Environmental Research 113 (2012) 52–57

Contents lists available at SciVerse ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Low-level arsenic exposure, AS3MT gene polymorphism and cardiovascular diseases in rural Texas counties

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ARTICLE INFO

Article history:
Received 1 July 2011
Received in revised form
20 December 2011
Accepted 4 January 2012
Available online 15 February 2012

Keywords:
Arsenic
Heart
Hypertension
Hyperlipidemia
AS3MT

ABSTRACT

Most Americans living in rural areas use groundwater for drinking. Exposure to low-level (around the current U.S. standard 10 μg/L) arsenic in drinking water is associated with increased mortality of cardiovascular diseases. The current study was to determine if coronary heart disease, hypertension, and hyperlipidemia were associated with low-level arsenic exposure and AS3MT gene single nucleotide polymorphism (SNP) A35991G (rs10748835) in rural Texas. Subjects (156 men, 343 women, 40–96 years of age with a mean of 61) were residents from rural counties Cochran, Palmer, and Bailey, Texas. Groundwater arsenic concentration at each subject's home was estimated with ArcGIS inverse distance weighted interpolation based on the residential location's distances to surrounding wells with known water arsenic concentrations. The estimated groundwater arsenic concentration ranged from 2.2 to 15.3 (mean 6.2) μg/L in this cohort. Logistic regression analysis showed that coronary heart disease was associated with higher arsenic exposure ($p < 0.05$) and with AS3MT genotype GG vs. AA ($p < 0.05$) after adjustments for age, ethnicity, gender, education, smoking status, alcoholism, and anti-hyperlipidemia medication. Hypertension was associated with higher arsenic exposure, while hyperlipidemia was associated with genotype AG vs. AA of the AS3MT gene ($p < 0.05$). Thus, coronary heart disease and its main risk factors were associated with low-level arsenic exposure, AS3MT polymorphism or both.

1. Introduction

Arsenic (As), a well-known poison (Vahidnia et al., 2007), is ubiquitous in the environment (Garelick et al., 2008). Arsenic exposure is mainly through ingestion and inhalation of arsenicals from drinking water, food, and air (Rahman et al., 2009; Aposhian et al., 2004). Once entering the body, arsenic and its metabolites generate free radicals, which damage proteins, fatty acids, DNA, and RNA, and cause oxidative stress or death to cells (Gong and O'Bryant, 2010). Inflammatory response is one of the hallmarks of arsenic-induced toxicity (Valko et al., 2005). Clinically, arsenic is well-known as a carcinogen, causing prostate, lung, liver, bladder, and other cancers (Jomova et al., 2011; Mink et al., 2008; Benbrahim-Tallaa and Waalkes, 2008; Celik et al., 2008; Chiu et al., 2004).

Previous studies have shown that cancer risk increases by 100-fold among people exposed to drinking water with arsenic concentration at 50 μg/L (Smith et al., 2002). As a result, U.S. Environmental Protection Agency (USEPA) set the current standard concentration of arsenic in drinking water to 10 μg/L effective in 2006 in the United States (Smith et al., 2002). Recent studies have demonstrated that bladder cancer risk increased significantly among Taiwanese men with long-term chronic arsenic exposure at low level and a recommended safe arsenic level in drinking water is 3.4 μg/L, far below the current USEPA standard, 10 μg/L (Liao et al., 2009). The National Research Council (2001) has recommended examining the effect of low-level arsenic exposure on health outcomes. Americans living in rural areas are particularly vulnerable since most of them (> 95%) use groundwater for drinking and cooking, where water contaminants are not regulated, and well arsenic level in many places may be above the currently allowable level (Ryker, 2001).

Arsenic exposure not only causes cancer but also increase the risks of many other diseases. Chen et al. (1988) reported that compared with the general population, mortality rates from cardiovascular diseases, peripheral vascular diseases, as well as cancers of bladder, skin, lung, and liver were significantly higher among patients with black foot disease resulting from exposure to high concentrations of arsenic (from 350 to 1140 ppb or μg/L with

Abbreviations: USEPA, US Environmental Protection Agency; As, arsenic; AS3MT, arsenic +3 oxidation state methyltransferase; GIS, geographic information system; SNP, single nucleotide polymorphism; TWDB, Texas Water Development Board; As^{III}, arsenite; As^{V}, arsenate; MMA^{V}, monomethylarsonic acid; DMAV, dimethylarsinic acid; MMA^{III}, Monomethylarsonous acid

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doi:10.1016/j.envres.2012.01.003

a median of 780 μg/L) in certain areas in Taiwan. Tseng et al. (2003) reported that ischemic heart disease prevalence was significantly correlated with cumulative arsenic exposure (arsenic concentration multiplied by the number of years individuals had lived there) in arseniasis-hyperendemic villages in Taiwan. A dose–response relationship existed between ischemic heart disease mortality and long-term arsenic exposure (Chen et al., 1996).

Because of the devastating impact of arsenic exposure, many areas with high arsenic concentration in groundwater started to use processed tap water for drinking and cooking in Taiwan (Chang et al., 2004). Chang et al. (2004) reported that coronary heart disease mortality declined significantly 17–20 years after switching from using high-arsenic well water to relatively pure tap water. In other countries such as Chile it is found that people were exposed to high concentrations of arsenic (≈ 860 μg/L) in drinking water and the risk for acute myocardial infarction, and its mortality increased significantly compared with those living in unexposed regions, while 10 years after measures taken to reduce arsenic exposures, acute myocardial infarction mortality decreased considerably (Yuan et al., 2007). Hypertension and atherosclerosis are also associated with ingested inorganic arsenic (States et al., 2009; Wang et al., 2002).

Particularly interesting is the finding of Meliker et al. (2007) that *low level* of arsenic exposure is a health hazard: mortality rates of circulatory diseases (hypertension, atherosclerosis, ischemic heart disease, cerebrovascular diseases, etc.) and diabetes significantly increased in six Michigan counties with mean and median well water arsenic concentrations of 11.0 and 7.6 μg/L, respectively, but not in the remainder of Michigan where the mean and median were 3.0 and 1.3 μg/L, respectively. More recently, Medrano et al. (2010) have shown that exposure to low-to-moderate levels of arsenic in drinking water is associated with higher mortality of cardiovascular diseases in Spain. We have recently reported that adults living in rural areas where arsenic concentration in groundwater estimated by the Geographic Information System (GIS) computer program ArcGIS was slightly above 10 μg/L had significantly lower scores for cognitive function than those exposed to GIS-estimated ground water arsenic < 10 μg/L (Gong and O'Bryant, 2010). Low-level arsenic exposure was also correlated with poorer scores in language, visuospatial skills, executive functioning, global cognition, processing speed, and immediate memory (O'Bryant et al., 2011). These findings suggest that low-level arsenic exposure increases the risk for non-cancer diseases. The mechanisms whereby arsenic causes cardiovascular disease, hypertension, hyperlipidemia, etc. are currently believed to be related to arsenic-induced oxidative stress (Gong and O'Bryant, 2010; Das et al., 2010; States et al., 2009).

However, not all people exposed to high arsenic concentration in drinking and cooking water develop cancer, cardiovascular diseases, etc. Genetic resistance or predisposition to arsenic exposure may play an important role in disease pathogenesis. After ingestion or inhalation, arsenicals are subject to biotransformation including methylation and reduction as follows (Valko et al., 2005): $As^{V} \rightarrow As^{III} \rightarrow MMA^{V} \rightarrow MMA^{III} \rightarrow DMA^{V} \rightarrow DMA^{III}$, where III and V denote trivalent and pentavalent As, respectively, while MM and DM represent monomethyl and dimethyl groups, respectively. Methylation is mediated by methyltransferase also known as arsenic +3 oxidation state methyltransferase (AS3MT) (Aposhian et al., 2004; Thomas et al., 2007). Studies have shown that polymorphisms in the AS3MT gene are associated with the efficiency of arsenic biotransformation and cancer risks (Valenzuela et al., 2009; Chung et al., 2009). Genetic predisposition plays an important role for coronary heart disease (Kullo and Keyue Ding, 2007), and certain genotypes of heme oxygenase-1 gene has been shown to be a risk factor for coronary heart disease when exposed to arsenic as recently demonstrated by Wu et al. (2010). However, potential effects of the AS3MT gene polymorphism on coronary heart disease have not been studied.

In the present study, we test the hypotheses that coronary heart disease, hypertension, and hyperlipidemia are linked to low-level arsenic exposure estimated individually by the GIS approach and to AS3MT gene polymorphism in a rural cohort in Texas.

2. Methods

2.1. Subjects

Subjects (156 men, 343 women, 40–96 years of age with a mean of 61) were residents from rural counties Cochran, Palmer, and Bailey, TX, and were participants of Project FRONTIER, which is an ongoing epidemiological study among rural dwelling individuals. These participants were selected from the total of 586 subjects currently enrolled in Project FRONTIER based on the following criteria: (1) having definite consensus diagnosis for hypertension, hyperlipidemia, and coronary heart disease (CHD diagnosis was based on history of angina pectoris, coronary heart disease, myocardial infarction); (2) having been genotyped for the AS3MT; (3) having complete demographic information for age, gender, ethnicity, smoking status, alcoholism status, anti-hyperlipidemia medication, and level of education; and (4) having groundwater arsenic level estimated by the GIS approach. Additional 10 subjects had only genotype data, which were included in the analysis of genotype and allele frequencies (i.e., a total of 509 subjects have been genotyped).

The Southwest part of the Texas Panhandle Plains, where these counties are located, is a geographic hot spot for groundwater arsenic in the United States (O'Bryant et al., 2011; Ryker, 2001). Details of research design and methodology of Project FRONTIER have been described previously (O'Bryant et al., 2009). All participants signed written informed consent and Project FRONTIER is conducted under an IRB approved protocol. One of the primary aims of Project FRONTIER is to evaluate the impact of cardiovascular diseases on the prevalence of cognitive disorders and dementia syndromes, which provides an opportunity to examine the potential impact of arsenic exposure on cardiovascular diseases in rural-dwelling adults. Using the community-based participatory research approach, the research team partnered with several local organizations including local hospitals, where the majority of interviews were conducted. Community recruiters were hired and recruitment was done via mail outs, brochures, newspaper advertisements, local presentations, and community events, as well as door-to-door solicitation. All participants underwent an interview that collected information regarding demographics, medical history, residential address, and duration of living in each address.

The study includes a standardized medical examination, clinical laboratory examinations, as well as a detailed interview with participant, and a brief interview with an informant. Inclusion criteria are (1) age 40 and above and (2) residing in one of the rural counties of Project FRONTIER. For the part of history of cardiovascular diseases and risk factors relevant to the current study, the subjects were asked whether a doctor, a nurse, or other health professional EVER told him/her that he/she had (1) a myocardial infarction, (2) angina or coronary heart disease, (3) hyperlipidemia, and (4) high blood pressure.

Myocardial infarction is a severe stage of coronary heart disease (CHD), while angina pectoris (or angina) is a symptom of CHD; we listed these terms in our questionnaire since physicians may have used one or more of the terms to describe participants' clinical distinctions. The diagnosis of CHD is based electrocardiogram (ECG) findings (ST-segment depression, inverse T wave, Q wave, etc.), stress tests (exercise or pharmacologic)-induced ST-segment depression, and/or chest pain), and or coronary artery angiogram (Mittal, 2005). Diagnosis of acute myocardial infarction was based on elevation of ST segment on ECG and cardiac enzymatic changes (Leuzzi and Modena, 2010; Park et al., 2011).

We measured blood pressure of all participants in the supine position after at least 10 min of rest. Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg was considered as having high blood pressure even if the subject had not been told of having high blood pressure. If the subject was under antihypertensive medication (was told to have had high blood pressure), then the subject was considered hypertensive even if blood pressure was within normal range. Alcoholism was determined by the Alcohol Use Disorders Identification Test (AUDIT), clinical lab data regarding liver functioning, and medical history.

We measured lipid profiles for all participants. Diagnosis of hyperlipidemia is made if any one of the following serum profiles exceeded the upper limit of the normal range: cholesterol > 199 mg/dL, triglyceride > 150 mg/dL or low density lipoprotein > 100 mg/dL.

All information is reviewed weekly by a consensus review group made up of geriatricians, internal medicine specialists, a psychologist, and a neuropsychologist who make diagnoses for research subjects' medical, psychological, and neurocognitive conditions.

It should be pointed out that Hispanics are a congregate of people with similar culture and is not a genetic or racial entity; they may identify themselves as white, black, American Indians, etc. according to U.S. Census Bureau. Genetically, they