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Incidence of Transitional Cell Carcinoma Due to Arsenic in Drinking Water: a Follow-up Study of 8102 Residents in an Arseniasis-endemic Area in Northeastern Taiwan

Hung-Yi Chiou[1], Yi-Hsiang Hsu[1], Min-Li Wei[1], Chin-Hsiao Tseng[2], and Chien Jen Chen[3]

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Abbreviations: BFD, blackfoot disease; CI, confidence interval; SMR, standardized mortality ratio; RR, relative risk; SIR, standardized incidence ratio; TCC, transitional cell carcinoma

[1]School of Public Health, Taipei Medical College, Taipei, Taiwan.

[2]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

[3]Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.

Reprint requests to Dr. Chien-Jen Chen, Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, 1 Jen-Ai Road Section 1, Taipei 10018, Taiwan. Fax: 886-2-3511955; Telephone: 886-2-3970800 ext. 8359; e-mail: cjchen@ha.mc.ntu.edu.tw.

Running head: Arsenic and Transitional Cell Carcinoma

Abstract

Significant association between ingested inorganic arsenic and risk of various internal cancers, particularly bladder cancer, have been reported in our previous studies in arseniasis-endemic area in southwestern Taiwan, where many households shared only few wells in their villages. In a newly-identified arseniasis-endemic area in northeastern Taiwan, where each household has its own well to supply drinking water, the risk of transitional cell carcinoma (TCC) related to ingested inorganic arsenic was examined among a cohort of 8102 residents. Individual exposure to inorganic arsenic of study subjects was based on arsenic concentration in water of their own wells which was determined by hydride generation combined with atomic absorption spectrometry. A standardized interview was used to obtain information on history of drinking well water and risk factors for various cancers including cigarette smoking and alcohol drinking. The occurrence of cancers was ascertained by follow-up interview and data linkage with community hospital records, national death certification profile and cancer registry profile. Cox's proportional hazards regression analysis was used to estimate the multivariate-adjusted relative risk (RR) and its 95% confidence interval (CI). There was a significantly increased incidence of urinary organ cancers compared with the general population in Taiwan showing a standardized incidence ratio (95% CI) of 1.86 (1.07-3.01). A significant dose-response relation between risk of cancers of urinary organs, especially for TCC, and arsenic exposure indices was observed after adjustment for age, sex and cigarette smoking. The multivariate-adjusted RR of developing TCC was 1.9, 8.2 and 15.3, respectively, for arsenic concentration of 10.1-50.0, 50.1-100 and >100 ug/liter compared with the referent group of $\leq$10.0 ug/liter.

ingested arsenic; incidence; transitional cell carcinoma

Arsenic is a ubiquitous element widely distributed in nature and mainly transported in the environment by water. Humans are exposed to arsenic through water, air, food and beverages. Arsenic in sea food is high and 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). The maximum contamination level for arsenic in drinking water set by the US Environmental Protection Agency is 50 ug/liter. In the United States, it has been estimated that about 350,000 people may drink water contained arsenic higher than this level (3).

Arsenic has been well documented as one of the major risk factors for blackfoot disease (BFD), a unique peripheral arterial disease characterized by the severe systemic arteriosclerosis as well as dry gangrene and spontaneous amputations of affected extremities at end stages (4,5). The BFD was endemic in southwestern coast of Taiwan where residents had used high-arsenic artesian well water for more than 50 years. The dose-response relationship between ingested inorganic arsenic and BFD has been well documented (4). BFD patients have a high prevalence of arsenic-induced skin lesions including hyperpigmentation, hyperkeratosis, and skin cancers (4). They also have a high mortality from cancers of the bladder and kidney (5).

Inorganic arsenic has been well documented as a human carcinogen of skin and lung (1,2,6,7). It is also involved in the development of several other cancers in humans without showing any organotropism. Significant association between ingested inorganic arsenic and risk from cancer of the bladder has been observed in patients treated with

arsenic contained medical solution (8,9). In a small cohort study of 478 patients treated with Fowler's solution which contains 1 percent potassium arsenite, a significant association between the cumulative dose of arsenic intake and mortality from bladder cancer was observed (9). Moselle wine vintners exposed to arsenical pesticide-contaminated wine also had increased risk of the bladder cancer (10). Inhaled inorganic arsenic has also been found to be associated with an increased mortality from bladder cancer among workers in the USA and Japan (8, 11-12). There was no report examing the dose-response relationship between inhaled arsenic and bladder cancer. Excess mortality from kidney cancer has also been observed among copper smelter workers and patients treated with Fowler's solution (8). In our previous studies, an increased mortality from cancers of the all sites combined, lung, liver, bladder, kidney, skin, and prostate gland has been observed among residents in the endemic area of BFD in Taiwan (13). Age adjusted mortality for these cancer sites also have significant dose-response relationship with the arsenic level in drinking water (14). A significant dose-response relation between the long-term exposure to inorganic arsenic through drinking water and the incidence from cancer of the bladder has also been reported in our recent cohort follow-up study and in Japan (15-16). The bladder cancer relative risk for the highest group of the cumulative arsenic exposure were 3.6 (95 percent CI 1.1-12.2). More recently, an increased mortality of the bladder and kidney cancer was observed among residents in arsenic exposed regions of Argentina and Northern Chile (17-19). Argentina studies showed that the standardized mortality ratio (SMR) for cancers of the bladder and kidney were 2.1 and 1.6 for men, and 1.8 and 1.8 for women, respectively, among residents in the highest exposed areas compared with the general population of the

country. Whereas the study of Northern Chile also found SMR of developing bladder cancer of 6.0 for men and 8.2 for women.

However, long-term exposure to inorganic arsenic of our previous studies in southwestern arseniasis-endemic area was based on the median arsenic content in well water of residential villages. Because only few wells were shared by many households in villages. Lanyang Basin where arsenic level in the well water varies from undetectable (<0.15 ug/liter) to >3000 ug/liter is located in the northeast of Taiwan Island. Each household has its own well in this area, it is thus possible to assess the individual exposure to inorganic arsenic in a much more precise way. The aim of this study was to assess the dose-response relation between TCC incidence and long-term exposure to ingested inorganic arsenic through drinking well water in this newly-identified arseniasis-endemic area in northeastern Taiwan.

Subjects and Methods

Study Area

A total of eighteen villages in four townships of Lanyang Basin were included in the present study. The area included four villages in Chiaohsi Township, seven villages in Chuangwei Township, three villages in Wuchieh Township and four villages in Tungshan Township. Because of the abundance of underground water, residents in Lanyang Basin had used shallow well water (< 40 m in depth) since 1940s for more than 50 years. Although the implementation of tape water system started in study area from early 1990s, some residents are still drinking well water. The variation in arsenic levels

in well water of study area was much more striking than those in artesian well water of arseniasis-endemic area in southwestern Taiwan(20). The main source of exposure to inorganic arsenic among residents in both areas was through drinking well water.

Recruitment of Study Cohort and Determination of Arsenic Content in Well Water

The recruitment of study subjects has been described previously (21). In brief, residents aged forty years or above were recruited into the cohort under their informed consent. A total of 8102 residents, including 4056men and 4046 women, who agreed to participate were interviewed at home from October 1991 through September 1994. The standardized personal interview based on a structured questionnaire was conducted by four public health nurses who were well-trained in interview technique and questionnaire details. Information obtained from the interview included history of well water consumption, residential history, sociodemographic characteristics, cigarette smoking, alcohol consumption, physical activities, history of sun light exposure, as well as personal and family history of hypertension, diabetes, cerebrovascular disease, heart disease, and cancers. A total of 3901 well water samples (one sample from each household) were collected during home interview, acidified with hydrochloric acid immediately and then stored at -20℃ until subsequent assay. Hydride generation combined with flame atomic absorption spectrometry was used to determine arsenic concentration in these samples. The arsenic level was found to range from undetectable ($<$0.15 ug/liter) to 3.59 mg/liter. The cumulative arsenic exposure level of each study subject was derived from arsenic concentration in well water of the household and duration of drinking well water (21). However, there were 1136 study subjects whose arsenic exposure data were not available because their own wells no longer existed.

Follow-up of Cancer Incidence

The occurrence of cancer of study subjects was followed-up by annual interview and data linkage with community hospital records and national death certification and cancer registry profiles. The vital status and causes of death for all subjects in the study cohort during the entire follow-up period from initial recruitment to December 31, 1996 were verified. A total of 276 newly diagnosed cancer cases (ICD9=140-208) including 6 various cancer sites occurred during follow-up period. There were 16 urinary organs cancers (ICD9=188-189) included in these incident cancer cases. In addition, 12 transitional cell carcinoma (ICD-O: 8120/2, 8120/3, 8130/3) were confirmed by pathologists among urinary organs cancers.

Data Analyses and Statistical Methods

To compare the incidence of various cancers between residents in Lanyang Basin and general population in Taiwan, an indirect adjustment method was used to estimate the standardized incidence ratio (SIR) (22). This method used age-sex-specific incidence rates from 1991 to 1995 in Taiwan as standard rates. The expected number of incidence for a given cancer was calculated by summing up the products of age-sex-specific incidence rates of the cancer in the standard population multiplying by age-sex-specific person-years under observation in the study cohort. The SIR was derived from dividing the observed incident case number by the expected incident case number and multiplying by 100. In order to compare the difference in incidence between various groups of arsenic exposure, the arsenic level in well water of each study ho[illegible] categorized into three groups, i.e. ≤ 10, 10.1-50, and

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incidence rate of various cancers by arsenic exposure was calculated using the direct adjustment method (22). This method used age sex specific population in Taiwan as standard population. Age-sex-adjusted incidence rate was derived from dividing the expected incidence number, which was calculated by summing up the products of age-sex-specific incidence rates of the given cancer in the study cohort multiplying by age-sex-specific standard population in Taiwan, by total number of standard population. The Mantel Haenszel chi-square test was used to examine the statistical significance of the difference in SIR rate among various exposure groups (22). In order to evaluate the association between risk factors and incidence of cancers of the all sites combined, lung, and urinary organs, Cox's proportional hazards regression analysis was used to estimate the multivariate-adjusted RR and its 95 percent CI for each independent variable included various arsenic indices (23-24). The statistical significance of a multivariate-adjusted RR was examined by the significance test for regression coefficient. The interactive effect on the development of cancers of the all sites combined, lung, and urinary organs between cumulative arsenic exposure and cigarette smoking habit was also evaluated through Cox's proportional hazards regression model.

Results

A total of 8102 study subjects were recruited in the study cohort. Most subjects were aged 40 to 59 years old, 40 percent of them were cigarette smokers and 19 percent of them had an alcohol drinking habit. Among the study cohort, 41 percent were illiterate , 51 percent had an educational level of elementary school, and only 8 percent had a level of junior high school or above. They were mainly farmers and fishermen.

Table 1 shows age-specific study subjects by various arsenic concentration in well water and its median, mean and 95 percent confidence interval. There were 4148 study subjects (55.0 percent) who drink well water with arsenic concentration less than 50 ug/liter. However, there still have 640 study subjects (8.5 percent) consume well water contained arsenic greater than 300 ug/liter. The difference between median and men of arsenic concentration in well water increase with arsenic content in well water increment showing a highly variant arsenic level in well water.

Table 2 shows SIR for various cancer sites. The risk of developing cancers of the all sites combined, nasopharynx, esophagus, stomach, small intestine, colon and rectum, liver, gallbladder, nasal cavities, larynx, lung, female breast, ovary and cervix uteri, and urinary organs among study subjects were significantly higher than those in the general population in Taiwan. The significantly higher risk of developing cancers of the all sites combined, nasopharynx, esophagus, stomach, colon and rectum, gallbladder, lung, and urinary organs were observed among men. While for women, the significantly higher risk of various cancer sites were the all sites combined, stomach, colon and rectum, nasal cavities, and female breast, ovary and cervix uteri.

The age sex adjusted incidence rates of cancers which were significantly increased in this study cohort were further analyzed by arsenic level in well water. As shown in Table 3, a significant dose-response relation between age sex adjusted SIR with their 95 percent CI and various arsenic exposure indices including arsenic concentration in well water (ug/liter) and cumulative arsenic exposure (mg/liter*year) was observed for cancers of urinary organs and TCC at a significant level ($p<0.05$).

The multivariate adjusted RR of developing cancers of the urinary organs and TCC with their 95 percent CI for various risk factors included in model I and II are

illustrated in Table 4. As shown in model I, there was a statistically significant higher risk for development cancer of the urinary organs among residents who drinking well water contained arsenic concentration greater than 100 ug/liter after adjustment for age, sex, and cigarette smoking. Cumulative arsenic exposure was used as the arsenic exposure index in the Model II in table 4. Compared with residents whose cumulative arsenic exposure less than 0.9 mg/liter*year as the referent group (RR=1.0), a statistically significant higher risk for development cancers of urinary organs was also observed for residents who had long-term arsenic exposure more than 5 mg/liter*year after adjustment for age, sex, and cigarette smoking. The biological gradient was even more prominent between risk of TCC and various arsenic indices showing significant multivariate-adjusted RR of developing TCC was 1.9, 8.2 and 15.3, respectively, for arsenic concentration of 10.1-50.0, 50.1-100 and >100 ug/liter compared with the referent group of $\leqq$10.0 ug/liter and 9.1, 21.9, respectively, for cumulative arsenic exposure of 1.0-4.9 and $\geqq$5.0 mg/liter*year compared wih the referent group of less than 0.9 mg/liter*year. A dose–response relation between risk for development cancers of the urinary organs and TCC and various arsenic exposure indices was observed at highly significant level. Moreover, a statistically significant higher risk of development cancers of the urinary organs and TCC for smokers after adjustment for age, sex, and various arsenic exposure indices were also shown in this Table.

Discussion

Significant associations between ingested inorganic arsenic and various cancers have been reported in our previous studies carried out in arseniasis-endemic area in southwestern Taiwan. These case-control and ecological studies showed that long-term

inorganic arsenic exposure through water consumption increases the risk of cancers of all sites combined, lung, liver, bladder, kidney, prostate gland and skin (4-5,8,13-14,25-26). Dose-response relations between incidence rates of cancers of all sites combined, lung, and bladder and cumulative arsenic exposure were also observed in a cohort follow-up study (15). Because there were only few wells shared be residents lived in villages of arseniasis-endemic area in southwestern Taiwan, median arsenic levels in well water of study villages were used to derived the individual exposure to ingested inorganic arsenic in these studies. In other words, the cumulative arsenic exposure was estimated in a less precise way which might result in a non-differential misclassification of individual exposure. In arseniasis-endemic area in northeastern Taiwan, each household had its own well for drinking water. Because the arsenic content in wells of a given village had a striking variation, residents lived in the same village had very similar socioeconomic status, lifestyles and medical care facilities with a significant difference in exposure to ingested inorganic arsenic through consumption of well water. This natural experiment circumstance was considered most appropriate for the assessment of cancer risk associated with ingested inorganic arsenic. In this study carried out in arseniasis-endemic area in northeastern Taiwan, we found a significantly increased risk of developing cancers of all sites combined, colon and rectum, liver, lung and urinary organs. The finding was consistent with those reported previously in arseniasis-endemic area in southwestern Taiwan(13,14-15,25). Furthermore, this study also found an increased incidence rates of cancers of the nasopharynx, esophagus, stomach, small intestine, gallbladder nasal cavity and female breast, ovary and cervix uteri, which were not observed in previous studies in arseniasis-endemic area in southwestern Taiwan.

Studies in arseniasis-endemic area in southwestern Taiwan showed a dose-response relation between the long-term arsenic exposure and risk of cancers of all sites combined, liver, lung, skin, bladder, kidney and prostate gland (4,14). The arsenic level in well water was grouped into <300, 300-599 and >600 ug/liter in these studies. Whether the current safety level of inorganic arsenic in drinking water of 50 ug/liter in the United States and many other countries should be lowered has been under intensive and critical examination in recent years. However, there has never been a study aimed to examine the human cancer risk associated with ingested inorganic arsenic at a level less than 50 ug/liter in the well based on individual arsenic exposure data. It is thus important to compare cancer risk at arsenic levels in drinking water around 50 ug/liter in order to assess the necessity to implement a new standard. In this study based on a much more precise estimation of arsenic exposure, we thus analyzed the incidence rates of urinary cancer for three groups of arsenic levels of ≤10, 10.1-50 and >50 ug/liter. An increased SIR of urinary cancer was observed in groups of 10.1-50 and >50 ug/liter compared with the group of ≤10 ug/liter. Skin cancer is the major health effects of inorganic arsenic (6-7). However, our study did not find the association between risk on the development of skin cancer and arsenic exposure indices. It might be due to the underreport of skin cancer incidence in Taiwan.

A statistically significant dose-response relation was observed between two arsenic exposure indices included arsenic level in drinking water and long-term exposure to arsenic, and urinary cancer after adjustment age, sex and cigarette smoking. The biological gradient was even more prominent between risk of TCC and various arsenic indices including arsenic concentration in drinking water and cumulative arsenic

exposure. Our study also observed a significantly increased risk of cigarette smoking in the development of cancers of the urinary organs and TCC after adjustment various arsenic exposure indices. It is implied that cigarette smoking might increase risk of urinary cancer independently. Arsenic has been suggested to play a role in the promotion or progression of cancer development (27-29), although its effect on the early carcinogenesis cannot be ruled out. Our finding seems to suggest that cigarette smoking may play a role in the development of arsenic-induced urinary organs cancers and TCC especially.

Inorganic arsenic seems to be a well-documented human carcinogen of skin and several internal organs. However, limited evidence shows the carcinogenicity of inorganic arsenic in experimental animals. The discrepancy between animal and human studies might be due to the higher capability of inorganic arsenic methylation in animals than in humans (30-32). In other words, humans are more sensitive to inorganic arsenic than animals. Although inorganic arsenic is inactive or extremely weak to induce gene mutations at specific loci (6,33), the possible modes of action for inorganic arsenic carcinogenicity might include induction of chromosome abnormality, inhibition of DNA repair, induction of oxidative stress, and increase of cell proliferation (34). The genotoxicity of arsenic includes changes in chromosome structure and number, increases in sister chromatid exchanges and micronuclei, gene amplification, cell transformation, and aneuploidy (15,3337). The role of inorganic arsenic in the carcinogenesis has been hypothesized as a co-carcinogen such as promoter or progressor rather than an initiator (27-28). However, the evidence was far from adequate to draw a definite conclusion on the exact mechanism of inorganic arsenic to induce various cancers in humans. Further

studies are needed to elucidate any possible carcinogenic mechanisms of inorganic arsenic.

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References

1. World Health Organization. Environmental Health Criteria 18: Arsenic. Geneva: World Health Organization, 1981.

2. US Public Health Service. Toxicological profile for arsenic. Washington DC: US Public Health Service, 1989.

3. Smith AH, Hopehayn-Rich C, Bates MN, et al. Cancer risks from arsenic in drinking water. Environ. Health Perspect. 1992;97:259-267.

4. Tseng WP. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 1977;19:109-119.

5. 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;8:452-460.

6. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: overall evaluations of carcinogenicity (Suppl. 7). Lyon: IARC Publ, 1987:100-106.

7. US Environmental Protection Agency. Risk assessment forum. Special report on ingested inorganic arsenic: skin cancer, nutrition essentiality. Washington DC: US Environmental Protection Agency, 1988.

8. Chen CJ, Hsueh YM, Chiou HY, et al. Human carcinogenicity of inorganic arsenic. In: Abernathy CO, Calderon RL, Chappell WR. eds. Arsenic:exposure and health effects. New York: Chapman & Hall, 1997:232-242..

9. Cuzick J, Sasien, P, Evan S. Ingested arsenic, keratosis, and bladder cancer. Am J Epidemiol 1992;136:417-421.

10 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;105:173-182.

11. Bates MN, Smith AH, Hopenhayn-Rich C. Arsenic ingestion and internal cancer: a review. Am J Epidemiol 1992;135:462-476.

12.Hotta N. Clinical aspects of chronic poisoning due to environmental and occupational pollution in and around small refining spot. Jpn J Constit Med 1989;53:49-70.

13. 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;45:5895-5899.

14. Chen CJ, Wu MM, Kuo TL. Arsenic and cancers. Lancet 1988;20:414-415.

15. 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 199555:1296-1300.

16. 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.

17.Hopenhayn-Rich C, Biggs ML, Fuchs a, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. Epidemiol 1996;7:117-124.

18. Hopenhayn-Rich C, Biggs ML, Smith AL. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. Int Epidemiol Assoc 1998;27:561-569.

19. 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;147:660-669.

20. Chen KP, Wu HY, Wu TC. Epidemiologic studies on blackfoot disease in Taiwan. 3. Physicochemical characteristics of drinking water in endemic blackfoot disease area. Memoir. College of Medicine National Taiwan University, 1962;8:115-129.

21.Chiou HY, Huang WI, Su CL, et al. J. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 1997;28:1717-1723.

22. Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. The analysis of cohort studies. Lyon: International Agency for Research on Cancer, 1987.

23. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187-220.

24. Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. Lyon: International Agency for Research on Cancer, 1987:120-176.

25. 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: 888-892.

26. Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res 1990;50: 5470-5474.

27. Gerhard S. Arsenic: opportunity for risk assessment. Arch Toxicol 1991;65: 525-531.

28. 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.

29.Chu KC. Biomathematical models for cancer: A nonmathematical view of mathematical models for cancer. J Chron Dis 1987;40(Suppl. 2):163s-170s.

30. Vahter M Marafante E. Intracellular interaction and metabolic fate of arsenite and arsenate in mice and rabbits. Chem-Biol Interact 1983;47:29-44.

31. Buchet JP, Lauwerys R, Roels H. Comparison of the urinary excretion of arsenic metabolites after a single dose of sodium arsenite monomethyl arsonate or dimethyl arsinate in man. Int Arch Occup Environ Health 1981a;48:71-79 .

32. Marafante E, Vahter M. Solubility, retention and metabolism of intratracheally and orally administered inorganic arsenic compounds in the hamster. Environ Res 1987;42:72-82.

33. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans-genetic and related effects: an updating of IARC monographs. Vols 1 to 42. Suppl 6, Lyon: IARC Publ, 1987:71-76.

34. US Environmental Protection Agency. Report on the expert panel on arsenic carcinogenicity: review and workshop. Washington, DC, 1997.

35. Waner JK, Moore LE, Smith MT, et al. Increased micronuclei in exfoliated bladder cells of individuals who chronically ingest arsenic-contaminated water in Nevada. Cancer Epidemiol Biomarkers Prev 1994;3:583-590.

36. 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.

37. Hsu YH, Li SY, Chiou HY, et al. Spontaneous and induced sister chromatid exchanges and delayed cell proliferation in peripheral lymphocytes of Bowen's disease patients and matched controls of arseniasis-hyperendemic villages. Mutat Res 1997;336:241-251.

TABLE 1. Age-specific study subjects by various arsenic concentration in well water and its median, mean and 95% confidence interval (CI)

Arsenic concentration in well water (μ g/liter)	Age 40-50 No (%)†	50-60 No (%)	60-70 No (%)	70+ No (%)	Total No (%)	Median	mean	95%CI
Undetectable	137(11.6)	288(11.7)	333(13.6)	247(12.3)	1005(12.4)	0	0	3.7-3.4
Undetectable -10	221(18.8)	412(16.7)	385(15.7)	310(15.5)	1328(16.4)	2.7	3.5	3.7-3.4
10.1-50	288(24.5)	647(26.2)	637(26.0)	535(26.7)	2107(26.0)	25.4	26.8	27.3-26.3
50.1-100	108(9.2)	281(11.4)	299(12.2)	224(11.2)	912(11.3)	74.7	74.5	75.5-73.5
100.1-300	143(12.1)	286(11.6)	263(10.7)	224(11.2)	916(11.3)	139.0	162.4	166.2-158.7
300.1-600	46(3.9)	132(5.3)	109(4.4)	109(5.4)	396(4.9)	403.0	414.3	422.5-406.1
600+	56(4.8)	95(3.8)	82(3.3)	69(3.4)	302(3.7)	911.9	1216.4	1296.8-1135.9
Unknow	178(15.1)	330(13.4)	342(14.0)	286(14.3)	1136(14.0)	.	.	.
Total no(%)‡	1177(14.5)	2471(30.5)	2450(30.2)	2004(24.7)	8102(100)			

† percentage based on age-specific total study subjects

‡ percentage based on 8102 study subjects

TABLE 2. Standardized incidence ratio (SIR) with their 95% confidence interval (CI) for various cancers among residents in the northeastern arseniasis-endemic area compared with the general population in Taiwan

	Total		
Cancer site (ICD-9)	Obs.	SIR	(95% CI)
All sites combined (140~208)	**276**	**2.03**	**(1.80-2.27)***
Oral cavity and pharynx (141-149,-147)	5	1.07	(0.35-2.49)
Nasopharynx (147)	**11**	**3.43**	**(1.71-6.14)***
Esophagus (150)	**8**	**2.37**	**(1.02-4.67)***
Stomach (151)	**44**	**3.30**	**(2.40-4.42)***
Small intestine (152)	**3**	**5.02**	**(1.03-14.64)***
Colon and rectum (153,154)	**37**	**1.91**	**(1.33-2.66)***
Liver (155)	**29**	**1.55**	**(1.04-2.23)***
Gallbladder (156)	**6**	**3.18**	**(1.17-6.92)***
Pancrease (157)	5	1.91	(0.62-4.46)
Nasal cavities (160)	**3**	**5.00**	**(1.03-14.61)***
Larynx (161)	2	1.32	(0.16-4.77)
Lung (162)	**52**	**2.48**	**(1.84-3.27)***
Thymus (164)	1	2.94	(0.07-16.35)
Connective tissue (171)	2	2.97	(0.36-10.73)
Skin (173)	9	2.17	(0.99-4.11)
Female breast, overy and cervix uteri (174,180,183)	**47**	**2.52**	**(1.83-3.37)***
Prostate gland (185)	5	1.29	(0.41-3.01)
Urinary organs(188+189)	**16**	**1.86**	**(1.06-3.01)***
Bladder (188)	9	1.76	(0.81-3.34)
Kidney(189)	**8**	**2.51**	**(1.08-4.95)***
Eye (190)	1	6.18	(0.16-34.42)
Brain (191)	2	1.96	(0.24-7.06)
Thyroid gland (193)	1	0.66	(0.02-3.69)
Lymph nodes (196)	1	0.56	(0.01-3.10)
Unspecified site (199)	5	1.50	(0.49-3.50)

*$p<0.05$

TABLE 3. Standardized incidence ratio (SIR) with their 95% confidence interval (CI) for cancer of urinary organs and trainsitial cell carcinomas among residents in the northeastern arseniasis-endemic area by various arsenic exposure indices

Arsenic Exposure index	Group (person-years)	Urinary organs (188-189)			TCC		
		No	SIR	95%CI	No	SIR	95%CI
Arsenic concentration in well water (μ g/liter)	≦10.0 (7978)	1	43.6‡	(1.1- 242.9)	1	68.5‡	(1.7-381.5)
	10.1-50.0 (6697)	3	149.4	(30.8- 436.2)	1	80.9	(2.0-450.6)
	50.1-100.0 (3013)	2	218.7	(26.5- 789.3)	2	361.5	(43.7-1305.0)
	>100.0	7	466.3	(187.0-960.7)*	6	626.0	(229.7-1364.7)*
Cumulative arsenic exposure (mg/liter*year)	<0.1 (6266)	0	0‡	—	0	0‡	—
	0.1-0.9 (6168)	3	175.4	(36.1- 512.2)	1	89.0	(2.3-496.0)
	1.0-4.9 (6733)	4	199.5	(54.3- 510.7)	4	322.4	(87.7-825.3)
	5.0+ (3740)	6	504.9	(185.3-1100.7)*	5	709.4	(229.8-1653.0)*

*p<0.05

‡ p<0.01 test for trend

TABLE 4. Multivariate-adjusted relative risk (RR) and 95% confidence interval (CI) of developing cancer of urinary organs and transitional cell carcinomas among 8102 residents in the northeastern arseniasis endemic area in Taiwan

		Urinary organs		TCC	
		Model I	Model II	Model I	Model II
Variable	Group	RR (95% C.I.)	RR (95% C.I.)	RR (95% C.I.)	RR (95% C.I.)
Age	every one year increment	1.1 (1.0-1.2)*	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
	Male	0.4 (0.1-2.7)	0.4 (0.1-2.4)	0.4 (0.1-2.4)	0.3 (0.1-1.9)
Cigarette smoking	No	1.0	1.0	1.0	1.0
	Yes	15.6 (1.9-129.0)*	17.3 (2.0-148.0)*	13.3 (1.5-115.7)*	16.2 (1.8-147.9)*
Content of arsenic in well water (μ g/liter)	0-10.0	1.0‡		1.0‡	
	10.1-50.0	5.3 (0.5-54.2)		1.9 (0.1-32.2)	
	50.1-100.0	7.5 (0.6-88.4)		8.2 (0.7-98.6)	
	>100.0	16.8(1.9-146.2)*		15.4 (1.7-140.9)*	
Cumulative arsenic exposure (mg/liter*year)	<0.9		1.0‡		1.0‡
	1.0.1-4.9		2.8 (0.6-12.8)		9.1 (1.0-85.6)*
	≧5.0		7.6 (1.8-31.4)*		21.9 (2.4-199.1)*

*p<0.05

‡ p<0.01 test for trend