



American Journal of EPIDEMIOLOGY

Volume 153

Number 5

March 1, 2001

Copyright © 2001 by The Johns Hopkins University

School of Hygiene and Public Health

Sponsored by the Society for Epidemiologic Research

Published by Oxford University Press

ORIGINAL CONTRIBUTIONS

Incidence of Transitional Cell Carcinoma and Arsenic in Drinking Water: A Follow-up Study of 8,102 Residents in an Arseniasis-endemic Area in Northeastern Taiwan

Hung-Yi Chiou,¹ Shu-Ti Chiou,² Yi-Hsiang Hsu,¹ Yi-Li Chou,¹ Chin-Hsiao Tseng,³ Min-Li Wei,¹ and Chien-Jen Chen⁴

A significant association between ingested arsenic and bladder cancer **has** been reported in an arseniasis-endemic area in southwestern Taiwan, where many households share only a few wells in their villages. In another arseniasis-endemic area in northeastern Taiwan, **each** household has its own well for obtaining drinking water. In 1991–1994, the authors examined risk of transitional cell carcinoma (TCC) in relation to ingested arsenic in a cohort of 8,102 residents in northeastern Taiwan. Estimation of each study subject's individual exposure to inorganic arsenic was based on the arsenic concentration in his or her own well water, which was determined by hydride generation combined with atomic absorption spectrometry. Information on duration of consumption of the well water was obtained through standardized questionnaire interviews. The occurrence of urinary tract cancers was ascertained by follow-up interview and by data linkage with community hospital records, the national death certification profile, and the cancer registry profile. Cox proportional hazards regression analysis was used to estimate multivariate-adjusted relative risks and 95% confidence intervals. There was a significantly increased incidence of urinary cancers for the study cohort compared with the general population in Taiwan (standardized incidence ratio = 2.05; 95% confidence interval (CI): 1.22, 3.24). A significant dose-response relation between risk of cancers of the urinary organs, especially TCC, and indices of arsenic exposure was observed after adjustment for age, sex, and cigarette smoking. The multivariate-adjusted relative risks of developing TCC were 1.9, 8.2, and 15.3 for arsenic concentrations of 10.1–50.0, 50.1–100, and >100 µg/liter, respectively, compared with the referent level of ≤10.0 µg/liter. *Am J Epidemiol* 2001;153:411–18.

arsenic; carcinoma, transitional cell; drinking; incidence; risk assessment; urologic neoplasms; water supply

Editor's note: An invited commentary on this article appears on page 419, and the authors' response appears on page 422.

Received for publication May 10, 1999, and accepted for publication April 4, 2000.

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio; TCC, transitional cell carcinoma.

¹School of Public Health, Taipei Medical University, Taipei, Taiwan.

²Health Bureau of I-Lan County, I-Lan, Taiwan.

³Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

⁴Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.

Reprint requests to Dr. Chien-Jen Chen, College of Public Health, National Taiwan University, 1 Jen-Ai Road, Section 1, Taipei 10018, Taiwan (e-mail: cjchen@ha.mc.ntu.edu.tw).

Arsenic is a ubiquitous element that is widely distributed in nature and is transported in the environment mainly by water. Humans are exposed to arsenic through water, air, food, and beverages. While seafood contains a high level of arsenic, arsenic in seafood appears predominantly in its organic forms, which are considered less toxic than inorganic arsenic. Sources of exposure to arsenic through ingestion include drinking water, drugs used to treat leukemia and psoriasis, and arsenic-contaminated wine (1, 2).

Inorganic arsenic has been well documented as a human carcinogen of the skin and lungs (1–4). It is also involved in the development of several other cancers in humans without showing any organotropism. A significant association between ingested inorganic arsenic and risk of bladder cancer has been observed among patients treated with arsenic. In a small cohort study of 478 patients treated with Fowler's solution, which

contains 1 percent potassium arsenite, a significant association between cumulative dose of arsenic and mortality from bladder cancer was observed (5). In Moselle, France, wine vintners exposed to arsenical pesticide-contaminated wine also had an increased risk of bladder cancer (6). Inorganic arsenic inhaled through occupational exposure was not associated with increased mortality from urinary tract cancers (7-9). In a previous study (10), we observed increased mortality from cancers of the bladder and kidney among residents in an arseniasis-endemic area in southwestern Taiwan. There was a dose-response relation between arsenic concentrations in drinking water and mortality from bladder and kidney cancer (11, 12). The biologic gradient between ingested arsenic and bladder cancer has also been reported in recent cohort studies carried out in Taiwan and Japan (13, 14). More recently, increased mortality from cancers of the bladder and kidney was observed among residents in arsenic-exposed regions of Argentina and northern Chile (15-17).

The exposure to inorganic arsenic in our previous studies in southwestern Taiwan was based on the median arsenic content of water in the wells of residential villages, because only a few wells were shared by many households in each village (10-13, 18, 19). Some previous studies were either ecologic correlation studies (10-12, 18) or case-control studies (19). The former type of study might involve an ecologic fallacy, and the latter might be subject to bias resulting from differential loss of recall. Furthermore, mortality rather than incidence was used to evaluate cancer risk in most previous studies. Incidence is better than mortality for the elucidation of associations between a disease and its risk factors (13).

Lanyang Basin is located in the northeastern portion of the island of Taiwan. Arsenic levels in the well water in this area vary from 4.15 µg/liter (undetectable) to >3,000 µg/liter. Because each household in Lanyang Basin has its own well and the wells have been in use for more than 50 years, it is possible to assess individual exposure to inorganic arsenic in a much more precise way. The aim of this study was to assess the dose-response relation between the incidence of transitional cell carcinoma (TCC) and long term exposure to ingested inorganic arsenic through drinking well water in this newly identified arseniasis-endemic area in northeastern Taiwan.

MATERIALS AND METHODS

Study area

A total of 18 villages in four townships in Lanyang Basin were included in the present study. The area included four villages in Chiaohsi Township, seven in Chuangwei Township, three in Wuchieh Township, and four in Tungshan Township. Because of the abundance of underground water in the area, residents in Lanyang Basin have been using water from shallow wells (<40 m in depth) since the late 1940s. Although the implementation of a community water system was begun in the study area in the early 1990s, some residents are still drinking well water. The variation in arsenic levels in the well water of the study area is much more striking than that in the artesian well water of the

arseniasis-endemic area in southwestern Taiwan (20). The main source of exposure to inorganic arsenic among residents in both areas is drinking water obtained from wells.

Recruitment of the study cohort

The recruitment of study subjects has been described previously (21). In brief, residents aged ≥40 years were recruited into the cohort with their informed consent. A total of 8,102 residents (4,056 men and 4,046 women) who agreed to participate were interviewed in their homes between October 1991 and September 1994. These study subjects were recruited from 4,586 households. The standardized personal interview was based on a structured questionnaire and was conducted by four public health nurses who were well trained in interview techniques and questionnaire details. Data obtained from the interview included information on history of well water consumption, residential history, sociodemographic characteristics, cigarette smoking, alcohol consumption, physical activities, and history of sunlight exposure, as well as personal and family history of hypertension, diabetes mellitus, cerebrovascular disease, heart disease, and cancer.

Determination of arsenic content in well water

A total of 3,901 well water samples were collected from 3,901 (85.1 percent) households (one sample from each household) during the home interview. Well water samples were immediately acidified with hydrochloric acid and then stored at -20°C until subsequent assay. Hydride generation combined with flame atomic absorption spectrometry was used to determine concentrations of arsenic in these samples (22). Arsenic levels were found to range from undetectable levels (<0.15 µg/liter) to 3.59 mg/liter. However, 1,136 study subjects in 685 households had no data on arsenic levels in well water, because their wells no longer existed.

Follow-up of cancer incidence

The occurrence of cancer was ascertained through annual personal interviews and through data linkage with community hospital records and national death certification and cancer registry profiles. Vital status and cause of death for all subjects in the study cohort during the entire follow-up period from initial recruitment to December 31, 1996, were verified. Eighteen new cases of urinary tract cancer (International Classification of Diseases, Ninth Revision, codes 188 and 189), including 11 TCCs (International Classification of Diseases for Oncology, First Edition, codes 8120.2, 8120.3, and 8130.3), were found during the follow-up period. Among these cases, 17 urinary tract cancers (94 percent), including the 11 TCCs (100 percent), were identified through linkage with the cancer registry profile. One case of urinary cancer was identified from the death certification profile only. There were 15 case subjects (83 percent) with urinary cancer and 10 case subjects (91 percent) with TCC for whom we had data on arsenic concentrations in well water.

Data analyses and statistical methods

Cross-tabulation was used to examine the correlations among various arsenic exposure indices. Pearson correlation coefficients were also used to estimate the magnitude of the correlations. To compare the incidence of urinary tract cancers and TCC between residents of Lanyang Basin and the general population of Taiwan, we used an indirect adjustment method to estimate standardized incidence ratios (SIRs) (23). This method used age- and sex-specific incidence rates from 1991–1995 in Taiwan as the standard rates. The expected incidence of a given cancer was calculated by summing the products of age- and sex-specific incidence rates of the cancer in the standard population and age- and sex-specific person-years under observation in the study cohort ($\Sigma(\text{incidence} \times \text{person-years})$). The SIR was derived by dividing the observed number of incident cases by the expected number of incident cases. For comparison of differences in incidence between various arsenic exposure groups, arsenic levels in well water and duration of drinking the well water were categorized into four groups and three groups, respectively: ≤ 10.0 , 10.1–50.0, 50.1–100.0, and >100.0 $\mu\text{g/liter}$ and <20.0 , 20.1–39.9, and ≥ 40.0 years. To evaluate associations between risk factors and incidence of urinary tract cancers and TCC, we used Cox's proportional hazards regression analysis to estimate multivariate-adjusted relative risks and 95 percent confidence intervals (23, 24). Three regression models were used to examine associations with arsenic exposure for urinary cancer and TCC. Age, sex, and cigarette smoking were included in all models. Model 1 included arsenic concentration in well water as the variable of arsenic exposure; model 2 included duration of drinking the well water, and model 3 included both concentration and duration. The statistical significance of each multivariate-adjusted relative risk was examined by significance testing of the regression coefficient. We also carried out a time-window analysis (25) to examine the latency period between arsenic exposure and cancer occurrence.

RESULTS

A total of 8,102 subjects were recruited into the study cohort. Most subjects were aged 40–59 years; 40 percent of them were cigarette smokers, and 19 percent were habitual alcohol drinkers. Forty-one percent of the study subjects were illiterate; 51 percent had an educational level of elementary school, and only 8 percent had a level of junior high school or above. The subjects were mainly farmers and fishermen. There was no difference between average concentrations of arsenic in the well water consumed by men (119.6 $\mu\text{g/liter}$) and women (114.2 $\mu\text{g/liter}$); the average duration of drinking of well water was also the same for men (42.4 years) and women (42.1 years). Table 1 shows the frequency distributions of arsenic concentration in well water and duration of drinking of well water by age at recruitment. A total of 6,966 study subjects (86 percent) had data on arsenic concentrations in well water. Another 1,136 subjects (14 percent) did not have data on arsenic concentration in the water of their wells, because the wells no longer existed. There were 4,440 subjects (54.8 percent) who drank well

water with an arsenic concentration of 50 $\mu\text{g/liter}$ or less and 698 subjects (8.6 percent) who drank well water containing arsenic at levels greater than 300 $\mu\text{g/liter}$. There were 2,119 subjects (26.2 percent) who had used more than one well in their houses, and their past arsenic exposure data were derived from their current well data. The difference between the median and mean arsenic levels in well water was larger in the higher exposure categories, with a higher right skewness. There were 4,074 (50.3 percent) study subjects who had drunk well water for more than 40 years (median, 53 years). Furthermore, over 70 percent of study subjects aged greater than 50 years had drunk well water for more than 30 years. The average duration of drinking of well water was 40.7 years.

The cross-tabulation of arsenic concentration in well water and duration of drinking well water is shown in table 2. There was no association between arsenic concentration in well water and duration of well water drinking ($r = 0.06$).

During the follow-up period, nine subjects were afflicted with bladder cancer, eight were afflicted with kidney cancer, and one was afflicted with both bladder and kidney cancer. Table 3 shows SIRs for urinary tract cancer among study subjects. The subjects' risk of developing cancers of the urinary organs was significantly higher than the risk in the general population of Taiwan (SIR = 2.05; 95 percent confidence interval (CI): 1.22, 3.24). The SIR for bladder cancer was 1.96 (95 percent CI: 0.94, 3.61), while the SIR for kidney cancer was 2.82 (95 percent CI: 1.29, 5.36).

Among the 18 study subjects with urinary tract cancer, there were 17 with pathologic confirmation data and 11 with TCC. The incidence rates for cancers of the urinary organs and TCC were further analyzed by arsenic level in well water and duration of well water drinking (table 4). The incidence rates of urinary tract cancer and TCC for subjects who drank well water with arsenic levels of 10.0, 10.1–50.0, 50.1–100.0, and 100.0 $\mu\text{g/liter}$ were 37.6, 44.8, 66.4, and 134.1 per 100,000 and 12.5, 14.9, 66.4, and 114.9 per 100,000, respectively; these results show a dose-response relation. The incidence rates for urinary cancer were 61.1, 46.7, and 77.3 per 100,000 for persons who had drunk well water for <20.0 , 20.1–39.9, and ≥ 40.0 years, respectively; the corresponding incidence rates for TCC were 0, 46.7, and 46.4 per 100,000, respectively. However, there was no dose-response relation between the risks of urinary tract cancer and TCC and the duration of well water drinking.

Table 5 shows multivariate-adjusted relative risks of developing cancers of the urinary organs and TCC for various risk factors included in models 1–3. As model 1 illustrates, a significant dose-response relation ($p < 0.05$) was observed between risk of cancers of the urinary organs, especially TCC, and arsenic concentration in well water, after adjustment for age, sex, and cigarette smoking. The multivariate-adjusted relative risks of urinary tract cancer were 1.5, 2.2, and 4.8 for arsenic concentrations of 10.1–50.0, 50.1–100, and >100 $\mu\text{g/liter}$, respectively, compared with the referent group of ≤ 10.0 $\mu\text{g/liter}$. The relative risk was statistically significant for residents who drank well water containing arsenic at levels greater than 100 $\mu\text{g/liter}$. The biologic gradient between risk of TCC and well water

TABLE 1. Frequency distributions of arsenic concentration in well water and duration of drinking of well water, by age at recruitment (October 1991–September 1994) among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan

Exposure group	Age (years) at recruitment										Mean	Median	Range	
	40-49		50-59		60-69		≥70		Total					
	No.	%	No.	%	No.	%	No.	%	No.	%				
Arsenic concentration in well water (µg/liter)														
Undetectable (<0.15)	231	12.7	343	12.6	271	12.8	178	12.5	1,023	12.6			0.15-10.0	
0.15-10.0	317	17.4	455	16.7	319	15.0	232	16.3	1,323	16.3	3.6	2.8	10.1-50.0	
10.1-50.0	453	25.0	682	25.0	568	20.8	391	27.4	2,094	25.8	26.9	25.5	50.1-100.0	
50.1-100.0	177	10.0	330	12.1	247	11.7	158	11.1	912	11.3	74.6	75.0	100.1-299.0	
100.1-300.0	219	12.0	299	11.0	256	12.1	142	10.0	916	11.3	162.4	139.1	301.1-599	
300.1-600.0	76	4.2	143	5.3	95	4.5	82	5.8	396	4.9	415.7	403.5	614.3-3,842.6	
≥600.1	81	4.5	105	3.8	70	3.3	46	3.2	302	3.7	1,230.7	924.8		
Unknown	270	14.8	374	13.7	295	13.9	197	13.8	1,136	14.0				
Total†	1,824	22.5	2,731	33.7	2,121	26.2	1,426	17.6	8,102	100	116.9	27.3	0.15-3,482.6	
Duration of well water drinking (years)§														
0	73	4.0	98	3.6	79	3.7	53	3.7	303	3.7	0	0	0	
0.1-10	39	2.1	56	2.1	30	1.4	12	0.1	137	1.7	5.9	6	0-10	
10.1-20	152	8.3	141	5.2	122	5.8	84	6.7	499	6.2	17.2	18	11-20	
20.1-30	381	20.9	443	16.2	278	13.1	210	14.7	1,312	16.2	26.6	27	21-30	
30.1-40	379	20.8	678	24.8	477	22.5	243	17.0	1,777	21.9	35.4	35	31-40	
≥40.1	800	43.9	1,315	48.2	1,135	53.5	824	57.8	4,074	50.3	55.6	53	41-92	
Total†	1,824	22.5	2,731	33.7	2,121	26.2	1,426	17.6	8,102	100	40.7	41	0-92	

* Percentages are based on age-specific total numbers of study subjects.

† Percentages are based on 8,102 study subjects.

‡ Pearson's correlation coefficient between age and arsenic concentration in well water: $r = -0.02$ ($p = 0.0685$).§ Pearson's correlation coefficient between age and duration of well water drinking: $r = 0.30$ ($p = 0.0001$).

TABLE 2. Frequency distributions of arsenic concentration in well water and duration of drinking of well water among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan, 1991-1994*

Arsenic concentration in well water (μ g/liter)	Duration of well water drinking (years)												Total						
	0			0.1-10.0			10.1-20.0			20.1-30.0				30.1-40.0			≥40		
	No.	%	No.	No.	%	No.	No.	%	No.	No.	%	No.		No.	%	No.	No.	%	
Undetectable (<0.15)	79	26.07	10	7.30	41	8.22	76	5.79	90	5.06	727	17.84	1,023	12.6					
0.15-10.0	36	11.88	11	8.03	61	12.22	196	14.94	310	17.45	709	17.40	1,323	16.3					
10.1-50.0	19	6.27	24	17.52	103	20.64	410	31.25	568	31.96	970	23.81	2,094	25.9					
50.1-100.0	13	4.29	11	8.03	46	9.22	157	11.97	204	11.48	481	11.81	912	11.3					
100.1-300.0	10	3.30	10	7.30	47	9.42	132	10.06	219	12.32	498	12.22	916	11.3					
300.1-600.0	4	1.32	4	2.92	20	4.01	76	5.79	103	5.80	189	4.64	396	4.9					
>600.1	6	1.98	13	9.49	34	6.81	50	3.81	65	3.66	134	3.29	302	3.7					
Unknown	136	44.88	54	39.42	147	29.46	215	16.39	218	12.27	366	8.98	1,136	14.0					
Total	303	3.74	137	1.69	499	6.16	1,312	16.19	1,777	21.93	4,074	50.28	8,102	100					

* Pearson's correlation coefficient between arsenic concentration in well water and duration of well water drinking: $r = -0.06$.

TABLE 3. Standardized incidence ratios for cancer of the urinary organs among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan compared with the general population of Taiwan, 1991-1994

Site of cancer (ICD-9† code)	No. of cases	SIR†	95% CI†
Any urinary tract organ (188 and 189)	18‡	2.05	1.22, 3.24*
Bladder (188)	10	1.96	0.94, 3.61
Kidney (189)	9	2.82	1.29, 5.36*

* $p < 0.05$.† ICD-9, *International Classification of Diseases*, Ninth Revision; SIR, standardized incidence ratio; CI, confidence interval.

‡ One case was afflicted with cancers of both the bladder and the kidney.

arsenic was more prominent, showing corresponding multivariate-adjusted relative risks of 1.9, 8.2, and 15.3. The relative risk was statistically significant for residents who drank well water containing arsenic at levels greater than 100 $\mu\text{g/liter}$.

The duration of well water drinking was analyzed in model 2. Using residents who had drunk well water for less than 40 years as the referent group (relative risk = 1.0), we observed a slightly higher risk (relative risk = 1.2) of cancers of the urinary organs among residents who had drunk well water for 40 or more years, after adjustment for age, sex, and cigarette smoking. There was no association between duration of well water drinking and risk of TCC.

In model 3, the relative risks of urinary tract cancers and TCC for various levels of arsenic in well water remained similar after further adjustment for duration of well water drinking. Moreover, statistically significant higher risks of cancers of the urinary organs and TCC were observed for cigarette smokers after adjustment for age, sex, and arsenic exposure (table 5). However, there was no significant synergistic interaction between arsenic exposure and cigarette smoking.

Table 6 shows multivariate-adjusted relative risks of TCC for an elevated concentration of arsenic in well water (>50 $\mu\text{g/liter}$ vs. ≤ 50 $\mu\text{g/liter}$), stratified by duration of well water drinking. The relative risk was higher for subjects who had consumed well water for 40 years or more (relative risk = 15.3; 95 percent CI: 1.5, 153.3) than for those who had consumed well water for less than 40 years (relative risk = 5.2; 95 percent CI: 0.5, 50.3).

DISCUSSION

Significant associations between ingested arsenic and urinary tract cancers have been reported in previous studies carried out in an arseniasis-endemic area in southwestern Taiwan. These case-control and ecologic studies showed that long term arsenic exposure through water consumption increases the risk of cancers of the bladder and kidneys (10, 11, 18, 26-28). A dose-response relation between incidence rates of bladder cancer and cumulative arsenic exposure was

TABLE 4. Incidence rates (per 100,000) for urinary tract cancers and transitional cell carcinoma among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan, by arsenic exposure, 1991-1994

Exposure group	Person-years of observation	Type of cancer			
		Urinary organs (ICD-9† codes 188 and 189)		TCC† (ICD-O† codes 8120.2, 8120.3, and 8130.3)	
		No. of cases‡	Rate	No. of cases‡	Rate
Arsenic concentration in well water (µg/liter)					
610.0	7,978	3	37.6**	1	12.5*
10.1–50.0	6,694	3	44.8	1	14.9
50.1–100.0	3,013	2	66.4	2	66.4
>100.0	5,220	7	134.1	6	114.9
Duration of well water drinking (years)					
520.0	1,637	1	61.1	0	0**
20.1–39.9	8,561	4	46.7	4	46.7
≥40.0	12,935	10	77.3	6	46.4

* $p < 0.05$; ** $p < 0.01$ (test for trend).† ICD-9, *International Classification of Diseases*, Ninth Revision; TCC, transitional cell carcinoma; ICD-O, *International Classification of Diseases for Oncology*.

‡ Three urinary cancer cases and one TCC case without data on arsenic concentration in well water were excluded.

observed in a cohort follow-up study (13). Because only a few wells were shared by residents living in each village in the arseniasis-endemic area in southwestern Taiwan, median arsenic levels in the well water of the study villages were used to derive individual exposures to ingested arsenic in these studies. In other words, cumulative arsenic exposure was estimated in an ecologic way, which might be less pre-

cise and might result in nondifferential misclassification of individual exposure.

In the current study, carried out in an arseniasis-endemic area in northeastern Taiwan, each household had its own well for obtaining drinking water. Because arsenic concentrations in the wells of a given village ranged from undetectable levels (4.15 µg/liter) to several hundred micrograms per liter,

TABLE 5. Multivariate-adjusted relative risks for cancers of the urinary organs and transitional cell carcinoma among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan, 1991-1994

Variable	Type of cancer											
	Urinary organs						Transitional cell carcinoma					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	RR§	95% CI§	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Age (per 1-year increment)	1.1	1.0, 1.1*	1.1	1.0, 1.1*	1.1	1.0, 1.1*	1.1	1.0, 1.2*	1.1	1.0, 1.2*	1.1	1.0, 1.2*
Sex												
Female	1.0		1.0		1.0		1.0		1.0		1.0	
Male	0.4	0.1, 2.4	0.4	0.1, 2.3	0.4	0.1, 2.4	0.3	0.1, 2.3	0.3	0.1, 2.1	0.4	0.1, 2.3
Cigarette smoking												
No	1.0		1.0		1.0		1.0		1.0		1.0	
Yes	11.3	1.7, 74.8*	12.1	1.8, 81.6*	11.3	1.7, 74.8*	13.6	1.6, 118.6*	15.4	1.7, 139.8*	13.6	1.6, 118.8*
Arsenic concentration in well water (µg/liter)												
0-10.0	1.0†				1.0†		1.0†				1.0†	
10.1-50.0	1.5	0.3, 8.0			1.6	0.3, 8.4	1.9	0.1, 32.5			1.9	0.1, 32.2
50.1-100.0	2.2	0.4, 13.7			2.3	0.4, 14.1	8.2	0.7, 99.1			8.1	0.7, 98.2
>100.0	4.8	1.2, 19.4*			4.9	1.2, 20.0*	15.3	1.7, 139.9*			15.1	1.7, 138.5*
Duration of well water drinking (years)												
<40			1.0		1.0				1.0		1.0	
≥40			1.2	0.4, 3.7	1.3	0.4, 3.9			1.0	0.2, 3.1	1.0	0.2, 3.3

* $p < 0.05$.† $p < 0.05$ (test for trend).‡ $p < 0.01$ (test for trend).

§ RR, relative risk; CI, confidence interval.

TABLE 6. Multivariate-adjusted relative risks for transitional cell carcinoma, by level of arsenic in well water and duration of drinking of well water, among 8,102 residents of an arseniasis-endemic area in northeastern Taiwan, 1991–1994

Arsenic concentration in well water ($\mu\text{g/liter}$)	Duration of well water drinking (years)			
	<40		≥ 40	
	RR†	95% CI†	RR	95% CI
≤ 50.0	1.0‡		1.0‡	
> 50.0	5.2	0.5, 50.3	15.3	1.5, 153.3*

* $p < 0.05$.

† RR, relative risk; CI, confidence interval.

‡ Referent.

residents living in the same villages had significant differences in exposure to ingested arsenic through consumption of well water. Wide variations in arsenic exposure were considered most appropriate for the assessment of cancer risk associated with ingested inorganic arsenic. Among residents of this arseniasis-endemic area in northeastern Taiwan, we found significantly increased risks of developing cancers of the urinary organs and TCC, with SIRs of 2.05 and 2.82, respectively. The findings were consistent with those reported previously in the arseniasis-endemic area in southwestern Taiwan (10–13, 18, 19, 28).

Studies conducted in the arseniasis-endemic area in southwestern Taiwan showed a dose-response relation between long term arsenic exposure and risk of cancers of the bladder and kidney (11–13). The arsenic levels in well water were grouped as <300 , 300 – 599.9 , and ≥ 600 $\mu\text{g/liter}$ in these studies. The lowest arsenic level was much higher than the current maximum contaminant level of inorganic arsenic in drinking water, i.e., 50 $\mu\text{g/liter}$. It is thus important to compare cancer risks at drinking water arsenic levels around 50 $\mu\text{g/liter}$ in order to assess the necessity for implementing a new standard. This study provided data necessary for the implementation of a new maximum contaminant level of arsenic in drinking water. In this study, most of the subjects had consumed well water for 20 years or more. There was no association between arsenic concentration in well water and duration of well water drinking or between arsenic concentration and age at recruitment. The data were considered quite appropriate for the elucidation of the risk of cancer associated with ingested arsenic at low levels. Since each household used its own well for drinking water, the estimation of individual exposure to arsenic was much more precise than that in the southwestern arseniasis-endemic area of Taiwan. In this study, we analyzed the incidence of urinary tract cancers and TCC at drinking water arsenic levels of ≤ 10 , 10.1 – 50 , 50.1 – 100.0 , and >100.0 $\mu\text{g/liter}$. A significant dose-response relation was observed between the arsenic concentration in well water and the risk of urinary tract cancers after adjustment for age, sex, and cigarette smoking. However, no association was observed for the duration of well water drinking. In other words, it was the arsenic concentration in well water rather than the duration of drinking the well water which determined the risk of urinary cancer in this northeastern arseniasis-

endemic area in Taiwan. The findings also suggested that arsenic ingestion may increase the risk of urinary tract cancer at levels around 50 $\mu\text{g/liter}$.

A dose-response relation between arsenic and bladder cancer was also found in Finland (29). In the Finnish study, relative risks for the arsenic categories of 0.1 – 0.5 $\mu\text{g/liter}$ and ≥ 0.5 $\mu\text{g/liter}$ relative to the category of <0.1 $\mu\text{g/liter}$ were 1.53 (95 percent CI: 0.75, 3.09) and 2.44 (95 percent CI: 1.11, 5.37), respectively. The arsenic concentrations in this study were much higher than those observed in the Finnish study. Relative risks for arsenic concentrations of 10.1 – 50 , 50.1 – 100 , and >100 $\mu\text{g/liter}$ (compared with ≤ 10 $\mu\text{g/liter}$) were 1.5, 2.3, and 4.9, respectively, after adjustment for age, sex, cigarette smoking, and duration of well water drinking. When the results of these two studies are considered together, arsenic appears to induce bladder cancer in a biologic gradient at levels less than 50 $\mu\text{g/liter}$.

A significant association between arsenic exposure and risk of urinary tract cancer has also been reported in many epidemiologic studies carried out in the United States, southwestern Taiwan, Japan, Argentina, Chile, and Finland (5, 12–17, 25, 29). However, the pathologic type of urinary cancer was not examined further in those studies. In this study, the biologic gradient between arsenic exposure and TCC risk was more prominent than that between arsenic exposure and urinary cancer risk. The findings suggest that TCC might be the major pathologic type of urinary cancer induced by arsenic.

In this study, cigarette smoking was independently associated with increased risks of urinary tract cancer and TCC. Arsenic has been suggested to play a role in the promotion or progression of cancer development (30–32), although its effect on early carcinogenesis cannot be ruled out. Our finding seems to suggest that cigarette smoking might play a role in the initiation of arsenic-induced cancer of the urinary organs, especially TCC, in this study area.

We used a time-window analysis to examine the latency period between arsenic exposure and TCC occurrence. The increase in arsenic-induced TCC was more prominent for subjects who had drunk well water for 40 years or more than for those who had drunk well water for less than 40 years. It implies the possible existence of a latency period between arsenic exposure and the Occurrence of TCC.

Although arsenic is a human carcinogen, there is no good animal model for studying the carcinogenicity of inorganic arsenic. Arsenic is inactive or extremely weak in inducing gene mutations at specific loci (3, 33). Modes of action for arsenic-induced carcinogenicity might include the induction of chromosome abnormality, inhibition of DNA repair, induction of oxidative stress, and an increase in cell proliferation (34). Inorganic arsenic has several genotoxic effects, including the induction of changes in chromosome structure and number, increases in sister chromatid exchanges and micronuclei, gene amplification, cell transformation, and aneuploidy (12, 33–37). A role for inorganic arsenic as a cocarcinogen, such as a tumor promoter or progressor rather than a tumor initiator, has also been hypothesized (30, 31). However, the evidence is far from adequate for drawing a definite conclusion on the exact mechanism by which inorganic arsenic might induce various cancers in humans.

ACKNOWLEDGMENTS

The authors thank Drs. Che-Long Su and Shu-Feng Chang of the Department of Neurology, Lotung Poh-Ai Hospital (I-Lan, Taiwan) for their assistance.

This study was supported by the National Science Council of Taiwan (grants NSC-86-2314-B-002-336, NSC-87-2314-B-002-005, and NSC-87-2314-B-038-035).

REFERENCES

- World Health Organization. Arsenic. In: Environmental health criteria. Geneva, Switzerland World Health Organization, 1981:33-49.
- Agency for Toxic Substances and Disease Registry, US Public Health Service. Toxicological profile for arsenic. Washington, DC: US Public Health Service, 1989. (Publication no. ATSDR/TP-88/02).
- International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: overall evaluations of carcinogenicity. An updating of IARC monographs volumes 1 to 42. (Suppl 7). Lyon, France: International Agency for Research on Cancer, 1987:100-6.
- Environmental Protection Agency. Risk assessment forum. Special report on ingested inorganic arsenic: skin cancer, nutrition essentiality. Washington, DC: Environmental Protection Agency, 1988.
- Cuzick J, Sasien P, Evan S. Ingested arsenic, keratosis, and bladder cancer. *Am J Epidemiol* 1992;136:417-21.
- Luchtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers: pathoanatomical investigations of post-mortem examinations performed between 1960 and 1977. *J Cancer Res Clin Oncol* 1983;105:173-82.
- Welch K, Higgins I, Oh M, et al. Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. *Arch Environ Health* 1982;37:325-35.
- Sobel W, Bond GG, Baldwin CL, et al. An update of respiratory cancer and occupational exposure to arsenicals. *Am J Ind Med* 1988;13:263-70.
- Mabuchi K, Lilienfeld AM, Snell LM. Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev Med* 1980;9:51-77.
- Chen CJ, Chuang YC, Lin TM, et al. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res* 1985;45:5895-9.
- Chen CJ, Kuo TL, Wu MM. Arsenic and cancers. (Letter). *Lancet* 1988;20:414-15.
- Wu MM, Kuo TL, Hwang YH, et al. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 1989;130:1123-31.
- Chiou HY, Hsueh YM, Liaw KF, et al. Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. *Cancer Res* 1995;55:1296-300.
- Tsuda T, Babazono A, Yamamoto E, et al. Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. *Am J Epidemiol* 1995;141:198-209.
- Hopenhayn-Rich C, Biggs ML, Fuchs A, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology* 1996;7:117-24.
- Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int J Epidemiol* 1998;27:561-9.
- Smith AL, Mario G, Retina H, et al. Marked increase in bladder and lung cancer mortality in a region of north Chile due to arsenic in drinking water. *Am J Epidemiol* 1998;147:660-9.
- Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res* 1990;50:5470-4.
- Chen CJ, Chuang YC, You SL, et al. A retrospective study on malignant neoplasms of bladder, lung, and liver in blackfoot disease endemic area in Taiwan. *Br J Cancer* 1986;53:399-405.
- Chen KP, Wu HY, Wu TC. Epidemiologic studies on blackfoot disease in Taiwan. 3. Physicochemical characteristics of drinking water in endemic blackfoot disease area. *Memoirs Coll Med Natl Taiwan Univ* 1962;8:115-29.
- Chiou HY, Huang WI, Su CL, et al. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke* 1997;28:1717-23.
- Kuo TL. Arsenic content of arsenic well water in endemic area of chronic arsenic poisoning. *Rep Inst Pathol Natl Taiwan Univ* 1968;19:7-13.
- Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. The analysis of cohort studies. (IARC scientific publication no. 82). Lyon, France: International Agency for Research on Cancer, 1987:120-76.
- Cox DR. Regression models and life tables (with discussion). *J R Stat Soc [B]* 1972;34:187-220.
- Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol* 1995;141:523-30.
- Tseng WP. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect* 1977;19:109-19.
- Chen CJ, Wu MM, Lee SS, et al. Atherogenicity and carcinogenicity of high-arsenic artesian well water: multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 1988;8:452-60.
- Chen CJ, Chen CW, Wu MM, et al. Cancer potential in liver, lung, bladder, and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* 1992;66:888-92.
- Kurtio P, Pukkala E, Kahelin H, et al. Arsenic concentrations in well water and risk of bladder and kidney cancer in Finland. *Environ Health Perspect* 1999;107:705-10.
- Gerhard S. Arsenic: opportunity for risk assessment. *Arch Toxicol* 1991;65:525-31.
- Brown CC, Chu KC. A new method for the analysis of cohort studies: implication of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *Environ Health Perspect* 1983;50:293-308.
- Chu KC. Biomathematical models for cancer: a nonmathematical view of mathematical models for cancer. *J Chronic Dis* 1987;40(suppl 2):163s-70s.
- International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: genetic and related effects. An updating of selected IARC monographs from volumes 1 to 42. (Suppl 6). Lyon, France: International Agency for Research on Cancer, 1987:71-6.
- Environmental Protection Agency. Report of the expert panel on arsenic carcinogenicity: review and workshop. Washington, DC: Environmental Protection Agency, 1997.
- Waner JK, Moore LE, Smith MI, et al. Increased micronuclei in exfoliated bladder cells of individuals who chronically ingest arsenic-contaminated water in Nevada. *Cancer Epidemiol Biomarkers Prev* 1994;3:583-90.
- Larramendy ML, Popescu NC, DiPaolo JA. Induction by inorganic metal salts of sister-chromatid exchanges and chromosome aberrations in human and in Syrian hamster cell strains. *Environ Mutagen* 1981;3:597-606.
- Hsu YH, Li SY, Chiou HY, et al. Spontaneous and induced sister chromatid exchanges and delayed cell proliferation in peripheral lymphocytes of Bowen disease patients and matched controls of arseniasis-hyperendemic villages. *Mutat Res* 1997;336:241-51.