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Levels of plasma selenium and urinary total arsenic interact to affect the risk for prostate cancer

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ABSTRACT

This study investigated whether plasma selenium levels modified the risk for prostate cancer (PC) related to arsenic exposure. We conducted a case-control study that included 318 PC patients and 318 age-matched, healthy control subjects. Urinary arsenic profiles were examined using HPLC-HG-AAS and plasma selenium levels were measured by ICP-MS. We found that plasma selenium levels displayed a significant dose-dependent inverse association with PC. The odds ratio (OR) and 95% confidence interval (CI) for PC was 0.07 (0.04–0.13) among participants with a plasma selenium level >28.06 μg/dL vs. ≤19.13 μg/dL. A multivariate analysis showed that participants with a urinary total arsenic concentration >29.28 μg/L had a significantly higher OR (1.75, 1.06–2.89) for PC than participants with ≤29.89 μg/L. The combined presence of a low plasma selenium level and a high urinary total arsenic concentration exponentially increased the OR for PC, and additively interacted with PSA at levels ≥20 ng/mL. This is the first epidemiological study to examine the combined effects of plasma selenium and urinary total arsenic levels on the OR for PC. Our data suggest a low plasma selenium level coupled with a high urinary total arsenic concentration creates a significant risk for aggressive PC.

1. Introduction

Prostate cancer continues to be one of the most frequently diagnosed malignancies in men. The incidence of prostate cancer has increased rapidly ($1.4/10^5$–$8.6/10^5$) from 1982 to 1996 in Taiwan. The prostate-specific antigen (PSA) test is inevitable performed for men who visit a urologist with lower urinary tract symptoms. However, there is no massive PSA screening in Taiwan. In fact, the lack of such screening is one of the main reasons for the higher percentages of advanced and metastatic prostate cancer diagnosed among patients in Taiwan when compared with many Western countries (Chen et al., 2008; Huang et al., 2010; Pu et al., 2004). The increasing incidence of prostate cancer may be related to a Westernization of lifestyle, increased obesity and increased dietary fat intake (Pu, 2000). Environmental factors including diet (Labbe et al., 2015), exercise, aging (Damaschke et al., 2013) and medication use (Loeb et al., 2015) have been investigated in association with the risk of prostate cancer.

Many studies have reported that antioxidants, such as selenium and vitamin E supplements, decrease the risk for prostate cancer (Loeb et al., 2015; Yang et al., 2013). However, one study did not show selenium and vitamin E supplements to be related to the risk

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of prostate cancer (Heinonen et al., 1998). In contrast, another study showed that selenium supplementation of 140 μg/day or more after diagnosis of non-metastatic prostate cancer may increase the risk of prostate cancer mortality (Kenfield et al., 2015). However, data on the association between selenium supplementation and the risk of prostate cancer are conflicting. Bleys reported increased serum selenium levels to be associated with a decreased mortality of all cancers, including prostate cancer (Bleys et al., 2008). Another recent study found that plasma selenium was not associated with a risk of high-grade prostate cancer or prostate cancer recurrence (Gerstenberger et al., 2015). Therefore, the association between plasma selenium and the risk of prostate cancer remains unclear.

Inorganic arsenic is a potent human carcinogen most frequently associated with skin and lung cancer (IARC, 2004). The association between arsenic exposure and cancer of the liver, kidney and bladder is also well documented among Taiwanese patients (Chen et al., 1988). The first evidence that arsenic was associated with prostate cancer in patients from Taiwan was presented by Chen (Chen et al., 1988). Subsequently, epidemiologic evidence from Taiwan populations chronically exposed to high arsenic levels in drinking water showed significant mortality from prostate cancer, with a dose-response relationship (Chen and Wang, 1990; Wu et al., 1989). Additionally, a study showed that mortality from prostate cancer declined gradually after improvement of the drinking water supply system; this suggests that arsenic exposure is causally related to prostate cancer (Yang et al., 2008). A recent study has also reported that low to moderate exposure to inorganic arsenic was prospectively associated with increased mortality for cancer of the lung, prostate and pancreas (Garcia-Esquinas et al., 2013). However, the association between arsenic exposure and prostate cancer has received less attention.

A distinctive feature of arsenic toxicity is its remarkable variability in intra- and inter- individual effects (Tseng, 2009). Once inorganic arsenic is ingested, arsenate (As^{V}) is reduced to arsenite (As^{III}), which then undergoes methylation with s-adenosylmethionine (SAM) as the methyl donor, forming monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}); these are then are rapidly excreted in the urine (Thompson et al., 2013). Methylation of inorganic arsenic has always been considered a detoxification mechanism because pentavalent MMA (MMA^{V}) and DMA (DMA^{V}) have relatively low toxicity (Yamauchi and Fowler, 1994). However, monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) are metabolic intermediates in the arsenic methylation pathway that are more toxic than inorganic arsenite (Styblo et al., 2002). Population studies have shown that individuals with an inefficient capacity to methylate inorganic arsenic to DMA^{V} are at risk for skin cancer (Hsueh et al., 1997), bladder cancer (Melak et al., 2014) and peripheral vascular disease (Newman et al., 2016). Previous studies used arsenic concentrations in drinking water as an arsenic exposure index; however, investigation is needed to determine whether internal dose-urinary inorganic arsenic and its metabolites are associated with prostate cancer.

Arsenic and selenium have marked differences in their biological effects (Csanaky and Gregus, 2003). While selenium is an essential trace element necessary for antioxidant enzyme activity (Shafik and El Batsh, 2016), arsenic has no known biological function and induces oxidative stress (Ince et al., 2016; Shafik and El Batsh, 2016) that contributes to its acute and chronic toxicity. However, few observational studies have examined the joint association of arsenic exposure and plasma selenium on the risk for developing prostate cancer. Therefore, our current study was conducted to investigate whether internal dose-urinary arsenic profiles are associated with prostate cancer, and the association between plasma selenium levels and prostate cancer risk. Additionally, we also examined whether plasma selenium modifies the risk for prostate cancer and if aggressive prostate cancer is related to arsenic exposure.

2. Materials and methods

2.1. Study participants

We conducted a hospital-based case-control study; 318 prostate cancer cases and 318 age-matched, healthy controls were recruited from the National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital from May 2007 to August 2013. All prostate cancer cases were diagnosed by histological confirmation; the International Classification of Diseases revision 9 (ICD9) code was 185 and for ICD10 was C-61. None of the prostate cancer cases presented with other histology or benign lesions. Disease stage was determined by clinical and pathology findings, pelvic computed tomography or magnetic resonance imaging and radionucleotide bone scans, according to criteria established by the American Joint Committee on Cancer tumor-node-metastasis (TNM) classification system (American Joint Committee on Cancer, 2002). Pathologic grading was recorded as the Gleason score. Healthy control subjects with no history of any cancer were recruited from adults receiving a health examination or senior citizen health examination at the Department of Family Medicine. The normal volunteers were recruited based on their own report of never having been diagnosed with cancer by a physician. Control subjects were age-matched one-to-one with prostate cancer patients (±5 years). All study participants lived in Taipei City, which is 200–300 km away from arsenic-contaminated areas. None of the prostate cancer cases or control subjects worked in an arsenic-contaminated area, and no study subjects were working in an environment in which they could potentially be exposed to heavy metals. The participants drank tap water supplied by the Taipei Water Department of the Taipei City Government, and the average arsenic concentration in tap water in Taipei City is 0.7 μg/L. This study was approved by the Research Ethics Committee of National Taiwan University Hospital and Taipei Medical University, and all participants provided written informed consent before questionnaire interview and biological specimen collection. This study complied with the World Medical Association Declaration of Helsinki.

2.2. Questionnaire interview and biospecimen collection

Personal information from all participants, including demographic and socioeconomic characteristics; consumption of alcohol and cigarette smoking habits were collected by well-trained interviewers using a structured questionnaire. Cigarette smoking status was classified as never, former or current at the time of enrollment. Ever-smokers included former and current smokers.

A spot urine and peripheral blood sample was collected at the time each prostate cancer case was diagnosed, but before the patient received any medication or surgical treatment. Urine was stored in 50 mL acid-washed tubes, which were immediately transferred to a −20 °C freezer for storage until the arsenic species were analyzed. Ethylene-diamine-tetraacetic-acid (EDTA)-coated vacuumed syringes were used to collect 5–8 mL samples of peripheral blood. After collection the plasma was separated and frozen at −80 °C for measurement of selenium levels.

2.3. Determination of urinary arsenic species and plasma selenium levels

Frozen urine samples were thawed at room temperature, dispersed by ultrasonic waves and filtered through a Sep-Pak C18