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Urinary arsenic profiles and the risks of cancer mortality: A population-based 20-year follow-up study in arseniasis-endemic areas in Taiwan

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ABSTRACT

Few studies investigated the association between chronic arsenic exposure and the mortality of cancers by estimating individual urinary arsenic methylation profiles. Therefore, we compared with the general population in Taiwan to calculate the standardized mortality ratio (SMR) in arseniasis-endemic area of Taiwan from 1996 to 2010 and evaluated the dose-response relationships between environmental arsenic exposure indices or urinary arsenic profiles and the mortality of cause-specific cancer. A cohort of 1563 residents was conducted and collected their urine sample and information regarding arsenic exposure from a questionnaire. All-cause death was identified using the National Death Registry of Taiwan. Urinary arsenic profiles were measured using high performance liquid chromatography–hydride generator–atomic absorption spectrometry. We used Cox proportional hazard models to evaluate the mortality risks. In results, 193 all-site cancer deaths, and 29, 71, 43 deaths respectively for liver, lung and bladder cancers were ascertained. The SMRs were significantly high in arseniasis-endemic areas for liver, lung, and bladder cancers. People with high urinary InAs% or low DMA% or low secondary methylation index (SMI) were the most likely to suffer bladder cancer after adjusting other risk factors. Even stopping exposure to arsenic from the artesian well water, the mortality rates of the residents were higher than general population. Finally, urinary InAs%, DMA% and SMI could be the potential biomarkers to predict the mortality risk of bladder cancer.

1. Introduction

Inorganic arsenic is a well-documented potent human carcinogen. Chen et al. (1988b) point out the significant dose-response relationships between arsenic level in drinking water and age-adjusted mortality for cancer of bladder, kidney, skin, prostate, lung and liver in the arseniasis townships of Peimen, Hsuechia, Putai and Iche from 1973 to 1986. In addition, this significantly higher adjusted mortality of cancer was observed in the residents of arseniasis-endemic area than in the general population in Taiwan.

Arsenic in drinking water exists mostly in the form of arsenate (iAs^{5+}) (Andreae, 1977). Once it enters the human body, iAs^{5+} is reduced to arsenite (iAs^{3+}) and bio-transformed to monomethylarsonic acid (MMA^{5+}) and dimethylarsinic acid (DMA^{5+}). This transformation occurs mainly in the liver and these metabolites are ultimately excreted in the urine (Vahter, 2002). Metabolism of inorganic arsenic was previously considered a detoxification mechanism, but increasing evidence suggests that trivalent methylated arsenic species may be more toxic than inorganic arsenic species (Lin et al., 1999). Therefore, the relative proportion of urinary arsenic metabolites is often used as a biomarker of arsenic methylation capacity. Subjects with low ratio of DMA^{5+} and MMA^{5+} combined with high cumulative arsenic exposure (CAE) had a higher bladder cancer risk (Chen et al., 2003). Our previous follow-up study demonstrated an inverse dose-response relationship between DMA^{5+}% and the risk of urothelial carcinoma in an arseniasis-endemic area (Huang et al., 2008). Similar findings pointed out that poor urinary arsenic profiles (including high total arsenic or high MMA% or low DMA%) were related to arsenic-related cancer in other areas of Taiwan and other

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countries (Pu et al., 2007; Steinmaus et al., 2010; Melkonian et al., 2011).

Mortality rates of heart diseases, cancers and other diseases have increased among arsenic-exposed populations in Taiwan, Chile, Argentina and Bangladesh (Hopenhayn-Rich et al., 1996; Chen et al., 1996; Smith et al., 1998, 2011; Sohel et al., 2009). However, these studies assessed arsenic exposure using the average arsenic concentration of well water, the duration of drinking artesian well water (year) or the CAE as individual arsenic exposure indices. Recently, prospective cohort studies from Bangladesh evaluated the positive association between total urinary arsenic and mortalities of all-cause and chronic disease as well as cardiovascular disease (Argos et al., 2010; Chen et al., 2011). However, the dose-response relationship between all-site cancer mortality and arsenic methylation capability remains to be defined.

Residents in the arseniasis-endemic area have been not using artesian wells water (100–200 m deep) until a tap water supply system was implemented in early 1970s in Taiwan (Chen et al., 1962). They exposed the arsenic level in drinking water ranging from 0.010 to 1.752 ppm. Concerning about the increasing risk of arsenic-related blackfoot disease, artesian well water was no longer used for drinking and cooking after the mid-1970s (Chen et al., 1992). Previously we constructed a cohort since 1988 and 1989 in the arseniasis-endemic area that residents stopped drinking artesian well water about 20 years when they were recruited. Therefore, we want to construct a prospective study and compare the standardized mortality ratio (SMR) in the arseniasis-endemic area with those in Taiwan to examine the long-term health effects of residents. Further, we explore the relations between urinary arsenic profiles and the risks of all-site cancer and cause-specific cancer mortality.

2. Methods

2.1. Study area and study cohorts

From 1988 to 1989, Chen et al. (1996) constructed a cohort of residents from the arseniasis-endemic areas of Homei, Fuhsin, and Hsinming in Putai Township of the southwestern Taiwan to assess the health hazards of long-term arsenic exposure. This endemic area included three villages with the highest prevalence of blackfoot disease (BFD). The median arsenic concentration of the artesian well water ranged from 0.7 to 0.93 mg/L measured in the early 1960s. The detailed procedure of the study design has been described previously (Chen et al., 1995). Briefly, there were 2258 residents (30 years or older) registered in household registration office and about 70% of this cohort subjects ($n=1571$) were eligible and lived 5 or more days a week in the arseniasis-endemic area. Excluding eight with missing information on the questionnaire, there were 1563 study subjects followed and analyzed in this study. The Institutional Review Board of National Taiwan University approved this study.

2.2. Questionnaire interview and biological specimen collection

Two well-trained public health nurses carried out a standardized personal interview using a structured questionnaire. Detailed information on demographics and socioeconomic characteristics, lifestyle-related risk factors such as cigarette smoking and alcohol consumption, residential and occupational history, and history of drinking well water were obtained (Chen et al., 1988a,b). Urine samples of 1078 subjects were collected at the time of recruitment from 1988 to 1989 and immediately transferred to a $-20\,^{\circ}C$ freezer until required for urinary arsenic profile analyses.

2.3. Follow-up of cancer mortality

The follow-up period for study subjects began from September 1988 and June 1989 to 31 December 2009. The mean length of follow-up was approximately 17.8 years. The information regarding all-cause death was identified by the subjects' unique national identification numbers, which were linked to the National Death Registry of Taiwan, which records the deaths of all citizens. Of total 1563 subjects, 545 participants died during follow-up. According to the code numbers of death certificates, 193 died from all-site cancer (ICD 9, 140–208). Among these 193 subjects, the predominant cancer deaths included 29 from liver cancer (ICD 9, 155.2), 71 from lung cancer (ICD 9, 162), and 43 from bladder cancer (ICD 9, 188).

2.4. Cumulative arsenic exposure assessment

The duration of drinking artesian well water (years) and complete histories of residential address were obtained from the questionnaire. The information of median arsenic level in artesian well water of each village was acquired from previous studies carried out in the early 1960s (Lai et al., 1994). Because some study subjects had moved from one village to another, there were different of the arsenic concentrations in artesian well water of these villages. For individual, CAE (mg/L × years) was derived to reflect long term arsenic exposure by summarizing the products obtained from multiplying the median arsenic level in artesian well water (mg/L) by the duration of drinking water (years) during consecutive periods of living in different villages. The detailed calculation was described elsewhere (Chen et al., 1996). The average arsenic concentration in artesian well water (mg/L) was derived by the CAE divided the sum of duration of drinking artesian well water in the village (years). Both CAE and average arsenic concentration in artesian well water were not available if the median arsenic level in artesian well water of each village was unknown. Calculated CAE data were available in total 1191 subjects after excluding subjects with incomplete information of arsenic exposure in the questionnaire.

Urinary arsenic species measurement Concentrations of urinary arsenic profiles were measured by high-performance liquid chromatography equipped with a hydride generator and atomic absorption spectrometer (HPLC–HG–AAS). Details of the experimental procedure were described in Hsueh et al. (1998). Freeze-dried SRM 2670 urine containing 480 ± 100 μg/L arsenic was acquired from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA). It was analyzed along with the urine samples from subjects as a standard. The mean value of SRM 2670 determined by our system was 507 ± 17 μg/L ($n=4$). Recovery rates ranged from 93.8 to 102.2% for iAs^{3+}, DMA^{5+}, MMA^{5+}, and iAs^{5+} with detection limits of 0.02, 0.08, 0.05, and 0.07 μg/L, respectively. All arsenic assays were performed within 6 months of sample collection to maintain the stability of urinary arsenic profiles (Chen et al., 2002).

2.5. Statistical analysis

We calculated standardized mortality ratios (SMR) for cancers of the all-site, liver, lung, and bladder, separately for males and females. We calculated expected deaths for each cancer based on cancer mortality rates in the vital statistics of Taiwan from 1996 to 2010, stratified by 5-year age groups, from 30–34 to 80–84 years stratum and calculated the gender- and age-specific rates. We multiplied these gender- and age-specific rates by the number of male and female of arseniasis-endemic area cohort to obtain the expected deaths for the study period. The ratios of the observed to expected death (O/E) by cause of death and gender were the SMRs. We calculated 95% confidence intervals (CI) based on the method of Breslow and Day (Breslow and Day, 2011). The 1976 world population was used as the standard population to compare successfully the results with other investigations. Total urinary arsenic level (μg/L) was calculated as the sum of iAs^{3+}, iAs^{5+}, MMA^{5+} and DMA^{5+} levels in urine. InAs ($iAs^{3+} + iAs^{5+}$) %, MMA% and DMA% were calculated by dividing the concentration of each arsenic species by the total urinary arsenic concentration, which were further multiplied by 100. The value of primary methylation indices (PMI) was defined as the ratio between MMA^{5+} and InAs ($iAs^{3+} + iAs^{5+}$) levels, and the secondary methylation index (SMI) was defined as the ratio between DMA^{5+} and MMA^{5+}. The person-years of follow-up for each subject was calculated from the date of recruitment to the date of death due to all causes or the last date that linked their identification numbers to the National Death Registry on 31 December 2009 if no censoring event occurred. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) of mortality. The cutoff values for different arsenic exposure indices and urinary arsenic profiles were the respective tertiles of the controls. SAS statistical package (SAS, version 9.1, Cary, NC) was used for all data analyses.

3. Results

Average age at recruitment of 1563 residents was 48.88 years (standard error 0.28). The frequency of male and smokers were 45.1% and 25.5%, respectively. A total of 558 (35.7%) were illiterate, 741 (47.4%) had an educational level of elementary school and 260 (16.6%) had a level of junior high school and above. During an average follow-up period of 17.8 years, 193 of 1563 residents (12.3%) enrolled in our study died due to all-site cancers. Among 193 subjects with all-site cancers deaths, 29 (15%), 71 (37%), and 43 (22%) deaths were separately for liver, lung, and bladder cancer. The SMRs and 95%