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Urinary strontium and the risk of breast cancer: A case-control study in Guangzhou, China ☆, ☆☆

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ABSTRACT

Strontium has been widely used in industries like electronic and pharmacy. It has a carcinogenic potential, however, and no study has been conducted to evaluate its effects on cancer risk. The aim of this study was to explore the possible association between strontium and breast cancer risk in a case-control study including 240 incident invasive breast cancer patients and 246 age-matched controls. We measured the urinary concentrations of strontium by inductively coupled plasma mass spectrometry, and conducted face-to-face interviews to obtain information on potential breast cancer risk factors. Multivariable analysis was used to estimate the association. Creatinine-adjusted levels [median (25th, 75th) μg/g] of strontium were 155.59 (99.05, 230.70) in the breast cancer patients and 119.62 (81.97, 163.76) in the controls. Women in the highest tertile of strontium showed 124% increased risk of breast cancer, when compared with those in the lowest tertile after adjustment for the potential risk factors [OR (95% CI): 2.24 (1.42–3.81)]. This association was particularly strong for HER2 positive breast cancer [OR (95% CI): 10.92 (3.53–33.77)], and only occurred among premenopausal women. These results suggest a potential role of strontium in the development of breast cancer and urge further studies on the environmental contamination and the physiological and pathological mechanisms of strontium.

1. Introduction

Strontium ranks 15th in order of element abundance and comprises 0.02–0.03% of the Earth's crust (Pors Nielsen, 2004). It is present in air, soil, water as well as in living organisms and is subjected to a number of pollutants due to different anthropogenic activities (industrial, agricultural, transport, etc.), permitting an efficient transfer through the soil–plant–food chain to human body (Davidson et al., 2005; Krishna and Govil, 2007; Pors Nielsen, 2004; Sanchez-Chardi and Lopez-Fuster, 2009). The major industrial uses of strontium include the production of glass for color television picture tubes, ferrite magnets, and refining of zinc (Kirrane et al., 2006; Usuda et al., 2007). It is one of the main elements as a potential tracer profile for contaminated roadside soils (Schauer et al., 2006).

Strontium has a bone-seeking property (Pors Nielsen, 2004). Strontium ranelate has been shown to reduce bone resorption and stimulate bone formation in preclinical studies (Marie et al., 1993), consequently increase bone mineral density (BMD), and be associated with a proportional reduction in bone fracture incidence (Bruyere et al., 2007a,b; Cesareo et al., 2010). Hence, strontium ranelate has been emerging as a new antiosteoporotic agent authorized in 27 European countries since 2004 (Jupsin et al., 2005; Neuprez et al., 2008). Some experimental studies, however, which were designed to understand the mechanisms for the anabolic effect of strontium on bone, have suggested a carcinogenic property of strontium. It has been shown that strontium, like calcium, enhances extracellular signal-regulated kinase (ERK) 1/2 mitogen-activated protein kinase (MAPK)

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signaling pathway (Chattopadhyay et al., 2007; Choudhary et al., 2003; Peng et al., 2009). Peng et al. (2009) have identified that RAS is activated by strontium. It has been well known that the RAS–RAF–MAPK/(ERK) kinase (MEK)–ERK signaling pathways play central roles in the signal transduction networks promoting tumor initiation and tumor progression (Mirzoeva et al., 2009). Therefore, strontium may activate these signaling pathways contributing to carcinogenesis. This hypothesis is also strengthened by the fact that calcium, physically and chemically similar to strontium (Pors Nielsen, 2004), has been found to be associated with breast cancer (Almquist et al., 2007; Divekar et al., 2011; Garner et al., 2007; Martin et al., 2010).

In the present study, we evaluated the association of urinary level of strontium with breast cancer risk in a case-control study in Guangzhou, China. Previous studies have shown that strontium is cleared from blood almost immediately and exclusively deposited in bone after intravenous injection; then it is excreted mainly through kidney (Pors Nielsen, 2004). The terminal half-life may reach 3 years for humans and urinary strontium concentration reflects a relatively long term exposure level (Dahl et al., 2001). Hence, urinary strontium was selected as a biological marker for its exposure in this study.

2. Materials and methods

2.1. Study population

Female patients, newly histologically diagnosed with breast cancer between October 2009 and July 2010 in the First- and the Second-Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, were consecutively included in this study. Women with metastasized breast cancer or previous history of other cancers were excluded. A total of 270 eligible breast cancer cases during the study period completed in-person interviews with response rates from 75% to 85% depending on the hospitals. Age (within 5 years) frequency-matched controls were identified from the primary care databases of the same hospitals as the breast cancer cases during the same period. Women who self-reported a history of cancer were excluded. Of the 330 eligible controls, 81.8% completed in-person interviews. All the subjects must have resided in Guangzhou area for at least 5 years. Informed consent was obtained from all the study participants, and the Ethical Committee of the School of Public Health at Sun Yat-sen University approved the study.

2.2. Data collection

The cases and the controls were interviewed face to face by trained interviewers using the same questionnaire. The following information was obtained during the interview: demographic factors, menstrual and reproductive history, lifestyle, family history of cancer, height and weight, and hormone therapy. Urine samples were collected from 240 cases (88.9% of those eligible) immediately after admission to the hospitals and from 246 controls (91.1% of those eligible) after the interview. None of the participants reported a history of strontium ranelate administration. The clinical characteristics of the breast cancer patients were collected from medical records. The statuses of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) for the breast cancer were determined by pathologists using immunohistochemistry tests. The definition of statuses of ER, PR and HER2 were previously described in detail (He et al., 2011).

2.3. Urine process and test of strontium

All the urine samples were placed in high-density polyethylene containers and stored at −80 °C until they were analyzed. The samples were processed at the Laboratory of Guangdong Testing Center of Occupational Hygiene, which is one of the members executing a national project to establish national standards of trace elements in biological specimens in China. Strontium in urine were quantified using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500ce ICP-MS, Agilent Technologies, McMillan, Texas) with the isotope of 88 Sr. The batches of assays contained samples from both the cases and controls in a random fashion, and the operator was unaware of the participant group.

Immediately before analysis, the urine samples were diluted in a ratio of 1:9 with dilute nitric acid solution (0.5%) in trace metal clean polypropylene autosampler tubes. Strontium quantification was done using external standards (Spex Industries, Metuchen NJ, USA) with internal normalization. An internal standard was on-line added to every sample. The values were acquired in peak jumping mode with a minimum of three replicate analyses done on each sample after a 30-s uptake and a 25-s stabilization period. A 15-s rinse [0.5% (v/v) nitric acid + 0.01% (v/v) Triton] between samples virtually eliminated carryover and improved the quantification limits. The analytic batches consisted of 50 urine samples along with 5 quality-control samples. The latter included both bench and blind samples. The concentrations were blank-baseline corrected using the mean of three batch specific matrix blanks. The limit of detection was 1.0 μg/L for strontium. Two samples (0.4%) were below the limit. Urine standard reference from Bio-Rad (Bio-Rad, Hercules, CA, USA) was used for external calibration. The coefficients of variation between duplicates for urinary strontium were under 10%, averaging 5.4%.

In addition, a second aliquot of each urine sample was shipped to the clinical examination center in Guangdong Prevention and Treatment Center for Occupational Diseases, for the measurement of creatinine concentration by an enzymatic method. Urinary concentrations (μg/L) of strontium were divided by individual creatinine concentration (g/L) to correct for the variability in urine dilution and kidney function according to a previously detailed methodology (Barr et al., 2005; McElroy et al., 2006).

2.4. Statistical analysis

Multivariate unconditional logistic regression models were used to assess the associations of suspected or established risk factors with breast cancer risk (Table 1), and the effects of urinary levels of strontium on breast cancer, controlling for age and suspected or established risk factors [age, body mass index (BMI), age at menarche, marital status, education, parity, menopausal status, and family history of breast cancer], which were defined categorically except for age (Table 1). The models were fit using concentrations of strontium as continuous (linear) and categorical (tertiles) variables. To evaluate the correlations between the urinary levels of strontium and the clinical characteristics of breast cancer, χ^2 and rank correlation tests for categorical variables and Student's t-test for continuous variables were used. Urine samples that were below the limit of detection were assigned one half of the value.

Stratified analyses for associations between strontium levels and the risk of breast cancer were performed by menopausal status and clinical characteristics of HER2, ER, and clinical stage. The heterogeneity of odds ratios between different levels of the clinical characteristics was assessed using a multivariable logistic regression model restricted to cases (case-only analysis) with the clinical characteristic as the outcome variable while adjusting for other clinical features. The interaction between strontium levels and menopausal status on breast cancer risk were evaluated by a multiplicative model and an additive model. We tested for multiplicative interaction by including the product term in multivariable logistic regression. Additive interaction was assessed by synergy index (S) and its 95% CI (Rothman, 1976).

All statistical tests were two-tailed with $P<0.05$ considered to be significant. The S and 95% CI were obtained using SAS software (Version 9.1, SAS Institute, Cary, NC, USA). Other statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Breast cancer patients, when compared with the controls of similar age, were more likely to be premenopausal, nulliparous, and less educated. They were comparable in marital status, BMI, age at menarche, age at menopause, and family history of breast cancer (Table 1). Creatinine-adjusted levels [median (25th, 75th) μg/g] of strontium were 155.59 (99.05, 230.70) in cases, and 119.62 (81.97, 163.76) in controls.

We used multivariable analysis to compute odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer by tertile of strontium levels, as defined by levels in control subjects. After adjustment for age only, women in the highest tertile (T3) of strontium had an increased risk of breast cancer as compared with those in the lowest tertile (T1) (OR=2.45; 95% CI=1.57–3.80), whereas women in the second tertile (T2) were not significantly different in the risk of breast cancer. In the multivariate adjustment with potential risk factors of breast cancer, the results were not essentially changed, and the ORs and 95% CIs were 1.02 (0.59–1.77) and 2.24 (1.42–3.81) for women in the second and highest tertile of strontium, respectively, as compared with those in the lowest tertile. The trend was statistically significant at $P<0.01$ (Table 2), indicating that there was a