

Association between Multi-level Inorganic Arsenic Exposure from Drinking Water and Skin Lesions in China

Xiaojuan Guo^{1*}, Yoshihisa Fujino², Xiaolei Ye¹, Jun Liu³, Takesumi Yoshimura⁴, and Japan Inner Mongolia Arsenic Pollution Study Group

¹Department of Preventive Medicine, School of Environment and Public Health, Wenzhou Medical College, Wenzhou City, Zhejiang, 325035, China

²Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Japan

³Center for Endemic Disease Control and Research of Inner Mongolia, China

⁴Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan

*Correspondence to Dr. Xiaojuan Guo. Email: juan@med.uoeh-u.ac.jp

Received: 05 October 2005 / Accepted: 07 July 2006 / Published: 30 September 2006

Abstract: Arsenic is one of the most important toxicants in the environment. In Inner Mongolia of China, 300,000 residents are believed to be drinking water containing $>50\mu\text{g}/\text{liter}$. Skin lesions have been known as the most common consequences resulting from chronic exposure to arsenic. To clarify the prevalence of arsenic-induced skin lesions, it is important to assess the impact of this problem among the target population, and to make future planning. We evaluated the association between multi-levels inorganic arsenic exposure from drinking water and skin lesions in an arsenic-affected area in Inner Mongolia, China. One hundred nine and 32 subjects in high ($>50\mu\text{g}/\text{liter}$) and low ($<50\mu\text{g}/\text{liter}$) arsenic-affected villages were recruited and had the detailed physical examination with special emphasis on arsenic-related skin lesions. Arsenic exposure was measured for each participant with respect to iAs concentration of primary well and the duration using the well. Arsenic-induced skin lesions including keratosis, pigmentation, and/or depigmentation were diagnosed in 56 and 3 subjects in the two villages, respectively. Logistic regression was conducted to calculate odd ratios of skin lesions associated with arsenic exposure with adjustments for sex, age group, smoking and duration of exposure. A consistent dose-response relationship between arsenic exposure level and skin lesion risk was observed. Compared to those with iAs concentration $<50\mu\text{g}/\text{liter}$, the adjusted odds ratios of skin lesions for the subjects with 51-99, 100-149 and $>150\mu\text{g}/\text{liter}$ were 33.3% (OR =15.50, 95% CI: 1.53-248.70), 46.7% (OR =16.10, 95% CI: 3.73-69.63) and 55.7% (OR= 25.70, 95% CI: 6.43-102.87), respectively. Duration of using well was not associated with increased risk of skin lesions in this population; (OR=1.68, 95% CI: 0.40-6.91 for 6-15 years, OR = 2.30, 95% CI: 0.58-9.14 for over 15 years) compared with the duration of less than 5 years.

Keywords: Inorganic arsenic, Arsenic exposure, Skin lesions, Dose-response relationship

Introduction

Arsenic is one of the most important toxicants in the environment. In the 20th century, arsenic exposure from drinking water has been recognized as one of the most serious public health issues in terms of the severity of associated adverse health effects, and high prevalence in many countries, such as Argentina, Bangladesh, Chile, Hungary, India, Mexico, Peru, Thailand, and the United States of America were found [1, 2]. In Inner Mongolia of China, arsenic-related health problems from the use of

groundwater for drinking were first recognized in the region in 1990 [3], and around 300,000 residents are believed to be drinking water containing arsenic $>50\mu\text{g}/\text{liter}$ [4].

Chronic ingestion of inorganic arsenic has been known to cause adverse health effects to human beings. Keratosis, hyperpigmentation and depigmentation are the most common clinical manifestations of skin lesions, and they play an important role in the diagnosis of arsenic poisoning [5]. The World Health Organization (WHO) has articulated that skin lesions are often used as the useful precursors of

the more severe effects like skin cancer or other internal organs. Proper epidemiological study comparing their incidence in arsenic exposed and control population with similar age, sex and socioeconomic status needs to be carried out. This will help in identifying specific clinical features which could be considered diagnostic of chronic arsenic toxicity [6].

Our 1996 survey indicated that up to 26 percent of wells or other water sources with arsenic concentrations equal to or higher than 50 µg/liter in Hetao plain area of Inner Mongolia and the highest arsenic level was 1354 µg/liter. Moreover the prevalence of skin lesions was 44% [7]. Some of the patients showed the skin lesion with keratosis, and other people with both keratosis and pigmentation. It needs to be emphasized that many villagers remain asymptomatic in spite of drinking arsenic contaminated water for many years. However, there are not sufficient epidemiological studies clarifying the associations between skin lesions and arsenic exposure. Such studies are important to assess the impact of this problem among the target population, and to make future planning. The purpose of this study was to examine the prevalence of skin lesions in the arsenic affected villages and the associations among arsenic dermatosis, arsenic concentration in drinking water, and exposure duration.

Methods

Study Population

The study was conducted at an arsenic-affected village in Wuyuan county of Inner Mongolia, China in September 2000, where there was no industry or mining. All irrigation water was drawn from the Yellow River. In this village four public open-shallow wells (depth ~3-5 m) were used for drinking water until the 1970s, but the villagers have used private tubule-type wells (depth ~ 15-30 m) because of hygienical reasons since 1980.

In this study, 129 (90.2%) of the 143 inhabitants in the arsenic-affected village participated. The total numbers of inhabitants in the village are based on the registered records in the local government office of Wuyuan County. After the local government personnel explained the purpose and asked for participation, the subjects were given written, informed consent. As control, 32 of 36 people (88.9%) who living neighboring small village while the survey was conducting participated in our investigation, whose well water sources like the arsenic-affected village, but arsenic contained <50µg/liter. Of the participants, 109 and 32 adults engaged in agriculture were aged \geq 18 years and were therefore included in our analysis in the arsenic-affected village and control village, respectively.

Interviews and Skin Examination

Subjects were invited to participate in a survey enquiring about socio-demographic conditions, residential history, occupation, working conditions, duration of using tube-well and health-related lifestyle habits, such as:

smoking and alcohol consumption. After the interviews, subjects were also invited to undergo a skin examination by an expert physician. The skin disorders were diagnosed by the Chinese physicians using their established clinical criteria for the survey [8]. Subjects who had obvious skin abnormalities, including hyperkeratosis of the palms and soles, hyperpigmentation or leukomelanosis of the torso and limbs were diagnosed as having arsenic dermatosis. At the time of skin examination, the physician was not informed what the subjects answered to the interviews.

In order to reduce the observation bias all of the subjects were examined by one physician and one interviewer. The subjects generally had known the fact that the village was affected by arsenic, but the subjects as well as the investigators had not been informed about the individual arsenic levels in their tube-well until all examinations were completed.

Water Sample Collection

The field team collected water samples from all tube wells used by participants for at least 6 months in the last 20 years. Samples were collected from all of 49 and 7 tube-wells in the arsenic-affected village and control, respectively. Water samples were stored in a cooler containing an ice block and transported to the laboratory in Wuyuan. The water samples were then kept frozen at -20°C until they were transported on dry ice to the Miyazaki University of Japan for arsenic analysis. Total iAs was determined using an atomic absorption spectrophotometer with an Arsenic Speciation Pretreatment System (Model No: AA-6800, ASA-2sp; Shimadzu Corporation, Kyoto, Japan). The standard reference materials were Arsenic Standard Solution (Wako Pure Chemical Industries, Ltd). Detection limit for iAs is 1.0, and the values under the detection limit were accounted as 0, rather than missing.

Statistical Analyses

Information about tube well usage at each residence and work site and the results of the arsenic measurements were used to construct arsenic exposure histories. Descriptive analyses were conducted by comparing general characteristics, mean arsenic concentrations, and the number of tube wells used by the subjects. Logistic regression was used to estimate the odds ratio (OR) for arsenic dermatosis. The model included age, sex, and the levels of arsenic in drinking water. The multi-level of exposure level was classified into four groups: \leq 50µg/liter, 51-99µg/liter, 100-149 and $>$ 150µg/liter. We selected \leq 50µg/liter as a reference for the analysis because the permitted standard of arsenic in drinking water is \leq 50µg/liter in China. The ORs of exposure duration for arsenic dermatosis were also estimated, dividing the duration of exposure into three levels (less than 6 years, 6-15 years, and over than 15 years). In all analyses, age was included as a continuous variable. Calculations were performed using StataSE 8.0.

Results

Table 1 shows descriptive characteristics of the 141 subjects in arsenic affected village and control village. The mean age, sex ratio and mean number of years of using well-water were similar in both groups. More subjects in the control village were smokers. Mean arsenic concentration in drinking water in the arsenic-affected village was 150.2µg/liter (SD= 36.0), and the maximum level was 197.3µg/liter. Although arsenic concentration of well-water was less than 50µg/liter, the maximum of 18.7µg/liter arsenic concentration was detected in the control village. There were 56 and 3 cases of skin lesions including keratosis, pigmentation, and/or depigmentation were diagnosed in two villages, respectively.

Table 1: The characteristics of the subjects in the present study.

Subjects	Arsenic-affected village n = 109	Control village n = 32
Sex (%)		
Male	59 (54.1)	16 (50.0)
Female	50 (45.9)	16 (50.0)
Age in years (mean SD*)	43.1 (13.4)	42.1 (10.1)
Smoker (%)		
Never smoked	59 (54.1)	15 (46.9)
Current smoked	50 (45.9)	17 (53.1)
Arsenic exposure levels (mean (SD))	150.2 (36.0)	5.4 (5.1)
Range of arsenic exposed (µg/liter)	2.3-197.3	1-18.7
No. of years of using well (mean SD*)	14.1 (7.1)	11.8 (7.0)

* SD, standard deviation

Table 2 shows the distribution of prevalence of skin lesions among the subjects by sex and age groups in arsenic affected village and control village. In arsenic affected village, the prevalence of skin lesion was the highest in the group aged 50-59 years both for males and females, and was slightly higher in males (57.6%) than in females (44.0%) (p = 0.217). There were 3 cases with keratosis in control village. Compared with arsenic affected village, cases of skin lesion in control village were younger (30-39 years group) males and females. The prevalence was 6.3% for males and 12.5% for females.

Table 2: Distribution of the prevalence of skin lesions by sex and age group among subjects

Age group	Arsenic-affected village			Control village		
	No. of subjects	No. of cases	Prevalence (%)	No. of subjects	No. of cases	Prevalence (%)
<i>Male</i>						
18-29	9	1	11.1	1	0	0.0
30-39	13	6	46.2	6	1	16.7
40-49	21	16	76.2	4	0	0.0
50-59	9	7	77.8	4	0	0.0
60-	7	4	57.1	1	0	0.0
Total	59	34	57.6	16	1	6.3
<i>Female</i>						
18-29	8	1	12.5	1	0	0.0
30-39	15	8	53.3	8	2	25.0
40-49	15	8	53.3	3	0	0.0
50-59	6	4	66.7	4	0	0.0
60-	6	1	16.7	0	0	0.0
Total	50	22	44.0	16	2	12.5
<i>Both sexes</i>						
18-29	17	2	11.8	2	0	0.0
30-39	28	14	50.0	14	3	21.4
40-49	36	24	66.7	7	0	0.0
50-59	15	11	73.3	8	0	0.0
60-	13	5	38.5	1	0	0.0
Total	109	56	51.4	32	3	9.4

Table 3 shows the prevalence of skin lesion in 141 subjects divided according their residential village, sex, smoking and drinking, as well as levels of arsenic exposure and the use length of well-water. In the arsenic affected village there was a significantly higher prevalence of skin lesion (OR=10.21, 95% confidence interval [CI]:2.68-38.97) than in the control village. Associations among skin lesions risk and smoking and drinking did not occur. Logistic regression was conducted to calculate prevalence odds ratios of skin lesions by levels of arsenic exposure and duration of using well. A consistent dose-response relationship between arsenic exposure level and skin lesion risk was observed. Compared to those exposed to iAs concentration <50µg/liter, the prevalence odds ratios of skin lesions for subjects with 51-99µg/liter, 100-150µg/l and >150µg/liter were 33.3% (OR =3.88, 95% CI: 0.49-30.59), 46.7% (OR =6.78, 95% CI: 1.70-27.10), and 55.7% (OR=9.75, 95% CI: 2.74-34.67), respectively. Compared with the duration of using well less than 5 years, the prevalence odds ratios of skin lesions for subjects with 6-15 years and >15 years were 43.9% (OR =2.68, 95% CI: 0.91-7.88) and 49.3% (OR =3.33, 95% CI: 1.22-9.07).

Table 3: The Odds Ratios and 95% Confidence Intervals, from logistic regression analysis, for skin lesions

Subjects	No. of subjects	Prevalence of skin lesions %	OR*	95% CI*	P
Village					
Control village	32	9.4	1.00		
Arsenic affected village	109	51.4	10.21	2.68, 38.97	0.000
Sex					
Male	75	46.7	1.00		
Female	66	36.4	0.65	0.33, 1.29	0.217
Smoking					
Never	74	45.9	1.00		
Current	67	37.3	0.70	0.36, 1.38	0.301
Drinking					
No	89	40.4	1.00		
Yes	51	43.1	2.45	0.80, 7.49	0.103
Levels of arsenic in well					
As \leq 50 μ g/l	35	11.4	1.00		
51-99 μ g/l	6	33.3	3.88	0.49, 30.59	0.166
100-149 μ g/l	30	46.7	6.78	1.70, 27.10	0.001
150 μ g/l<	70	55.7	9.75	2.74, 34.67	0.000
Duration of exposure					
1-5 years	31	22.6	1.00		
6-15 years	41	43.9	2.68	0.91, 7.88	0.062
15< years	69	49.3	3.33	1.22, 9.07	0.013

*OR, odds ratio; CI, confidence interval

After adjusting for sex, age group, smoke and duration of using well, the association between water arsenic concentration and skin lesion showed a significant increasing linear trend with increasing level of arsenic exposure (Table 4). The odds ratio for the highest arsenic level compared with the lowest was 25.70 (95% CI: 6.43-102.87). However, significantly elevated odds ratios were not found for those who had used their well 6-15 years (OR=1.68, 95% CI: 0.40-6.91) as well as for those who had

used well for 15 years more (OR=2.30, 95% CI: 0.58-9.14), compared with those who used their well less than 5 years.

Table 4: Multivariate-adjusted Odds Ratios, from logistic regression analysis, for levels arsenic exposure and skin lesions

Levels/ Exposure	No. of skin lesions	Adjusted OR ^{a,b}	95% CI	P	P for trend
Levels of arsenic in well^a					
As \leq 50 μ g/l	4	1.00			
51-99 μ g/l	2	15.50	1.53, 248.70	0.022	
100-149 μ g/l	14	16.10	3.73, 69.63	0.000	
150 μ g/l<	39	25.70	6.43, 102.87	0.000	0.000
Duration of exposure^b					
1-5	7	1.00			
6-15	18	1.68	0.40, 6.91	0.471	
15<	34	2.30	0.58, 9.14	0.236	0.119

*OR, odds ratio; CI, confidence interval

^aAdjusted for sex, age group, smoke, duration of exposure.

^bAdjusted for sex, age group, smoke.

Discussion

The present study designed to assess the prevalence of skin lesion associated with level and duration of arsenic exposure and skin lesions in Inner Mongolia. Most of well arsenic concentration in the village was above China drinking water standard (50 μ g/liter), the maximum was 197.3 μ g/liter. The prevalence of arsenic dermatosis was 41.8 % (46.7% for males, 36.4% for females). Despite the arsenic exposure level in drinking water was not remarkably high in the arsenic affected village, comparing with the areas reported by others, and the prevalence of skin lesion was higher. Such as in Bangladesh, Ahsan *et al.* [9] conducted a cross-sectional study in three rural villages. Out of 167 subjects, the prevalence of hyperpigmentation and keratosis was 22%. In India, Mazumder reported that age-adjusted prevalence of hyperpigmentation for males was 0.4 % in the lowest arsenic level (< 50 μ g/liter), and 22% in the highest level (>800 μ g/liter) [10]. In Huhhot area, a capital city area of Inner Mongolia, 3,228 villagers in where the highest arsenic level in water was 2,000 μ g/liter were investigated, the prevalence of keratosis and pigmentation was 5.4% and 3.8%, respectively, and the prevalence of any arsenic dermatosis was 6.3 % in Tucker's report in 2001 [11]. These reports concerning prevalence of arsenic dermatosis were low compared with our results. Currently, there are not universal diagnosis criteria for arsenic dermatosis, which is generally diagnosed by inspections. Inspection method tends to be subjective, and

observation bias can not be avoided in any way. For instance, in Tucker's report, the skin disorders were diagnosed using their own established clinical criteria [11] for keratosis, pigmentation. The term keratosis in this report referred to obvious thickening of skin on the palms and soles in palpable or Wart-like bumps ranging in size from about 0.2 to 1.5 cm or larger, either separated or coalesced. Pigmentation referred to coarse skin with moderately-sized spots of pigmentation, distributed in a web-like form. In our studies, the patients suffering from arsenic dermatosis were identified by referring to the clinical diagnostic standard of endemic arsenic poisoning in Inner Mongolia [8]. The standard is no size limit of keratosis. Thus, when compared to the previous studies that were conducted by the same examiner of the present study, similar prevalence rates are obtained. In 1996, we conducted a cross-sectional study of 433 residents at Hetao Plain and of 1176 residents at Alashan area in Inner Mongolia [7]. The prevalence rates of these two areas were 45% and 37%, respectively. The different diagnostic criteria in each country or area are the possible reasons to bring the diversity of prevalence rates of arsenic dermatosis.

Nevertheless, for dose-response relationships between arsenic dermatosis and the levels of arsenic, the present result is consistent with the previous reports. Haque *et al.* investigated 192 cases of arsenic dermatosis and 213 controls matched by age and sex in West Bengal, India and examined the dose-response relationship of skin lesions [12]. The ORs of arsenic dermatosis were 3.1 for 50-99 $\mu\text{g}/\text{liter}$, and 5.0 for 100-199 $\mu\text{g}/\text{liter}$, when compared with the arsenic levels of <50 $\mu\text{g}/\text{liter}$. Comparing with those dose-response relationships, there were higher ORs of 15.50 for 51-99 $\mu\text{g}/\text{liter}$, and 25.70 for >150 $\mu\text{g}/\text{liter}$ in our results. On the other hand, if villagers had begun to use the tube wells at young age, due to their highly labour intensity and consumption of large quantity of drinking water, their long-term arsenic accumulation and capability of arsenic toxicosis were high. It might explain that prevalence of skin lesions was high in villagers of 40 years of age or older. However, the people who are exposed to arsenic in drinking water longer do not show more likely to have skin lesions.

Recently, in China, the population at high risk is reported to be more than 4.5 million with over 35,000 confirmed arsenicosis patients. The arsenic concentration in wells as drinking water source was reported in the range of 200-2000 $\mu\text{g}/\text{liter}$ with the highest level at 4440 $\mu\text{g}/\text{liter}$ [13]. However, the arsenic affected area with less than 200 $\mu\text{g}/\text{liter}$ as the highest arsenic concentration, like the present study area is uncommon. Relative health effect study has not been previously reported and is important because of the potential for large numbers of people to likely be exposed to low-level arsenic. In addition, the dose of arsenic in drinking water induced skin lesions always is a topic in China. The association we observed with multi-level arsenic exposure and skin lesions, further supports the potential for adverse health effects in people exposed to low arsenic concentrations.

Conclusion

The findings of this study reinforce the significant impact of arsenic problem in Inner Mongolia. A higher prevalence of skin lesions (41.8%) in the study area was discovered, where range of arsenic exposed concentration was 2.3-197.3 $\mu\text{g}/\text{liter}$. A consistent dose-response relationship between arsenic exposure level and skin lesion risk was observed. Moreover, the level of arsenic exposure is likely more important than the duration of arsenic exposure with regard the risk of skin lesion in this population.

Acknowledgment: This JIMAP study has been partly supported by the Core Research for Evolutional Science and Technology (CREST) program of Japan Science and Technology Corporation (JST).

Reference

1. World Health Organization. ARSENIC IN DRINKING WATER: Fact Sheet No 210, **2001**, Available, <http://www.who.int/mediacentre/factsheets/fs210/en/>.
2. IPCS: Summary. In: IPCS, editor. Environmental Health Criteria 224: Arsenic and Arsenic Compounds. Second ed. Geneva: *World Health Organization*; **2001**, pp. 1-8.
3. Luo, Z. D.; Zhang, Y. M.; Ma, L.; Zhang, G. Y.; He, X.; Wilson, R.; Byrd, D. M.; Griffiths, J. G.; Lai, S.; He, L.; Grumski, K.; Lamm, S. H.: Chronic Arsenicism and Cancer in Inner Mongolia -Consequences of Well-Water Arsenic Levels Greater than 50 mg l-1." In: C. O. Abernathy, R. L. Calderon, and W. R. Chappell, eds., *Arsenic Exposure and Health Effects London: Chapman and Hall*, **1997**, 55-68.
4. Ma, H. Z.; Xia, Y. J.; Wu, K. G.; Sun, T. Z.; Mumford, J. L.: Human Exposure to Arsenic and Health Effects in Bayingnormen, Inner Mongolia." In: W. R. Chappell, C. O. Abernathy, and R. L. Calderon, eds., *Proceedings of the Third International Conference on Arsenic Exposure and Health Effects. Amsterdam: Elsevier*, **1999**, 127-131.
5. Tseng, W. P.; Chu, H. M.; How, S. W.; Fong, J. M.; Lin, C. S.; Yeh, S.: Prevalence of cutaneous cancer in an endemic area of chronic arsenicism in Taiwan. *J Nat Cancer Inst*, **1968**, 40:453-463.
6. World Health Organization, Chapter4: Diagnosis and treatment of chronic arsenic poisoning, **2000**, pp: 30.
7. Guo, X. J.; Fujino, Y.; Kaneko, S.; Kegong, Wu.; Yajuan, Xia; Takesurni, Y.: Arsenic contamination of groundwater and prevalence of arsenical dermatosis in the Hetao plain area, Inner Mongolia, China. *Mol Cell Biochem*, **2001**, 222(1-2): 137-40.
8. The Office for Control and Treatment of Endemic of the Hygiene Ministry of China. Clinical Diagnostic criteria for arsenism in Inner Mongolia. *J Endem Dis Cont Treat in Inner Mongolia* **1994**, 19: third page in cover.
9. Ahsan, H.; Perrin, M.; Rahman, A.; Parvez, F.; Stute M.; Zheng, Y.; Milton, A. H.; Brandt-Rauf, P.; van Geen, A.; Graziano, J.: Associations between drinking water and

- urinary arsenic levels and skin lesions in Bangladesh. *J Occup Environ Med*, **2000**, *42*(12): 1, 195-201.
10. Mazumder, D. N.; Das Gupta, J.; Santra, A.; Pal, A.; Ghose, A.; Sarkar, S.: Chronic arsenic toxicity in west Bengal--the worst calamity in the world. *J Indian Med Assoc*, **1998**, *96*(1): 4-7, 18.
 11. Tucker, S.: Relationship between consumption of arsenic-contaminated well water and skin disorders in Huhhot, Inner Mongolia, **2001**, Available, http://phys4.harvard.edu/%7Ewilson/inner_mongolia.html
 12. Haque, R. ; Mazumder, D. N. ; Samanta, S. ; Ghosh, N. ; Kalman, D. ; Smith, M. M.; Mitra, S.; Santra, A.; Lahiri, S.; Das, S.; De, B. K.; Smith, A. H.: Arsenic in drinking water and skin lesions: dose-response data from West Bengal, India. *Epidemiology*, **2003**, *14*(2):174-82.
 13. Zheng, B. S.; Ding, Z. H.: Issues of Health and Disease Relating to Coal Use in Southwestern China, *Int. J. Coal Geol*, **1999**, *40*, 119-132.