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Associations between arsenic in drinking water and occurrence of end-stage renal disease with modifications by comorbidities: A nationwide population-based study in Taiwan

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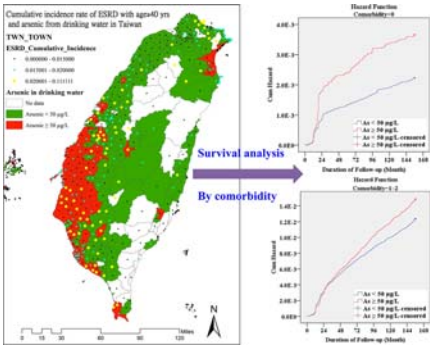
HIGHLIGHTS

- Arsenic may affect renal function, but studies on its renal toxicity are limited.
- We studied the association between [As] in drinking water and renal disease.
- We used data from national health insurance and a drinking water survey in Taiwan.
- Arsenic exposure was associated with the risk of end-stage renal disease (ESRD).
- The effect was modified by comorbidities, which should be treated in early stages.

GRAPHICAL ABSTRACT



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ABSTRACT

Arsenic may affect the function of proximal convoluted tubules and glomeruli, but epidemiological data on the association between arsenic ingestion and end-stage renal disease (ESRD) are limited. Therefore, we conducted a nationwide population-based study in Taiwan, where the incidence of ESRD is the highest in the world, to study the potential association. Using the National Health Insurance Database in Taiwan, we constructed a cohort of 362,505 members with age ≥ 40 years in 1998. We identified patients of ESRD newly diagnosed between January 1, 1998 and December 31, 2010 and performed Cox proportional hazard regressions to identify risk factors for ESRD and evaluate their effects. Arsenic levels in drinking water were assessed on the basis of a nationwide census survey conducted by the government, of which measurement reports were available for 311 townships. We identified 5442 new patient of ESRD during the study period and found that residents of areas with arsenic levels ≥ 50 μg/L in the drinking water had a hazard ratio (HR) of 1.14 (95% confidence interval [CI]: 1.08–1.21) for ESRD. After adjusting for sex, age, income, and comorbidities, we found an adjusted HR of 1.12 (95% CI: 1.06–1.19), which was still statistically significant. Furthermore, the effect was modified by comorbidities, with more

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prominent effects on patients with less than three comorbidities (adjusted HR = 1.51; 95% CI: 1.22–1.86 for low comorbidity score). In conclusion, a high arsenic level in drinking water was a risk factor for ESRD, independent of other documented risk factors. Reducing high-risk comorbidities in patients with early-stage renal dysfunction is important for slowing the progression of the disease to ESRD, even in the endemic area of arsenic exposure.
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1. Introduction

Exposure to arsenic (As) in groundwater is a worldwide public health problem, which may cause life-threatening diseases (Chen, 2014; Naujokas et al., 2013). There is growing evidence showing that arsenic is a human carcinogen (IARC, 2012), and the United States Environmental Protection Agency reduced its Maximum Contaminant Level for arsenic in drinking water from 50 μg/L (0.05 mg/L) in 1942 to the current 10 μg/L accordingly (Smith et al., 2002), the same as the Maximum Permissible Level of arsenic proposed by the guidelines for drinking-water quality from World Health Organization (WHO, 2011).

Arsenic in drinking water is reduced to arsenite after ingestion and then undergoes methylation in the liver to become low less toxic forms, which are excreted in urine by the kidney (Vahter, 2002). During this process, arsenic concentrates in the kidney and may affect the functions of the proximal tubules and glomerulus (Prasad and Rossi, 1995; Singh et al., 2011). The toxicity of arsenic to the kidney may be mediated by reactive oxygen species, which enhance lipid peroxidation and cellular damages, including apoptosis (Giberson et al., 1976). Long-term exposure to arsenic may cause glomerular sclerosis, glomerular collapse, and tubular interstitial damage. Acute renal damage due to arsenic exposure is characterized by acute tubular necrosis and cast formation with increased blood urea nitrogen (BUN) and creatinine (Cr) levels (Sasaki et al., 2007). Therefore, tubular interstitial damage and changes in BUN and Cr levels are important indices of renal function declination, which can progress to chronic kidney disease (CKD).

CKD is a major worldwide public health burden that can progress to end-stage renal disease (ESRD) (Iseki et al., 2003) and lead to other cardiovascular complications (Weiner et al., 2004), which increase the risk of mortality. According to the U.S. Renal Data System (Collins et al., 2014), both the prevalence and incidence of ESRD in Taiwan are among the highest in the world. There are around 60,000 ESRD patients (approximately 0.3% of the population) in Taiwan who use about 7% of the national health insurance budget for dialysis. Many renal diseases have been documented to be associated with arsenic exposure from drinking water in Taiwan (Chen, 2014). Several ecological studies have shown that the arsenic level in drinking water is positively associated with the prevalence of renal disorders and the mortality from renal diseases (Chiou et al., 2005; Chiu and Yang, 2005). In a previous nationwide study of 8854 patients, we found that an arsenic level ≥ 50 μg/L in drinking water was a risk factor for rapid progression of CKD, independent of most of the documented risk factors (Cheng et al., 2017). There are also studies in other countries that support an association between arsenic exposure and ESRD. For example, a study of 3821 American Indian men and women found that the arsenic concentration in urine was associated with albuminuria (Zheng et al., 2013).

In spite of the supporting evidence, epidemiological studies on the association between arsenic exposure and the occurrence ESRD are still limited. Therefore, we conducted a nationwide population-based cohort study in Taiwan to evaluate the association and identified related risk factors.

2. Materials and methods

2.1. Assessment of arsenic exposure levels

We adopted data from a national census survey of wells conducted by the Taiwan Provincial Institute of Environmental Sanitation (Lo et al., 1977), which used the standard mercuric bromide stain method to assess arsenic levels in drinking water. The survey measured arsenic levels in >80,000 wells, mostly between 1974 and 1976, and covered nearly 85% of total 369 townships in Taiwan (Chung et al., 2013) and 94% of our study population. Using resident area in 1998 as personal arsenic exposure indicator, participants without information on arsenic exposure were excluded from the multi-variate analyses. According to the cut-off adopted by the survey reports, which was the regulatory standard at the time of the survey, we defined a high arsenic level as ≥50 μg/L (Lo et al., 1977). We used the geographical information system software (ArcGIS V10.2.2) to address maps showing the arsenic exposure category and the incidence rate of ESRD in each township (Fig. 2).

2.2. Data source and study participants

The Taiwan Bureau of National Health Insurance (NHI) program was initiated in March 1995. Up to 99% of the 23 million residents of Taiwan currently receive medical care through the NHI program. Over 96% of the hospitals (including over 100 regional and tertiary care hospitals) and clinics in Taiwan are contracted to provide health care services and get reimbursement by the Bureau of NHI, and all the data related to these services are managed and input into the NHIRD by the National Health Research Institutes (NHRI) to provide a comprehensive record of medical care. The NHRI release these data for research purposes, and many high quality studies on diseases related to renal diseases have been published based on data from the NHIRD (Chang et al., 2014; Hsieh et al., 2016).

Using data extracted from the Longitudinal Health Insurance Database (LHID2000) with 1,000,000 randomly sampled enrollees (approximately 5% of Taiwan's population) during 1996–2010, we conducted a retrospective cohort study of participants aged 40 years or older at January 1, 1998 (Fig. 1). There are two endemic areas of exposure to arsenic from drinking water in Taiwan, one on the southwestern coast and the other on the northeastern coast. Residents in these two areas started using artesian well water that contained high levels of arsenic in the early 1910s and late 1940s, respectively, and public tap water supply systems using surface water were later established in the 1970s and 1990s, respectively (Chen, 2014), after which residents generally stopped drinking the well water. While there were alternative sources of drinking water such as spring water, they were very limited, and therefore almost all the participants in these areas have to use well water. We excluded those who were under 40 years of age in 1998 because they were unlikely to drink water from wells as the tap water system had been constructed widely in the country in the 1970s.

Personal identification information was removed, and the patients remained anonymous throughout the study process. The study protocol was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital (No. BR-99-142), and the research had been conducted according to principles of Declaration of Helsinki.

2.3. Assessment of kidney disease and comorbidity

We used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to define ESRD and co-existing medical conditions. Because ESRD is a catastrophic illness listed by the NHI, we identified the newly diagnosed cases between January 1, 1998 and

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