in a growing child. Children's cells divide rapidly, and deoxyribonucleic acid is replicated hastily and is frequently in the uncoiled state, thus enhancing opportunities for environmental exposure, genetic damage, and replication error(s). In addition to rapid cell division, enhanced toxicity that results from (1) the cell's reduced capacity to metabolize arsenic and (2) increased doses of arsenic that occur from consumption of large quantities of water might make children more susceptible to cancer than adults—at lower concentrations of the metal.^{30,31}

In conclusion, the results of this study do not support the hypothesis that arsenic in drinking water is associated with childhood leukemia inasmuch as only 2 cases were observed in Nevada during the past 20 yr. Some evidence for a small increase in risk associated with arsenic in drinking water and nonleukemia childhood cancer incidence was found. The evidence was weak, and before drawing any conclusions one would have to investigate rates of childhood cancers in populations exposed to levels of arsenic that exceed those determined in our study.

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Submitted for publication June 29, 2001; revised; accepted for publication October 8, 2001.

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