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Arsenic in Drinking Water and Incidence of Urinary Cancers

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The associations between arsenic ingestion and cancers of the bladder and kidney have been documented in Taiwan. To evaluate further such associations for urinary cancers of various cell types, we conducted an ecologic study encompassing 243 townships using cancer registry data of patients diagnosed between 1980 and 1987. We used the proportions of wells with various specified arsenic levels in each township as indicators of exposure and evaluated the effects of urbanization and smoking by an urbanization index and the number of cigarettes sold per capita. In both genders, we observed associations of high arsenic levels in drinking water with transitional cell carcinomas of the bladder, kidney, and ureter and all urethral cancers combined. We also observed such associations in adenocarcinomas of the bladder in males, but not in squamous cell carcinomas of the bladder or renal cell carcinomas or nephroblastomas of the kidney. There was also a positive association between the urbanization index and transitional cell carcinomas of the ureter in males. The number of cigarettes sold per capita was not a good predictor for urinary cancers. The results indicate that the carcinogenicity of arsenic may be cell type specific. (Epidemiology 1997;8:545–550)

Keywords: arsenic, drinking water, cancer, urinary system, urbanization, cigarette smoking, ecologic study, histologic subtypes.

The association between consumption of artesian well water and skin cancer in Taiwan has been documented since the 1960s.[1,2] Tseng *et al*[3] reported a dose-response relation between arsenic concentration in well water and prevalence of skin cancer, and the U.S. Environmental Protection Agency used the data to conduct risk assessments for ingested arsenic,[4,5] which served as the scientific basis for current drinking water standards. Later, researchers reported similar associations for internal cancers, including cancers of the bladder, kidney, lung, liver, and colon; bladder and kidney cancers had the highest relative risks.[6–10] Almost all of these studies focused on six townships along the southwestern coast,[6–9] although other areas also had wells with high arsenic levels,[11] and all studies identified cases by death certificates,[6–10,12] which generally do not contain pathologic diagnoses. To evaluate the associations between arsenic ingestion and urinary cancers of various cell types, we conducted an ecologic study encompassing 243 townships in Taiwan, including the six most frequently studied.

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Methods

Arsenic Levels in Drinking Water

We used reports from a nationwide census survey of wells conducted by the government[11] to assess arsenic levels in drinking water. This survey applied the standard mercuric bromide stain method[13] to measure arsenic levels in more than 80,000 wells, mostly between 1974 and 1976. According to arsenic concentrations of the standard solutions used and the precision of this method,[14] arsenic levels can be grouped into six categories: below 0.05 parts per million (ppm), 0.05–0.08 ppm, 0.09–0.16 ppm, 0.17–0.32 ppm, 0.33–0.64 ppm, and above 0.64 ppm. A follow-up survey, using the same method on a subgroup of the wells, found the two sets of results highly correlated.[7] When atomic absorption spectrophotometry, a more reliable method, became available, researchers applied it to test some of the wells again and found the results no more than one category apart in about 90% of the wells.[15] Original measurement reports from the survey are available for 243 townships with a total of about 11.4 million residents.

Incidence Rates of Urinary Cancers

Using data from the National Cancer Registration Program operated by the government, which include pathologic diagnoses coded according to the International Classification of Diseases for Oncology (ICD-O)[16] and

the township of residence of each patient, we calculated the incidence rates (IRs; cases per 100,000 person-year). We included patients diagnosed between January 1, 1980, and December 31, 1987, and defined those with ICD-O codes from 188.0 to 188.9 as bladder cancers, 189.0 or 189.1 as kidney cancers, 189.2 as ureter cancers, and 189.3 as urethral cancers. We identified 1,962 bladder cancers, 726 kidney cancers, 170 ureter cancers, and 57 urethral cancers. Table 1 summarizes the distribution of the pathologic cell types. Except for urethral cancer, there were many more cases in males than females. This finding is consistent with those of previous studies and was also true for areas not included in this study.[2,10] Considering the stability of estimates, we only analyzed data on main pathologic cell types of the bladder, kidney, and ureter as well as all urethral cancers combined.

Urbanization Index and Cigarette Sales

To assess the associations between urbanization and incidence of cancers, our analyses applied an urbanization index that was assigned to each township on the basis of 19 socioeconomic factors shown to be good indicators of urbanization, including population density, per capita annual income and spending, density of manufacturing plants, density of business establishments, density of physicians, density of health care facilities, etc.[17,18] The study townships had urbanization indexes ranging from −1.410 to 3.257 (mean = 0.224; standard deviation = 1.128).

In addition, we used cigarette sales to evaluate the effects of smoking. In Taiwan, cigarette selling was a monopoly business operated by the Tobacco and Alcohol Monopoly Bureau. We adopted records collected from the Bureau in a previous study[18] to estimate the number of cigarettes sold per capita per year in each township (range = 14.94–689.93; mean = 63.76; standard deviation = 66.11).

TABLE 1. Pathologic Diagnoses of Urinary Cancer Patients

	Males		Females	
Pathology	Cases	%	Cases	%
Bladder cancers				
Transitional cell	1,185	88	363	83
Adenocarcinoma	43	3	17	4
Squamous cell	32	2	17	4
Other	81	7	41	9
Subtotal	1,341	100	438	100
No histopathology	120		73	
Total	1,461		511	
Kidney cancers				
Transitional cell	158	39	81	40
Renal cell	156	39	54	26
Nephroblastoma	23	6	22	11
Other	64	16	48	23
Subtotal	401	100	205	100
No histopathology	80		40	
Total	481		245	
Ureter cancers				
Transitional cell	93	94	53	84
Other	6	6	10	16
Subtotal	99	100	63	100
No histopathology	7		1	
Total	106		64	
Urethral cancers				
Transitional cell	11	42	10	40
Adenocarcinoma	9	35	8	32
Squamous cell	4	15	5	20
Other	2	8	2	8
Subtotal	26	100	25	100
No histopathology	3		3	
Total	29		28	

Data Analysis

We analyzed the data by multivariate linear regression models with the IR of a cancer as the dependent variable and the percentage of wells in each arsenic exposure category, the average number of cigarettes sold per capita, and the urbanization index as independent variables. This approach generated estimates of unit rate differences (RDs), that is, incremental risks for a one-unit increase in independent variables. For example, a multiple linear regression model can be expressed as:

$$IR = \alpha + \beta_1 X_1 + \ldots + \beta_5 X_5 + \gamma U + \delta T, \quad (1)$$

where, for each township, X_j is the proportion (as percentage) of wells with arsenic concentrations in category j, U is the urbanization index, and T is the number of cigarettes sold per capita. In this case, α (intercept) is the estimated background risk, β_j indicates the RD associated with each 1% increase in wells in category j, γ indicates the RD associated with each one-unit increase in urbanization index, and δ indicates the RD associated with each additional cigarette sold per capita.

Model 1 is derived assuming the existence of a universal model at the individual level:

$$Y = \alpha + \beta_1 z_1 + \ldots + \beta_5 z_5 + \gamma U + \delta t + \epsilon, \quad (2)$$

where Y is an indicator for the outcome (for patients, $Y = 1$; otherwise, $Y = 0$), z_j indicates exposures to arsenic (for people who drank from wells in category j, $z_j = 1$; otherwise, $z_j = 0$), U is the urbanization index of the residential township, and t is the number of cigarettes sold to that individual. Therefore, an ecologic study that included a township with n people would in fact observe the sum of n equations from Model 2:

$$N = \Sigma\alpha + \beta_1 \Sigma z_{1i} + \ldots + \beta_5 \Sigma z_{5i} + \gamma \Sigma U_i + \delta \Sigma t_i + \Sigma \epsilon_i,$$

where N is the number of cases, and Σz_{ji} is the number of residents drinking from wells in category j. As every resident in a given township had the same background risk and urbanization index, $\Sigma\alpha = n\alpha$, and $\Sigma U_i = Nu$. In addition, given the assumption that the errors ϵs are randomly distributed around 0 in each township, $\Sigma\epsilon_i$ has

an expected value of 0. Therefore, the summary equation can be written as

$$E(N) = n\alpha + \beta_1 \Sigma z_{1i} + \ldots + \beta_5 \Sigma z_{5i} + \gamma Nu + \delta \Sigma t_i.$$

When the dependent variable is the disease rate R ($R = N/n$), instead of the number of cases (N), the equation becomes

$$E(R) = \frac{n\alpha}{n} + \beta_1 \frac{\Sigma z_{1i}}{n} + \ldots + \beta_5 \frac{\Sigma z_{5i}}{n} + \frac{\gamma Nu}{n} + \frac{\delta \Sigma t_i}{n} = \alpha + \beta_1 X_1 + \ldots + \beta_5 X_5 + \gamma U + \delta T, \quad (3)$$

where, as defined in Model 1, X_j denotes the proportion of wells in category j, and $T = \Sigma t_i/n$. From Model 2 at the individual level to Model 3 at the township level, all regression coefficients (α, β_j, γ, and δ) remain the same.

To adjust for age, we obtained from the government statistics on the number of residents at the end of 1983 in each township and added the proportion of people in each age group (5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, and above 74 years old) to independent variables.[19] In addition, we applied weighted regression models with the total population in each township as the weight. Since the number of cigarettes sold per capita did not appear to be a good predictor for any cancer studied in either gender and was not available on 39 of the 243 townships, we excluded it from further analyses. The urbanization index and indicators of arsenic exposures were good predictors of some types of cancers, and therefore, we included them in the final models. The final models can be expressed as:

$$IR = \alpha + \beta_1 X_1 + \ldots + \beta_5 X_5 + \gamma U + \theta_1 A_1 + \ldots + \theta_8 A_8, \quad (4)$$

where all of the parameters and coefficients are defined as in Model 1, except that A_p is the proportion of residents in age group p.

Results

After adjusting for urbanization and age, the proportion of wells with arsenic levels above 0.64 ppm had positive associations with the incidence of transitional cell carcinomas of the bladder, kidney, and ureter and all urethral cancers combined in both genders. A 1% increase in the proportion of wells in this category was associated with an increase of risk ranging from 0.027 (urethral cancers in females) to 0.57 (transitional cell bladder cancers in males) per 100,000 person-years. It was also a good predictor for adenocarcinomas of the bladder in males (a 1% increase was associated with 0.027 additional cases per 100,000 person-years), but not for squamous cell carcinomas of the bladder or renal cell carcinomas or nephroblastomas of the kidney (Table 2). In addition, a 1% increase in the proportion of wells in the category 0.33–0.64 ppm was associated with an increase of 0.05 transitional cell carcinoma of the kidney per 100,000 person-year in males. The indicator of the next highest exposure category (0.17–0.32 ppm) and those of the lower-exposure categories, however, were not good predictors for incidence of this or other types of cancers studied (Table 2).

After adjusting for arsenic levels in drinking water and age, a high urbanization index appeared to be associated with a high incidence of transitional cell ureter cancers in males (a one-unit increase in the index was associated with an increase of 0.08 per 100,000 person-years).

Discussion

Since the 1950s, occurrence of urinary cancers has been noted among arsenic-intoxicated patients.[20] A high incidence of urinary cancers associated with arsenic in drinking water has been reported not only in Taiwan[5–10] but also in Japan[21,22] and Argentina.[23–25] A study on arsenic in drinking water and bladder cancer in the United States reported odds ratios up to 3.33.[26] Users of Fowler's solution (containing potassium arsenite)[27] and Moselle wine growers exposed to arsenical pesticides through drinking alcoholic beverages and spraying pesticides[28] also had increased risks of bladder cancer (Table 3). Studies of copper smelter workers exposed to arsenic through inhalation, however, showed less consistent results. Enterline *et al*[29] observed excess mortalities from kidney cancers but not from bladder cancers and all other urinary cancers combined. Welch *et al*[30] found excess mortalities from urinary cancers, but workers who were heavily exposed to arsenic and those who were not had similar risks. Most other studies on occupational exposures did not observe excess urinary cancers.[31–33] In comparison with community studies, however, these studies observed much smaller populations, and the exposure routes were different. Overall, there is adequate evidence to argue that arsenic ingestion may cause urinary cancers (Table 3).

Most studies on arsenic in drinking water and urinary cancers have limited quantitative data on exposures. The study by Tsuda *et al*[22] in 1995 included three arsenic levels, but cases were observed only at the highest level. The arsenic levels observed by Bates *et al*[26] ranged from 0.0005 to 0.160 ppm, but no association with bladder cancer was found. The study by Hopenhayn-Rich *et al*[25] covered three exposure groups but reported arsenic measurements only for the "high-exposure" group. Although some studies observed increased risks of urinary cancers in geographical areas with mean or median arsenic levels below 0.3 ppm,[7–10,25] such areas may still have people with exposure levels above 0.33 ppm. Nonetheless, even with the mean or median level as the indicator, excess risks were not found below 0.1 ppm.[9] Therefore, these findings are compatible with our observations: high arsenic levels in drinking water (0.33 ppm and above) are good predictors of urinary cancers, but lower arsenic levels are not.

There are many possible reasons for not observing stable positive associations between arsenic exposures below 0.33 ppm and urinary cancers in our study. The

TABLE 2. Estimates of Rate Difference (RD) (per 100,000 Person-Years) for One-Unit Increase in the Predictor, and Associated Standard Errors (SE) for Urinary Cancers by Gender, Organ, and Cell Type

	Bladder Cancer											
	Transitional Cell				Adenocarcinoma				Squamous Cell			
	Males		Females		Males		Females		Males		Females	
Predictor	RD	SE	RD	SE	RD	SE	RD	SE	RD	SE	RD	SE
Intercept	−2.18		−10.84		0.698		−3.486		−1.245		0.819	
Arsenic (ppm)												
0.05–0.08	−0.04	0.04	−0.03	0.02	−0.003	0.004	0.003	0.004	0.002	0.004	−0.002	0.003
0.09–0.16	0.00	0.05	0.05	0.03	0.006	0.005	−0.003	0.004	0.005	0.005	0.003	0.004
0.17–0.32	0.09	0.06	−0.01	0.04	−0.007	0.007	0.005	0.005	−0.002	0.006	0.005	0.005
0.33–0.64	−0.12	0.08	−0.03	0.05	0.000	0.009	0.001	0.007	−0.004	0.009	−0.007	0.007
>0.64	0.57	0.07	0.33	0.04	0.027	0.008	0.000	0.006	0.008	0.008	0.001	0.006
Urbanization	0.24	0.16	0.13	0.12	−0.013	0.018	−0.008	0.017	0.006	0.017	−0.006	0.016

	Kidney Cancer											
	Transitional Cell				Renal Cell				Nephroblastoma			
	Males		Females		Males		Females		Males		Females	
Predictor	RD	SE	RD	SE	RD	SE	RD	SE	RD	SE	RD	SE
Intercept	−3.66		−4.320		−3.63		0.537		0.722		−1.418	
Arsenic (ppm)												
0.05–0.08	−0.01	0.01	0.005	0.008	−0.01	0.01	0.003	0.006	0.000	0.003	−0.005	0.004
0.09–0.16	0.01	0.01	0.001	0.009	0.01	0.01	−0.004	0.007	−0.002	0.004	0.008	0.004
0.17–0.32	0.00	0.01	0.002	0.011	0.01	0.01	0.013	0.009	−0.002	0.005	−0.011	0.005
0.33–0.64	0.05	0.02	−0.028	0.015	−0.03	0.02	−0.016	0.012	−0.001	0.007	0.009	0.007
>0.64	0.03	0.02	0.142	0.013	0.01	0.02	−0.003	0.011	0.001	0.006	−0.003	0.007
Urbanization	−0.02	0.04	−0.025	0.036	0.03	0.04	0.015	0.029	−0.020	0.014	0.007	0.018

	Ureter Cancer: Transitional Cell				Urethral Cancer: All Cell Types Combined			
	Males		Females		Males		Females	
Predictor	RD	SE	RD	SE	RD	SE	RD	SE
Intercept	−0.22		1.81		0.542		−0.979	
Arsenic (ppm)								
0.05–0.08	0.01	0.01	0.01	0.01	0.009	0.004	0.000	0.004
0.09–0.16	0.00	0.01	−0.01	0.01	−0.010	0.004	0.001	0.005
0.17–0.32	0.02	0.01	0.00	0.01	0.008	0.006	−0.002	0.006
0.33–0.64	−0.02	0.02	−0.01	0.01	0.006	0.007	0.001	0.008
>0.64	0.11	0.02	0.10	0.01	0.056	0.007	0.027	0.007
Urbanization	0.04	0.04	0.08	0.03	0.021	0.015	−0.004	0.020

excess risks associated with arsenic levels below 0.33 ppm might be too small. This situation may also apply to higher exposure categories when an association was found in one gender but not in the other with fewer cases, such as adenocarcinomas of the bladder. Uncontrolled risk factors, such as the mutagenic humic substances in well water along the southwestern coast of Taiwan, might also have contributed to the results observed.[34] Nonetheless, some studies have indicated that arsenic may be an essential nutrient with a safety level of ingestion,[4,35–38] and some have hypothesized that lack of arsenic intake may be associated with the occurrence of cancer.[39] As recognized by the U.S. Environmental Protection Agency, studies in Taiwan have provided the "best data available" for quantitative cancer risk assessment of ingested arsenic.[4] These studies, however, seldom reported data on pathologic diagnoses. In fact, only a few published studies identified the cell types of urinary cancers associated with ingested arsenic,[22,23,40,41] and the results are compatible with our observations (Table 4). In most countries, the proportion of renal pelvic tumors (mostly transitional cell carcinomas) among kidney cancers is around 7%, but this proportion in Taiwan was estimated as 47%.[42] Our findings confirm the relatively high proportion of transitional cell carcinomas among kidney cancers in Taiwan and suggest that arsenic exposure may contribute to this phenomenon.

Absence of an association between cigarette sales and urinary cancers in our study is consistent with the findings in a recent study in Taiwan that showed associations between smoking and lung cancer but not bladder cancer after adjusting for exposure to arsenic.[43] None-

TABLE 3. Studies on Ingested Arsenic and Urinary Cancers Conducted Outside Taiwan Studies

Author and Reference	Cancer Site	Population (Arsenic Levels in Water)	Cases N	RR	95% CI
Drinking water					
Bates *et al*,[26] 1995	Bladder	117 cases and 266 controls (unspecified)	117	Various estimates ranging from 0.21 to 3.33	
Hopenhayn-Rich *et al*,[25] 1996	Bladder	690,421 people with "low" exposure (unspecified)	113 male	0.80	0.66–0.96
			39 female	1.21	0.85–1.64
		406,000 people with "medium" exposure (unspecified)	93 male	1.42	1.14–1.74
			24 female	1.58	1.01–2.35
		273,014 people with "high" exposure (estimated mean: 0.178 ppm for wells with detectable arsenic)	131 male	2.14	1.78–2.53
			27 female	1.82	1.19–2.64
Tsuda *et al*,[21] 1990	Urinary	141 arsenic-intoxicated patients (unspecified)	2	7.66	1.36–27.95
Tsuda *et al*,[22] 1995	Urinary	254 people (<0.05 ppm)	0	0.00	0.00–12.50
		76 people (0.05–0.99 ppm)	0	0.00	0.00–47.05
		113 people (≥1 ppm)	3	31.18	8.62–91.75
Besuschio *et al*,[23] 1980	Urinary	688 arsenical cancer patients (unspecified)	51		
Biagini,[24] 1992	Urinary	116 arsenic-intoxicated patients (unspecified)	3		
Medicine					
Cuzick *et al*,[27] 1992	Bladder	478 people taking Fowler's solution	5	3.1	1.0–7.3
Pesticides (in alcoholic drinks)					
Lüchtrath,[28] 1983	Bladder	258 arsenic-intoxicated patients	5	1.2	1.0–1.3

theless, it is also possible that excess risks associated with smoking were too small to be detected by either study. Moreover, the number of cigarettes sold in a township may not be a good indicator of the number of cigarettes actually consumed by the residents.

Risk estimates generated by this study might be affected by possible incomplete reporting of cancer cases. If there is a correlation between reporting rates and arsenic exposure levels, proper validation studies on the registry, which are not currently available, are necessary to determine the direction and magnitude of the biases. Such a correlation, however, is unlikely to be limited to certain cell types and thus is unlikely to account for the associations observed. This argument also holds true for other risk factors that were not controlled in our analyses.

Because our analyses used ecologic data, the results might be affected by "ecologic fallacy" as well as other common limitations of ecologic study design, such as biases introduced by the effects of population mobility. Although using a smaller unit of population, such as a village, might reduce the effects of the ecologic fallacy, the stability of estimates will decrease as a tradeoff, and such data are in fact unavailable.

TABLE 4. Studies on Pathologic Cell Types of Urinary Cancers Associated with Arsenic Ingestion

Author and Reference	Cancer Site	Cases N	Pathologic Cell Types
Besuschio *et al*,[23] 1980	Bladder	28	26 transitional cell carcinomas and 2 squamous cell carcinomas
	Ureter	2	Squamous cell carcinomas
Koh *et al*,[47] 1989	Ureter	1	Transitional cell carcinoma
Nomura *et al*,[48] 1986	Urinary	2	Transitional cell carcinomas
Tsuda *et al*,[23] 1995	Bladder	2	Transitional cell carcinomas
	Kidney	1	Transitional cell carcinoma

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