

Drinking Water Arsenic in Utah: A Cohort Mortality Study

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The association of drinking water arsenic and mortality outcome was investigated in a cohort of residents from Millard County, Utah. Median drinking water arsenic concentrations for selected study towns ranged from 14 to 166 ppb and were from public and private samples collected and analyzed under the auspices of the State of Utah Department of Environmental Quality, Division of Drinking Water. Cohort members were assembled using historical documents of the Church of Jesus Christ of Latter-day Saints. Standard mortality ratios (SMRs) were calculated. Using residence history and median drinking water arsenic concentration, a matrix for cumulative arsenic exposure was created. Without regard to specific exposure levels, statistically significant findings include increased mortality from hypertensive heart disease [SMR = 2.20; 95% confidence interval (CI), 1.36–3.36], nephritis and nephrosis (SMR = 1.72; CI, 1.13–2.50), and prostate cancer (SMR = 1.45; CI, 1.07–1.91) among cohort males. Among cohort females, statistically significant increased mortality was found for hypertensive heart disease (SMR = 1.73; CI, 1.11–2.58) and for the category of all other heart disease, which includes pulmonary heart disease, pericarditis, and other diseases of the pericardium (SMR = 1.43; CI, 1.11–1.80). SMR analysis by low, medium, and high arsenic exposure groups hinted at a dose relationship for prostate cancer. Although the SMRs by exposure category were elevated for hypertensive heart disease for both males and females, the increases were not sequential from low to high groups. Because the relationship between health effects and exposure to drinking water arsenic is not well established in U.S. populations, further evaluation of effects in low-exposure populations is warranted. *Key words:* arsenic, cancer, cohort studies, drinking water, epidemiologic studies, mortality, noncancer, standardized mortality ratio, United States, Utah. *Environ Health Perspect* 107:359–365 (1999). [Online 26 March 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p359-365lewis/abstract.html>

The 1996 Safe Drinking Water Act Amendments (1) mandate that the EPA revise the current drinking water standard for arsenic of 50 µg/liter (ppb) by the year 2000. Cross-sectional studies conducted in Taiwan in the late 1960s (2,3) reported associations with blackfoot disease, a vaso-occlusive disorder that has never been reported in U.S. populations, and skin cancer. Previous studies of arsenic in drinking water in the United States have evaluated nonmelanoma skin cancer (4–8), bladder cancer (9), vascular disease (10), reproductive effects (11,12), and toxic effects (13–15). The results from these studies have been mostly negative. In a review of U.S. skin cancer prevalence studies (16), populations with adequate exposure and health outcome data had drinking water arsenic concentrations of <500 ppb. In contrast, studies in other countries have indicated associations with much higher concentrations of arsenic in drinking water supplies and a wide range of health effects, including a variety of cardiovascular effects, diabetes mellitus, and cancer other than skin cancer. Other investigators in the United States have presented analyses that suggest larger and more comprehensive U.S. studies are possible (9,10).

In the late 1970s the EPA conducted a small study in Millard County, Utah, on a

population exposed to drinking water with a mean arsenic concentration of at least 150 ppb (range 53–750 ppb). To conduct a mortality study, we established a cohort of Millard County residents based on the 1970s-era studies. The objective of the current study was to examine the health effects of chronic consumption of arsenic-contaminated drinking water in a U.S. population. This paper describes the results of an analysis of drinking water arsenic exposures of <200 ppb and cancer and noncancer health effects in a U.S. population. Results on both cancer and noncancer causes of death are presented, along with drinking water arsenic exposure concentrations that consider residence time in the geographic study area.

Materials and Methods

Cohort assembly. The cohort was assembled from historical ward membership records of the Church of Jesus Christ of Latter-day Saints (LDS) (also known as the Mormons). These records represent the registry of all members who ever lived in a ward during a specific time period. The registers were compiled by ward members. An LDS church ward is a defined geographic area whose residents constitute a single congregation. In this study, the boundaries of the LDS church wards are

closely aligned with their respective town boundaries. The wards and years for which the historical membership books were kept, which were used in constructing the cohort (i.e., enrolling the cohort members), include 1) Delta for the years 1921–1924 (original ward), 1927–1941 (first ward), 1939–1941 (second ward), and 1918–1941 (third ward); 2) Hinckley (1932–1941); 3) Deseret (1933–1945); 4) Oasis (1900–1945); and 5) Abraham (1900–1944). Therefore, for individuals entered into the cohort from these records, the earliest cohort entry date for residence and follow-up purposes was 1900, and the latest entry date for an individual was 1945. Information was recorded on individual characteristics, including name, church ward, family relationships, birth date, death date, location of death, and date that the person moved into or out of that church ward. Follow-up for residence history for the purpose of estimating exposure to drinking water arsenic was provided by LDS church censuses. This is discussed further in the Arsenic Exposure section. Additional data were collected from other sources as follows.

- From the historical LDS church membership records: name, church ward affiliation, birth date, birth town, birth state, death date, death town, death state, cause of death, church-related events, gender, age, spouse name(s), father's name, and mother's name
- From the LDS church census records: date of census, name, and residence at the time of the census

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- Current vital status was provided by the LDS church (these records are updated by the church on a weekly basis)
- From the LDS Ancestral File (LDS, Salt Lake City, UT), the International Genealogical Index (LDS), and the Social Security Death Index (LDS): date of birth and place of death
- From the death certificates: death date, death town, death state, underlying cause of death, and other causes of death
- From the Utah Health Department (Salt Lake City, UT): information on the duration of residence in the community, and coding of the underlying cause of death according to the *International Classification of Diseases, Ninth Revision (ICD-9)* codes (17).

The cohort was assembled from a 1977 study (14) that consisted of 2,073 cohort members during the first phase of data collection. Most of these cohort members had at least 20 years of exposure history in their respective towns. This cohort was expanded in a second phase of data collection to include all individuals who lived for any length of time in the study communities. The second phase of data collection resulted in a total combined cohort of 4,058 individuals. Cohort members were enrolled from historical LDS ward registries (18): 1,191 (29.4%) from Delta and 1,192 (29.4%) from Hinckley; the remaining 1,675 (41.2%) were enrolled from historical ward registries from the surrounding areas of Deseret, Abraham, and Oasis. More than 70% had attained the age of 60 years at the end of the follow-up period or by the time they were deceased. In all, 2,092 (51.6%) were male and 1,966 (48.5%) were female. At the end of the cohort assembly in November 1996, 1,551 (38.2%) were alive, 2,203 (54.3%) were deceased, and 300 (7.4%) were lost to follow-up. Four individuals were younger than 1 year of age and were not included in further analysis. The current analysis focuses on the 2,203 deceased.

Vital status determinations were made by the LDS church using current records. For deceased members, death certificates were requested from the state where the death occurred. Because most of the deceased cohort members died in the State of Utah, the Utah Bureau of Vital Records (BVR; Salt Lake City, UT) provided the majority of the death certificates. Death certificates were requested from other states where cohort members died. The Utah BVR assisted in the coding of all death certificates according to the *ICD-9* (17).

All death certificates were verified to ensure a match on identity, gender, and date of birth as compared to the abstracted

information from the historic ward membership files. Quality control review of the underlying cause of death was performed on 10% of death certificates from the initial phase of the cohort study by a first nosologist. Cause-of-death codes that were in question were submitted to a second nosologist at the National Center for Health Statistics (Research Triangle Park, NC), who verified the coding of the first nosologist. All death certificates collected in the most recent enrollment were verified for *ICD-9* coding by the first nosologist. The corrected codes were entered into the database and used in the analysis.

Water samples. Community drinking water arsenic concentrations were determined by historical records of arsenic measurements in drinking water maintained by the state of Utah dating back to 1964.

An overview of arsenic concentrations in drinking water and source-of-exposure information for the study area were presented in a previous feasibility assessment (18). In the current study, arsenic exposure levels for the communities were based on measurements performed by the Utah State Health Laboratory (Salt Lake City, UT), which participated in the EPA's quality assurance program and water quality proficiency testing. In addition, the samples must have originated from a water source used for culinary or potable purposes (not for agricultural or irrigation purposes), and the location of the source of the water sample (i.e., community) had to be clearly identified. The analysis date must have been 1976 or later, when the sample collection method involved acidification of the collection containers. This resulted in 151 samples of drinking water that were used in assessing the potential exposure of cohort members to arsenic in drinking water. The distribution of the concentrations of arsenic in drinking water in the study communities is provided in Table 1 in order of highest to lowest median concentration. Drinking water samples for 60 of the arsenic concentrations were collected during an EPA study in June 1997, with the rest of the samples dating from 1976 or

later. The Delta water samples came from the Delta public water system, and samples from Abraham, Deseret, Oasis, Sugarville, and Sutherland were taken from private drinking water wells. No additional water samples were taken for Hinckley because the original wells were abandoned in 1981 when a new, low-arsenic source (<50 ppb) of public drinking water was provided to Hinckley residents.

Arsenic exposure. Previous studies of the relationship between arsenic in drinking water and health effects have used a cumulative exposure index in which the overall exposure to arsenic for each subject is the product of the length of residence and the concentration of arsenic in drinking water (19,20). Using similar methods, an arsenic exposure index score was calculated for each individual in the cohort. The exposure index was derived from the number of years of residence in the community and the median arsenic concentration of drinking water arsenic in the community. Residence was determined by the members' entry into historical LDS church censuses, which the church conducted roughly every 5 years between 1914 and 1962 to determine where individual members lived throughout the world. Census years were 1914, 1920, 1925, 1930, 1935, 1940 (1945 skipped), 1950, 1955, 1960, and 1962. Data extracted from the censuses included date of census and residence at the time of the census.

The arsenic exposure index scores are expressed as ppb-years and are calculated as follows:

$$E_i = \sum(D_{xi} \times A_x) = \text{ppb-years}$$

where E = exposure index score value for individual i in ppb-years, D = duration of residence in years in community x for individual i , and A = median arsenic concentration in drinking water for community x in ppb.

The arsenic exposure index was categorized as low (<1,000 ppb-years), medium (1,000–4,999 ppb-years), and high ($\geq 5,000$ ppb-years). The rationale for this categorization is that 20 years of exposure is a reasonable

Table 1. Distribution of arsenic drinking water concentrations from historical and recent arsenic measurement data for Utah communities in the study area

Town	Number	Median	Mean	Min	Max	SD
Hinckley	21	166	164.4	80	285	48.1
Deseret	37	160	190.7	30	620	106.6
Abraham	15	116	134.2	5.5	310	67.2
Sugarville	6	92	94.5	79	120	15.3
Oasis	7	71	91.3	34	205	57.8
Sutherland	19	21	33.9	8.2	135	31.8
Delta	46	14	18.1	3.5	125	17.7

Abbreviations: Min, minimum arsenic concentration (ppb); Max, maximum arsenic concentration (ppb); SD, standard deviation.

period for most cancers to become manifest and an exposure to drinking water with 50 ppb arsenic or higher will yield a cumulative arsenic exposure of 1,000 ppb-years.

Analysis. Basic distributions of selected variables were made using SAS statistical software (21). The cohort data analysis uses standardized mortality ratios (SMRs) as the measure of association (22). The OCMAP program (23), adapted to a nonoccupational cohort, was used to compare the observed number of deaths with the expected number of deaths generated from death rates from the white male and white female general population of Utah within a given underlying cause of death category. Because a review of the race variable entered on the death certificates showed that all deceased individuals were white, death rates for white males and white females were used. Death rates for the state of Utah were available for the years 1960–1992 for diseases other than cancer, and from 1950 to 1992 for cancers. The death rates were applied in 5-year increments, with the exception of the 1990–1992 period. For those who died of causes other than cancer before 1960, the 1960–1964 death rates for causes other than cancer were applied. Similarly, for those who died of cancer before 1950, the 1950–1954 cancer death rates were applied. For those who died after 1992, the 1990–1992 death rates for either the cancer or noncancer cause of death were applied. To accommodate the needs of the program, a 1-year lag was imposed. This resulted in the exclusion of children less than 1 year old from the analysis ($n = 4$). At the end of the study, an individual was censored from the analysis on the date of death if deceased, the end of study date (27 November 1996) if alive, or at the last known residence date if lost to follow-up. The end date of the study was based on the

time when the last vital status determination was made on the last batch of records provided by the LDS church. LDS church records are updated weekly.

Results

Table 2 shows the distribution of basic demographic factors and arsenic exposure index distribution for the 2,203 deceased individuals with residence data. For non-cancer outcomes among males (Table 3), deaths from hypertensive heart disease (SMR = 2.20; 95% confidence interval (CI), 1.36–3.36) and nephritis and nephrosis (SMR = 1.72; CI, 1.13–2.50) were significantly elevated in the cohort as compared to the mortality experience for Utah white males. Death from arteriosclerosis (SMR = 1.24; CI, 0.69–2.04) and benign neoplasms (SMR = 1.05; CI, 0.29–2.69) was increased, but not statistically significant. Death from other cardiovascular causes (including cerebrovascular disease and ischemic heart disease) and respiratory causes (including non-malignant respiratory disease; bronchitis, emphysema, and asthma; and other respiratory disease) was significantly decreased as compared to the expected number of deaths for white males in the state of Utah. Among females (Table 3), death due to hypertensive heart disease (SMR = 1.73; CI, 1.11–2.58) and to all other heart disease (SMR = 1.43; CI, 1.11–1.80) was significantly elevated as compared to Utah white females. Deaths due to benign neoplasms (SMR = 1.96; CI, 0.85–3.86), diabetes mellitus (SMR = 1.23; CI, 0.86–1.71), arteriosclerosis (SMR = 1.18; CI, 0.68–1.88), and nephritis and nephrosis (SMR = 1.21; CI, 0.66–2.03) were increased. Deaths from ischemic heart disease and all external causes of death were less than that experienced by Utah white females.

To assess whether an increased exposure to drinking water arsenic could affect

mortality, SMRs were analyzed according to low, medium, and high arsenic exposure index values. Although the SMRs for hypertensive heart disease were elevated for males and females, the increases in the SMRs for low, medium, and high exposures did not increase sequentially. Other causes of death with elevated SMRs (nephritis and nephrosis for males and females, and all other heart disease for females) had elevated SMRs mostly in the medium or low arsenic exposure index categories. Causes of death with significantly decreased SMRs mostly had decreased SMRs within the low, medium, and high arsenic exposure index categories (e.g., cerebrovascular disease, all heart disease, and ischemic heart disease); however, the decreases did not descend sequentially from the high to low categories.

SMRs for cancer causes of death are listed for males and females in Table 4. Among males, prostate cancer was significantly increased (SMR = 1.45; CI, 1.07–1.91). Death due to kidney cancer (SMR = 1.75; CI, 0.80–3.32) was elevated in the medium and high exposure groups. Males in the mortality cohort had significantly less mortality due to all malignant cancers and cancer of the digestive organs and peritoneum, large intestine, and respiratory system than Utah white males. Mortality from lymphatic and haematopoietic cancers was decreased for both males and females. There were no cancer causes of death for females that were significantly elevated; however, moderate elevations in death due to cancer of the biliary passages and liver (SMR = 1.42; CI, 0.57–2.93), kidney cancer (SMR = 1.60; CI, 0.44–4.11), melanoma of the skin (SMR = 1.82; CI, 0.50–4.66), and all other malignant neoplasms (SMR = 1.34; CI, 0.84–2.03) are noted. Females in the mortality cohort had significantly less death due to all malignant neoplasms, cancers of the digestive organs and peritoneum, pancreas, respiratory system, and breast than did Utah white females. Mortality from uterine cancer and other female genital cancers was also decreased.

Among cancer causes of death for males, SMRs for the arsenic exposure index categories remained consistently elevated for prostate cancer, with the medium and high SMRs of similar magnitude and higher than the low group. Although the SMRs for low, medium, and high arsenic exposures for kidney cancer were elevated for males and females, the increases did not rise sequentially from low to high drinking water arsenic concentrations.

Discussion

Previous studies of drinking water arsenic concentration and health effects have indicated that skin cancer (2,3,24,25),

Table 2. Demographic distribution and arsenic exposure categories for deceased individuals in the Millard County, Utah, mortality cohort

	Low <1,000 ppb-years		Medium 1,000–4,999 ppb-years		High ≥5,000 ppb-years		Total
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Age at death							
<50	171	18.1	102	14.6	34	6.1	307
50–59	88	9.3	84	12.0	40	7.2	212
60–69	173	18.3	144	20.6	92	16.5	409
70–79	259	27.4	209	29.9	182	32.7	650
80+	255	27.0	161	23.0	209	37.5	625
Gender							
Male	536	56.7	415	59.3	291	52.2	1,242
Female	410	43.3	285	40.7	266	47.8	961
Years in cohort							
<40	401	42.4	276	39.4	59	10.6	736
40–59	335	35.4	197	28.1	153	27.5	685
60–69	147	15.5	102	14.6	101	18.1	350
70+	63	6.7	125	17.9	244	43.8	432
Total	946	–	700	–	557	–	2,203

internal cancers (25–35), cardiovascular effects (10,19,20,29,36), diabetes mellitus (34,37,38), and potentially neurologic effects (7,39) are linked with ingestion of increased concentration of drinking water arsenic. Most of these studies were conducted in non-U.S.

populations with markedly higher drinking water exposures that can exceed 2,000 ppb.

Although the Taiwan studies (2,3) linked skin cancer and blackfoot disease with very high exposures, there are few individuals in the U.S. population with

comparable exposures to arsenic in drinking water. In general, the highest exposures in U.S. studies are similar to the lowest exposures (or control exposures) in studies from other countries. The generalizability of the results from the Taiwan studies to the U.S.

Table 3. Standard mortality ratio (SMR) results for noncancer outcomes for males and females in the Millard County, Utah, mortality cohort

Cause of death	Males						Females					
	SMR estimate for exposure group ^a				All males		SMR estimate for exposure group ^a				All females	
	Low	Med	High	O/E	SMR	95% CI	Low	Med	High	O/E	SMR	95% CI
All causes of death	1.02	0.93	0.74	1,235/1,357.6	0.91	0.86–0.96	1.23*	0.99	0.74*	954/974.6	0.98	0.92–1.04
Benign neoplasms	2.77	–	–	4/3.8	1.05	0.29–2.69	2.89	1.60	1.38	8/4.1	1.96	0.85–3.86
Diabetes mellitus	0.93	0.95	0.42	20/25.3	0.79	0.48–1.22	1.14	1.72	0.89	35/28.5	1.23	0.86–1.71
Cerebrovascular disease	1.00	0.57*	0.74	76/96.5	0.79*	0.62–0.99	0.97	1.05	0.63*	100/115.1	0.87	0.71–1.06
All heart disease	0.87	0.78*	0.74*	412/514.4	0.80*	0.73–0.88	1.03	0.80	0.61*	273/337.9	0.81*	0.72–0.91
Ischemic heart disease	0.83*	0.74*	0.70*	281/369.6	0.76*	0.67–0.85	0.68*	0.62*	0.62*	130/203.3	0.64*	0.53–0.76
Disease of arteries and capillaries	0.97	0.98	0.82	27/29.1	0.93	0.61–1.35	1.24	0.78	0.56	20/23.3	0.86	0.52–1.32
Arteriosclerosis	1.23	1.62	0.84	15/12.2	1.24	0.69–2.04	1.98	1.06	0.53	17/14.5	1.18	0.68–1.88
Aortic aneurysm	0.44	0.79	1.15	9/11.9	0.76	0.35–1.44	–	–	1.30	2/4.2	0.48	0.06–1.73
Hypertensive heart disease	2.37*	1.91	2.29	21/9.6	2.20*	1.36–3.36	1.71	2.28*	1.34	24/13.9	1.73*	1.11–2.58
All other heart disease	1.09	0.97	0.71	56/59.7	0.94	0.71–1.22	2.26*	1.43	0.71	69/48.4	1.43*	1.11–1.80
Hypertension without heart disease	1.96	–	0.90	4/3.9	1.03	0.28–2.65	–	–	–	0/4.4	–	0.00–0.84
Nonmalignant respiratory disease	0.80	0.54*	0.69	81/118.6	0.68*	0.54–0.85	1.09	0.94	0.77	58/62.6	0.93	0.70–1.20
Bronchitis, emphysema, and asthma	0.65	0.50	0.65	19/31.5	0.60*	0.36–0.94	0.72	0.76	–	4/8.3	0.48	0.13–1.23
Nephritis and nephrosis	2.02*	2.10*	0.88	27/15.7	1.72*	1.13–2.50	2.32*	0.85	0.48	14/11.6	1.21	0.66–2.03

Abbreviations: O/E, observed/expected deaths; CI, 95% confidence interval.

^aLow exposure, <1,000 ppb-years; medium exposure, 1,000–4,999 ppb-years; high exposure, ≥5,000 ppb-years.

*Significant at the $p \leq 0.05$ level.

Table 4. Standard mortality ratio (SMR) results for cancer outcomes for males and females in the Millard County, Utah, mortality cohort

Cause of death	Males						Females					
	SMR estimate for exposure group ^a				All males		SMR estimate for exposure group ^a				All females	
	Low	Med	High	O/E	SMR	CI	Low	Med	High	O/E	SMR	CI
All malignant cancers	0.69*	0.96	0.83	182/222.5	0.82*	0.70–0.95	0.98	0.55*	0.65*	130/177.4	0.73*	0.61–0.87
Digestive organs and peritoneum	0.57*	0.87	0.73	45/63.0	0.72*	0.52–0.96	1.11	0.20*	0.70	34/49.4	0.69*	0.48–0.96
Stomach	0.67	0.85	1.20	13/14.8	0.88	0.47–1.50	1.00	0.40	0.70	6/8.3	0.72	0.26–1.57
Large intestine	0.79	0.45	0.35	11/20.0	0.50*	0.28–0.99	1.23	–	0.91	14/19.0	0.74	0.40–1.24
Biliary passages and liver	–	2.52	–	3/3.5	0.85	0.18–2.48	2.99	–	1.15	7/4.9	1.42	0.57–2.93
Pancreas	0.21	1.44	0.86	10/12.6	0.80	0.38–1.46	–	0.35	0.31	2/9.3	0.22*	0.03–0.78
Respiratory system	0.32*	0.96	0.44*	28/40.1	0.57*	0.38–0.82	0.44	0.66	0.22	6/13.7	0.44*	0.16–0.95
Prostate	1.07	1.70*	1.65	50/34.5	1.45*	1.07–1.91	–	–	–	–	–	–
Breast (female)	–	–	–	–	–	–	0.64	0.70	0.40	21/36.4	0.58*	0.36–0.88
Uterine	–	–	–	–	–	–	0.42	0.49	0.65	7/13.5	0.52	0.20–1.07
Other female genital organs	–	–	–	–	–	–	0.87	0.71	1.09	12/13.4	0.89	0.46–1.56
Kidney	2.51	1.13	1.43	9/5.2	1.75	0.80–3.32	2.36	1.32	1.13	4/2.5	1.60	0.44–4.11
Bladder and other urinary organs	0.36	–	0.95	3/7.2	0.42	0.08–1.22	1.18	–	1.10	2/2.5	0.81	0.10–2.93
Melanoma of the skin	0.72	0.79	1.06	3/3.6	0.83	0.17–2.43	5.30*	–	–	4/2.2	1.82	0.50–4.66
Central nervous system	–	0.90	–	2/6.4	0.31	0.38–1.12	1.21	–	–	2/4.8	0.42	0.05–1.50
Lymphatic, hematopoietic tissue	0.95	0.65	0.64	21/27.6	0.76	0.47–1.16	0.94	0.68	0.45	13/18.9	0.69	0.37–1.17
All other malignant neoplasms	0.98	1.10	0.77	18/18.7	0.96	0.57–1.52	1.26	1.18	1.57	22/16.4	1.34	0.84–2.03

Abbreviations: O/E, observed/expected deaths; CI, 95% confidence interval.

^aLow exposure, <1,000 ppb-years; medium exposure, 1,000–4,999 ppb-years; high exposure, ≥5,000 ppb-years.

*Significant at the $p \leq 0.05$ level.

general population has been questioned (40), as the lowest exposure category includes concentrations of up to 290 ppb (41). It is estimated that approximately 200,000 individuals are exposed to drinking water arsenic concentrations above 50 ppb (42). The median concentration of arsenic in drinking water in the Millard County mortality study is <200 ppb, and exposure to arsenic in drinking water could be regarded as typical of those concentrations of arsenic found in drinking water supplies in the United States. There are consistencies in the kinds of health effects that have associations in this study and in other international studies; however, the results of the present study need to be considered in the full context of all epidemiologic results currently available.

The major strength of this study is that it examines the effects of chronic exposure to arsenic in a U.S. population. Advantages of the cohort design include that the exposure precedes the effect, and that cohort studies have the capability to provide information on a variety of health effects from a single exposure (22). While the exposure is ecologic, i.e., not tied to an individual's actual consumption, the arsenic exposure estimates are believed to be accurate and the exposure is believed to have remained constant over time. During this study, the investigators were able to gather a considerable number of arsenic concentrations from private wells, so that estimates of exposure to arsenic from drinking water for individuals may be possible in future studies. Although individual data on confounding factors are not available, the historic membership of the cohort in the LDS church permits some assumptions regarding personal lifestyle including prohibition of tobacco use and of the consumption of alcohol or caffeine. Because church policy dictates that membership registration records are placed in the church ward of a member's residence, there is a high degree of confidence that the cohort members were exposed to the concentrations of drinking water arsenic for the communities in which they resided. Although the period of residence in the study area for the cohort members exceeds the period of available exposure information, historical documents indicate that drinking water quality has not changed considerably because of 100% reliance on groundwater supplies (18).

Other U.S. studies have not had the advantage of more population-specific arsenic monitoring data. A previous study (10) estimated the concentration of arsenic in drinking water in Millard County was 9.3 ppb. However, this estimate was based on a population-weighted mean arsenic

concentration in the public water supply data from the state of Utah. Because many residents of Millard County relied on private wells with much higher concentrations of arsenic, this estimate is not accurate.

Associations of drinking water arsenic with cardiovascular diseases, including hypertension (19), arteriosclerosis (29), cerebrovascular disease (36), ischemic heart disease (20), and other vascular diseases (10,35,43), have been reported. It has been hypothesized that exposure to arsenic in drinking water may be directly linked to ischemic heart disease and blackfoot disease via the atherogenic pathway (44). Indirect effects of arsenic on other cardiovascular risk factors including hypertension and diabetes (19,36) have also been proposed. Arsenic has been associated with vascular lesions including angiosarcomas and atherosclerotic plaques, suggesting that arsenic plays a role in somatic mutations and cell proliferation in the etiology of atherosclerotic plaques (45). In the current study, increased associations for hypertension and arteriosclerosis were found for both males and females. Death from all other heart disease in females was increased. This category included pulmonary heart disease, pericarditis, and other diseases of the pericardium.

The findings of cardiovascular effects in the context of a dose-response relationship with drinking water arsenic in this analysis are less clear. Although SMRs cannot be directly compared in an analysis that uses indirect adjustment, trends may be observed if the age and gender distributions in the exposure groups are similar. In Table 2, the age distributions are not similar (chi-square = 48.4, 8 degrees of freedom, $p < 0.01$), but the gender distributions are similar (chi-square = 1.9, 2 degrees of freedom, $p = 0.17$). Based on this, any conclusions on whether arsenic is an etiologic factor in consideration of increased or decreased SMRs among the groups is uncertain. Further evaluation of the relationship of each of these cardiovascular diseases with drinking water arsenic in this and other populations is needed. Positive associations with diabetes mellitus and the concentration of arsenic in drinking water have been reported in India, Bangladesh, and Argentina (34,37,38). In this study, there is no clear indication of any relationship between the concentration of arsenic in drinking water and diabetes mellitus.

Associations for nonmalignant respiratory diseases and bronchitis, emphysema, and asthma combined were also decreased, possibly indicating that the respiratory health of the cohort was good and smoking was not a major factor. Death from respiratory cancers was decreased significantly for

both males and females. Because the cohort was assembled based on historic LDS records, it is believed that the cohort was largely nonsmoking, as smoking is prohibited by the LDS church. Annual smoking prevalence rates for the state of Utah between 1984 and 1996 indicate that Utah consistently had the lowest prevalence of smoking among all states reporting, ranging from 13.2 to 16.8% among adults aged 18 years and older (46). Smoking rates for the Central Utah Health District, which includes Millard County, reported an average smoking rate among adults 18 and older of 13% for 1996 (47). During the same year, the entire state of Utah had a smoking prevalence of 12.4% and Salt Lake County had a smoking prevalence of 13.9% (47). For the incidence of cancers that are strongly related to smoking (including oral cavity, larynx, lung, esophagus, and bladder cancers), Mormon men had cancer incidence rates over a 15-year period from 1971 to 1985 that were approximately half those for U.S. men (48).

The current results indicating a positive association with prostate cancer are intriguing as this is the first known potential association between exposure to arsenic in drinking water and prostate cancer in the United States. In this analysis, prostate cancer was also the only health outcome that appeared to have a dose-response effect based on the low, medium, and high exposure index categories. The etiology of prostate cancer is largely unknown; however, it is believed that hormonal factors, family history, and dietary practices are involved (49). The incidence and mortality of prostate cancer increase dramatically after age 40. Worldwide, prostate cancer has the lowest rates among Chinese and Japanese men (50), with African-American men and Caucasian populations from North America experiencing the highest incidence rates. Mortality is lower in the United States as compared to high-risk countries (51). The ethnic background of the Millard County study population is primarily English, Scottish, and Scandinavian. For prostate cancer, Mormons have about a 10–15% higher incidence rate than U.S. men (48,52). Familial history is a strong risk factor for prostate cancer, as indicated by the results of a previous family study that also utilized Mormon records (53). In contrast, associations with mortality from cancers of the female reproductive tract in the Millard County mortality cohort were largely negative.

Previous studies from an endemic area of chronic arsenic toxicity in Taiwan (9,32,33,35) and an ecologic study in Argentina (26) have reported associations for increased exposure to drinking water

arsenic and risk for bladder cancer. A case-control study of bladder cancer in Utah (9) did not find an association with ingested arsenic, and in the Millard County mortality study only five deaths were due to bladder cancer. Whereas the studies in Taiwan and Argentina reported high exposures to drinking water arsenic, this study population was exposed to much lower levels, perhaps indicating that bladder cancer occurs in response to higher arsenic concentrations. In reviewing other causes of death from the urinary system, death from kidney cancer and nephritis and nephrosis were consistently elevated in both males and females. However, the SMRs did not increase with increasing levels of exposure. Other subclassifications of the types of nephritis and nephrosis were not available for the analysis, but competing causes such as infections need to be ruled out.

An increase in mortality due to melanoma in the lowest exposure category was found among females. Although skin cancer is etiologically linked with arsenic in drinking water, melanoma is not the histologic type of skin cancer usually associated with arsenic intake (54). In females, all of the melanoma deaths occurred in the lowest exposure category where the expected number was less than one. Based on these small numbers, it is not possible to draw conclusions about any involvement of exposure to arsenic in drinking water with this finding. Alternatively, continued follow-up of the cohort in the future could clarify whether the association between arsenic exposure and melanoma disappears. In contrast, the results for melanoma among males were negative.

Based on these cohort data, we do not believe that loss to follow-up, confounding, or multiple comparisons played a significant role in these results. Based on their review of several cohort studies, Breslow and Day (55) noted that loss to follow-up is acceptable if it is <10%. Our loss to follow-up is 7.4%. The distribution of this group by drinking water arsenic exposure was 163 in the low-exposure group, 96 in the medium-exposure group, and 41 in the high-exposure group. Because the net effect of loss to follow-up is to bias results toward the null value (55), and because most of the loss to follow-up is already in the low group in this cohort, the impact on our results would be to attenuate any observed effects rather than to spuriously increase them.

In this study, potential exposure to atmospheric arsenic is the most likely confounder because this variable is related both to health effects in previous studies of miners (56,57) and is associated with availability in sediments as a result of mining (58). Although data on atmospheric arsenic concentration was sought from the state of Utah to address potential confounding

effects from this alternate exposure to arsenic, this type of data is not routinely collected. However, future studies involving arsenic exposure assessment will consider atmospheric arsenic data collection. Because the study region in Millard County is primarily agricultural or vast desert with no mining activity, we do not believe a significant part of the exposure to arsenic was due to atmospheric exposure.

Because most of the significant associations we found in this analysis have been found by others and were not unanticipated, we do not believe multiple comparisons of exposure and outcome in these data represent a problem. To adjust for multiple comparisons would be incorrect because the correction theory is based on the universal null hypothesis that chance serves as the explanation for observed associations (59). Associations with hypertension and prostate cancer have been reported elsewhere (19,35). The association with nephritis and nephrosis is worthy of further investigation. Human autopsy data do not suggest arsenic accumulates more in the kidney than in other internal tissues (60,61). Although it is unknown whether the kidney represents a site of injury of arsenic, arsenate has been taken up by the phosphate carrier in cells of the proximal convoluted tubule (62).

In conclusion, this study represents a unique opportunity for health researchers to better understand the potential for health effects in association with relatively low exposure to arsenic in drinking water in a U.S. population. Although cohort members contributed many years to the highly exposed group and some died at an advanced age with no perceived adverse effects, further examination of this cohort is planned. Additional analysis of the data continues and includes a Cox proportional hazards analysis that will allow internal comparisons to be made between high, medium, and low exposure categories. Results from this study are important in the context of the ongoing review of the U.S. drinking water arsenic standard. This study will provide some insight into the role of both noncarcinogenic end points and carcinogenic end points in the review of the drinking water arsenic standard. Data from this cohort study will be especially useful in evaluating hazard identification and will provide some information on potential dose-response relationships as specified in the risk assessment paradigm.

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