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Modified effect of urinary cadmium on breast cancer risk by selenium

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ABSTRACT

Background: Previous experimental studies have shown an antagonistic interaction between cadmium and selenium. We explored the interaction between cadmium and selenium on human breast cancer risk.
Methods: A case–control study, enrolled 240 incident invasive breast cancer patients and 246 age-matched controls from 2 hospitals, was conducted in Guangzhou, China. Inductively coupled plasma mass spectrometry was used to examine urinary concentrations of cadmium and selenium. Association and interaction of the metal levels with breast cancer risk were tested using generalized additive and logistic regression models.
Results: As continuous variables, urinary cadmium [OR (95% CI): 1.16 (1.01–1.34)] but not selenium was significantly linearly associated with breast cancer risk. As tertiles, urinary cadmium did not significantly increase breast cancer risk; whereas women with the second tertile of selenium concentration had a significantly decreased risk of breast cancer as compared with those in the lowest tertile [OR (95% CI): 0.50 (0.30–0.81)]. Among the women with the lowest tertile of selenium, the highest tertile of cadmium significantly increased the risk of breast cancer [OR (95% CI): 2.83 (1.18–6.86)] compared to the lowest tertile of cadmium. A multiplicative interaction was found between tertiles of cadmium and selenium on breast cancer risk ($P = 0.018$), particularly among postmenopausal women.
Conclusions: These results suggested that the association of urinary cadmium with breast cancer risk was modified by urinary selenium.

1. Introduction

Cadmium is a toxic metal and a ubiquitously distributed environmental contaminant [1,2]. It may contribute to the development of various cancers, including breast cancer as it mimics estrogen effects in the mammary gland [3–5]. Several recent epidemiological studies have shown that women with a high level of urinary cadmium had a significantly increased risk of breast cancer compared to those with a low level [6–9], although the association of dietary cadmium with the risk of breast cancer was conflicting [10,11]. Some experimental studies have reported that selenium was able to counteract the effect of cadmium. Yiin and Ognjanovic found that selenium attenuated the lipid peroxidation induced by cadmium [12–14]. It was found that mice infected with murine mammary tumor virus had a mammary carcinoma incidence of 78.6%; selenium-rich feed caused the incidence to drop to 23.3%; a further cadmium feed increased the incidence back to 81.2%, indicating an antagonistic interaction between selenium and cadmium on mice mammary carcinoma [15]. However, there has been no population evidence to support these findings.

As the association between cadmium and human breast cancer was generally recognized, it would be helpful to understand its actual role in conjunction with selenium. Therefore, we measured the urinary levels of selenium as well as cadmium and explored their interaction on breast cancer risk in a case–control study in Guangzhou, China, an area with relatively high intakes of cadmium and selenium [1,16].

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

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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 of 75–85% 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 in the hospitals. The following information was obtained during the interview: demographic factors, menstrual and reproductive history, lifestyles (smoking, alcohol intake, and physical activity), family history of cancer, height and weight, and hormone therapy. The collected lifestyle information concerned habits throughout their lifetime. Postmenopausal status was defined as amenorrhea for the past 12 months without breastfeeding and hysterectomy. Urine samples were collected from 240 cases (88.9% of those eligible) immediately after admissions to the hospitals before any treatment began and from 246 controls (91.1% of those eligible) after the interview. The clinical characteristics of the breast cancer patients were collected from medical records. The statuses of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 for breast cancer were determined by pathologists using immunohistochemistry tests. The definitions of statuses of these 3 hormonal receptors were previously described in detail [17].

2.3. Urine processes and tests of cadmium and selenium

The participants were instructed to collect their midstream urines with high-density polyethylene containers and the urine samples were 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. Cadmium and selenium in urine were quantified using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500ce ICP-MS, Agilent Technologies) with the isotopes of 111Cd and 82Se. The total levels of these 2 metals were deduced using the abundance (fraction) of the isotopes (Spex Industries). The batches of assays contained samples from both the cases and controls in a random fashion, and the operator was unaware of the participants' group.

Immediately before analysis, the urine samples were diluted in a ratio of 1:9 with a dilute nitric acid solution (0.5%) in trace metal clean polypropylene autosampler tubes. Cadmium and selenium quantification was done using external standards (Spex Industries) 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 carry-over 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 limits of detection were 0.1 and 0.5 μg/l for cadmium and selenium, respectively. Two samples (0.4%) were below the limit for cadmium. Urine standard reference from Bio-Rad (Bio-Rad) was used for external calibration. The individual coefficient of variation between duplicates for urinary cadmium and selenium was <10% except for 1 pair of samples of cadmium, averaging 7.3% and 6.4% for urinary cadmium and selenium, respectively.

Because we used spot instead of 24-h urine samples to detect the metal levels and the urine dilutions from different individuals may be various, urinary concentrations (μg/l) of cadmium and selenium 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 [7,18]. The measurement of creatinine concentration was performed by an enzymatic method in the clinical examination center in Guangdong Prevention and Treatment Center for Occupational Diseases.

2.4. Statistical analysis

To evaluate the nonlinearities of relations of breast cancer risk to urinary cadmium and selenium, generalized additive models were fitted, using GAM procedure and smoothing spline function, while controlling for the potential confounders [age, body mass index, age at menarche, marital status, education, parity, menopausal status, and family history of breast cancer], which were defined as parameter variables. The Method = GCV was specified in the model statement in order to request that the generalized cross validation method be used to choose the smoothing parameters. Multivariate unconditional logistic regression models were used to assess the effects of urinary levels of cadmium and selenium on breast cancer risk, controlling for the potential confounders, which were defined categorically except for age. Concentrations of cadmium and selenium were fitted in the models as continuous as well as categorical (tertiles) variables. Tertiles of urinary levels were defined as follows: tertile 1, <1.59; tertile 2, 1.59–2.36; tertile 3, >2.36 for cadmium, and tertile 1, <32.69; tertile 2, 32.69–42.61; tertile 3, >42.61 for selenium, based on the values (μg/g creatinine) of the controls. Urine samples that were below the limit of detection were assigned one half of the value. Stratified analysis for associations between cadmium and selenium levels and the risk of breast cancer were performed by menopausal status and hormonal receptors. The interaction between cadmium and selenium on breast cancer risk was evaluated by a multiplicative model. We tested for multiplicative interaction by including the product terms in multivariate logistic regression. All statistical tests were 2-tailed with $P < 0.05$ considered to be significant. Statistical analyses were performed using SPSS 13.0 and SAS 9.2.

3. Results

The characteristics of breast cancer cases and controls have been shown in Table 1 as well as in our previous report [17]. Briefly, breast cancer patients, when compared to the controls with similar age, were more likely to be premenopausal, nulliparous, and less educated. They were comparable in marital status, body mass index, age at menarche, age at menopause, and family history of breast cancer. Creatinine-adjusted levels of cadmium and selenium were not normally distributed and stated as median (25th, 75th) μg/g creatinine, which were 1.99 (1.32, 2.88) and 34.1 (26.8, 46.4) in cases, and 1.91 (1.37, 2.79) and 37.1 (29.2, 47.0) in controls, respectively.

We firstly tested the nonlinearities of relations between breast cancer risk and urinary cadmium and selenium using generalized additive models. As shown in Fig. 1, the smoothing component plots suggested no significant nonlinearity for the relation between breast cancer risk and urinary cadmium ($df = 1.560$, $P = 0.111$), while there was a significant nonlinear contribution of urinary selenium to breast cancer risk ($df = 3.437$, $P = 0.017$). We then evaluated if the relation between breast cancer risk and urinary cadmium was linear in logistic model and found that the linear association was significant [OR (95% CI): 1.16 (1.01–1.34)], indicating that there was 16% increased risk for every 1 μg/g creatinine increase of cadmium. For urinary selenium, owing to a possible quadratic dependence on breast cancer risk