RESEARCH ARTICLE

Association of Urinary Cesium with Breast Cancer Risk

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Abstract

Background: The aim of this study is to examine the association of urinary cesium with breast cancer risk. Materials and Methods: We collected survey data and urine specimens from 240 women with incident invasive breast cancer before their treatment and 246 age-matched female controls between October 2009 and July 2010. Urinary concentrations of cesium were determined by inductively coupled plasma mass spectrometry. Interviews were conducted by face-to-face to obtain information on potential breast cancer risk factors. Logistic regression analysis was used to estimate the associations. Results: Creatinine-adjusted levels [median (25^{th}, 75^{th}) ug/g] of cesium in cases and controls were 17.6 (13.1, 24.0) and 19.3 (15.3, 25.7), respectively. After adjustment for potential risk factors, women in the second and highest tertile of cesium showed a decreased risk of breast cancer in a dose-dependent manner as compared with those in the lowest tertile [ORs and 95% CIs: 0.75 (0.46-1.22) and 0.50 (0.30-0.82), respectively]. This decrease was more evident in women with ER positive or localized clinical stage in an exploratory stratification analysis. Conclusions: These findings suggest that cesium may have anticancer efficacy and urinary cesium has potential as a biomarker for breast cancer risk assessment.

Keywords: Cesium - breast cancer - urine - risk

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Introduction).

Cesium originally caught attention in its radioactive form with radiation carcinogenesis and radiotherapeutic effects (Wasserman and Glass, 1968; Burns, 1972; Burrows et al., 1983; Kuhnlein and Chan, 2000). Anticancer efficacy for stable cesium therapy has been claimed since 1980s (Brewer, 1984; Sartori, 1984). *In vivo* studies have shown that tumor volume was significantly reduced after the administration of intraperitoneal injection or oral gavage of cesium chloride (CsCl) (El-Domeiri et al., 1981; Tufte and Tufte, 1984; Lyon and Mayhew, 2003; Guns et al., 2005; Low et al., 2007). In a clinical study, 25 out of 50 terminal patients with generalized metastatic disease were still alive after 3 years of receiving 6-9 g of CsCl every day, with a consistent disappearance of pain within the initial 3 days of Cs treatment (Sartori, 1984; Low et al., 2007). It was also reported that high dietary cesium led to low cancer incidence in the Hunza tribe of northern Pakistan and the Hopi and the Pueblo Indians of Arizona (Calloway et al., 1974; Brewer, 1984).

However, these human studies were either a clinical study without control group (Sartori, 1984; Low et al., 2007) or ecological association studies that might be a coincidence (Calloway et al., 1974; Brewer, 1984). There is no study on the association of cesium with cancer risk at a population level with an analytical method. Because of no sufficient scientific evidence, no government or organization, including the US Food and Drug Administration, has approved the use of cesium as an anticancer agent. Consequently, although a number of people are seeking for the chemotherapy and chemoprevention with cesium, they purchase CsCl products, including alternative medicines containing cesium, only by searching the internet or visiting underground clinics (Cui et al., 2004; Low et al., 2007). Therefore, there is a need to examine the anticancer effects of cesium with a modern scientific method.

In addition, assessment of breast cancer risk is still a challenge and environmental biomarkers may be the hope for this challenge (Cazzaniga et al., 2009; Su et al., 2011; Lin et al., 2012). Given that cesium normally exists in human body and is excreted mainly through urine (Ghosh et al., 1993), it would be meaningful to compare cesium levels in urine samples between cancer patients and normal controls for evaluating its anticancer efficacy and application as a biomarker of the risk assessment. In the present study, therefore, we evaluated the association of urinary cesium with breast cancer risk in a case-control study in Guangzhou, China.

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Materials and Methods

Study Population

Female patients, newly histologically diagnosed with breast cancer between October 2009 and July 2010 from the First-and the Second-Affiliated Hospital of Sun Yat-sen University in Guangzhou, China, were consecutively included in this study. However, those with previous history of any 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 recruited from women who attended health-screening assessments at the same hospitals as the breast cancer cases during the same period. Of the 330 eligible controls, 81.8% completed in-person interviews. All the subjects were residing in Guangzhou area for at least 5 years.

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: menstrual and reproductive history, lifestyle, family history of cancer, height and weight, and demographic factors. Urine samples were collected from 240 cases (88.9% of those eligible) immediately after admission 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 (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) for breast cancer were determined by pathologists using immunohistochemistry tests. The definitions of statuses of these 3 hormonal receptors were previously described in detail (Su et al., 2011). 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.

Urine process and cesium determination

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 which are executing a national project to establish national standards of trace elements in biological specimens in China. Cesium in urine was quantified by using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7500ce ICP-MS, Agilent Technologies, McMillan, Texas) with isotope 133Cs. The batches of assays contained samples from both the cases and controls, and the operator was unaware of the participant 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. Cesium quantification was done using external standards (Spex Industries, Metuchen NJ, USA) with internal normalization. Furthermore, an internal standard was on-line added to every sample. The values were acquired in the 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. Sample concentrations were blank-baseline corrected using the mean of the three batch specific matrix blanks. The limit of detection was 0.1 μg/L and two samples (0.4%) were below the limit. Urine standard reference from Bio-Rad (Bio-Rad, Hercules, CA, USA) was used for external calibration.

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 concentration (μg/L) of cesium was 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).

Statistics

Multivariate logistic regression models were used to

Table 1. Characteristics of Breast Cancer Cases and Controls

Characteristics	Cases n (%)	Controls n (%)	OR (95%CI)†
Education			
Junior middle school or below	102 (42.5)	66 (26.8)	1.00 (reference)
Senior middle school	74 (30.8)	118 (48.0)	0.58 (0.37-0.91)
College or above	58 (24.2)	62 (25.2)	0.81 (0.48-1.36)
Unknown	6 (2.5)	0 (0.0)	-
Marital status			
Never married	14 (5.8)	11 (4.5)	1.00 (reference)
Married/living as married	208 (86.7)	214 (87.0)	0.63 (0.27-1.50)
Separated/widow	11 (4.6)	21 (8.5)	0.42 (0.13-1.35)
Unknown	7 (2.9)	0 (0.0)	-
Body mass index (kg/m2)			
< 22	102 (42.5)	91 (37.0)	1.00 (reference)
22~	72 (30.0)	94 (38.2)	0.74 (0.47-1.16)
25~	64 (26.7)	61 (24.8)	1.14 (0.70-1.86)
Unknown	2 (0.8)	0 (0.0)	-
Age at menarche (years)			
≤12.0	41 (17.1)	53 (21.5)	1.00 (reference)
12.1-13.9	89 (37.1)	110 (44.7)	0.95 (0.57-1.59)
≥14.0	100 (41.7)	80 (32.5)	1.31 (0.76-2.23)
Unknown	10 (4.2)	3 (1.2)	-
Menopausal status			
Premenopausal	135 (56.3)	105 (42.7)	1.00 (reference)
Postmenopausal	103 (42.9)	141 (57.3)	0.45 (0.25-0.79)
Unknown	2 (0.8)	0 (0.0)	-
Age at menopause (years)*			
≤45.0	23 (22.3)	24 (17.0)	1.00 (reference)
~50.0	36 (35.0)	61 (43.3)	0.55 (0.26-1.17)
>50.0	35 (34.0)	47 (33.3)	0.69 (0.31-1.52)
Unknown	9 (8.7)	9 (6.4)	-
Parity			
0	30 (12.5)	19 (7.7)	1.00 (reference)
1	99 (41.3)	152 (61.8)	0.51 (0.26-1.01)
≥2	111 (46.2)	75 (30.5)	1.02 (0.49-2.13)
Family history of breast cancer			
Absent	5 (2.1)	7 (2.8)	1.00 (reference)
Present	233 (97.1)	239 (97.2)	1.43 (0.41–4.96)
Unknown	2 (0.8)	0 (0.0)	-

†Adjusted for age; *Postmenopausal women only. CI=confidence interval

assess the associations of the suspected or established risk factors of breast cancer (Table 1), and the effects of urinary levels of cesium 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 cesium as continuous (linear) as well as categorical (tertiles) variables. Tertiles of urinary cesium level were defined as follows: tertile 1, <16.91; tertile 2, 16.91-23.48; tertile 3, >23.48, based on the values (μg/g creatinine) of the controls. Tests for trend of the urinary cesium levels in breast cancer risk were performed by assigning ordinal scores (1, 2, 3) to the tertiles and modelling the variable as a continuous parameter in the logistic regression model.

Table 2. Multivariate Odds Ratio of Breast Cancer Associated with Creatinine-Adjusted Urinary Levels of Cesium#

Metal concentrationlevel	Cases n (%)	Controls n (%)	OR (95%CI)*	OR (95%CI)†
T1	107 (44.6)	82 (33.3)	1.0 (reference)	1.0 (reference)
T2	70 (29.2)	82 (33.3)	0.70 (0.44-1.10)	0.75 (0.46-1.22)
T3	63 (26.3)	82 (33.3)	0.53 (0.33-0.85)	0.50 (0.30-0.82)
P for trend			0.008	0.006
Continuous (per 1 μg/g)			0.73 (0.57-0.92)	0.71 (0.55-0.91)

#Tertile of concentration (in μg/g): T1, <16.91; T2, 16.91-23.48; T3, >23.48. OR=odds ratio; CI=confidence interval; *Adjusted for age; †Adjusted for age, BMI, age at menarche, marital status, education, parity, menopausal status, and family history of breast cancer

Stratified analyses for associations between cesium levels and the risk of breast cancer were performed by menopausal status and clinical characteristics of HER2, ER, and clinical stage. The interaction between menopausal status and urinary cesium on breast cancer risk were evaluated by multiplicative models by including the product term in multivariate logistic regression. 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. All statistical tests were two-tailed with $P < 0.05$ considered to be significant. Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Breast cancer cases, as compared with similarly aged controls, 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 (25^{th}, 75^{th}) μg/g] of cesium in cases and controls were 17.60 (13.11, 24.01) and 19.29 (15.31, 25.68), respectively.

After adjustment for age only, women in the second and the highest tertile of cesium decreased 30% and 47% risk of breast cancer with P values of 0.124 and 0.009, when compared with those in the lowest tertile, respectively (Table 2). This trend for decreased risk of breast cancer was statistically significant (p=0.008),

Table 3. Stratified Associations of Urinary Cesium Levels and Breast Cancer Risk by HER2, ER, Clinical Stage, and Menopausal Status

Metal level			Cases, n*(%)	Controls, n (%)	OR (95%CI)#	P for trend
Stratified by HER2	HER2 positive or equivocal	T1	32 (42.7)	82 (33.3)	1.0 (reference)	0.036
		T2	23 (30.7)	82 (33.3)	0.77 (0.38-1.59)	
		T3	20 (26.7)	82 (33.3)	0.44 (0.21-0.94)	
	HER2 negative	T1	68 (45.9)	82 (33.3)	1.0 (reference)	0.018
		T2	40 (27.0)	82 (33.3)	0.66 (0.37-1.16)	
		T3	40 (27.0)	82 (33.3)	0.50 (0.28-0.89)	
	P for heterogeneity				0.863	
Stratified by ER	ER positive	T1	75 (46.9)	82 (33.3)	1.0 (reference)	0.01
		T2	42 (26.3)	82 (33.3)	0.60 (0.34-1.04)	
		T3	43 (26.9)	82 (33.3)	0.49 (0.28-0.85)	
	ER negative	T1	26 (39.4)	82 (33.3)	1.0 (reference)	0.157
		T2	22 (33.3)	82 (33.3)	0.99 (0.46-2.14)	
		T3	18 (27.3)	82 (33.3)	0.54 (0.23-1.24)	
	P for heterogeneity				0.865	
Stratified by clinical-stage	Localized	T1	65 (45.8)	82 (33.3)	1.0 (reference)	0.014
		T2	43 (30.3)	82 (33.3)	0.74 (0.42-1.30)	
		T3	34 (23.9)	82 (33.3)	0.47 (0.26-0.86)	
	Regional/distant	T1	36 (43.4)	82 (33.3)	1.0 (reference)	0.105
		T2	23 (27.7)	82 (33.3)	0.69 (0.34-1.39)	
		T3	24 (28.9)	82 (33.3)	0.56 (0.28-1.14)	
	P for heterogeneity				0.645	
Stratified by menopausal-status	Premenopausal	T1	71 (52.6)	82 (33.3)	1.0 (reference)	0.042
		T2	32 (23.7)	82 (33.3)	0.50 (0.24-1.03)	
		T3	32 (23.7)	82 (33.3)	0.48 (0.23-1.02)	
	Postmenopausal	T1	35 (34.0)	82 (33.3)	1.0 (reference)	0.043
		T2	37 (36.0)	82 (33.3)	0.97 (0.45-2.11)	
		T3	31 (30.0)	82 (33.3)	0.42 (0.18-0.97)	
	P for interaction				0.93	

*The number may not equal to the total number due to missing; #Adjusted for age, BMI, age at menarche, marital status, education, parity, menopausal status, and family history of breast cancer

indicating that there was a dose-response relationship between levels of urinary cesium and breast cancer risk. In the multivariate adjustment with known and suspected risk factors of breast cancer, the results were not essentially changed. The fully adjusted ORs and 95% CIs were 0.75 (0.46-1.22) and 0.50 (0.30-0.82), respectively (Table 2). In the model using cesium concentrations as continuous (linear), for every 1 μg/g increase in cesium, we observed that the breast cancer risk was significantly decreased (OR=0.71; 95% CI=0.55-0.91).

Then, we attempted to examine whether the disease process or clinical characteristics per se may have altered the association between urinary levels of cesium and breast cancer risk by carrying out several exploratory stratified analyses. Similar associations to that combined between breast cancer risk and urinary levels of cesium were observed across HER2 statuses (positive or equivocal versus negative) and menopausal statuses (Table 3). However, the decrease of breast cancer risk was more evident in women with ER-positive (OR for T3 versus T1=0.49, 95% CI= (0.28 - 0.85) than ER-negative (OR for T3 versus T1=0.54, 95% CI= (0.23-1.24) and localized stage (OR for T3 versus T1=0.47, 95% CI= (0.26-0.86) than regional or distant stage (OR for T3 versus T1=0.56, 95% CI= (0.28-1.14), although the differences did not reach statistical significance (P for heterogeneity >0.05) (Table 3).

Discussion

In the present study, we found that the urinary level of cesium was significantly inversely associated with the risk of breast cancer in a dose-dependent manner, and this association was more evident in women with ER-positive or localized clinical stage.

Although cesium has not been approved as an anticancer drug in the United States or other countries, a few studies have suggested its anticancer efficacy. Cesium is a potassium channel blocker, which has been shown to stop cell proliferation and tumor growth in a variety of cell types via an arrest in the G0/G1 transition during the cell cycle (Wonderlin and Strobl, 1996; Lang et al., 2005; Weiger et al., 2007). Weiger et al found that cesium halted cell proliferation in the C6 glioma cells via a polyamine-dependent mechanism (Weiger et al., 2007). Brewer established a high pH cancer therapy of cesium based on the theory that the optimal pH range for cancer cells was 6.2-7.0 (Brewer, 1984). He found that CsCl increased the pH in the cancer cells, bringing them up in a few days to the pH 8 or above where the life of cancer cells was short (Brewer, 1984). In addition, the presence of cesium salt in the body fluids neutralizes the acid toxins leaking out of the tumor mass and renders them nontoxic (Brewer, 1984). Recently, Low and coworkers have shown that CsCl can slow the growth of the PC-3 nude mice tumor model when administered at 0.8-1.2 g/kg (Low et al., 2007). They further speculated that a mechanism for CsCl's therapeutic effect may be similar to its mechanism for disrupting cardiac function (Low et al., 2007). Cesium may block potassium channels, which play a role in repolarizing cells back to their resting potential at depolarized levels to ensure unlimited tumor growth (Low et al., 2007; Arcangeli et al., 2009). Cesium chloride may also mask cell differentiation (separating cancer cells from healthy cells) and selectively play roles in cancer cells (Giles, 2008).

Cesium is the 45th most abundant metal in the earth's crust, an intermediate place in the abundance table (Ghosh et al., 1993). It has both radioactive forms and stable forms. The former are produced in the high-yield fission of uranium and plutonium from atomic fallouts. Stable cesium, on the other hand, is present in air, soil, water as well as in living organisms, permitting an efficient transfer through the soil-plant-food chain to human body (Ghosh et al., 1993). It is mainly deposited in muscles and other soft tissues, giving a relatively long half-life of 50-150 days (Rundo, 1964; Ghosh et al., 1993). Based on the available data, cesium concentrations in human urine are found to vary among different populations. In a sample from the US National Health and Nutrition Examination Survey (NHANES III), it was 1.51 (μg/g of creatinine) (median) (Paschal et al., 1998), whereas the US CDC's Fourth National Report on Human Exposure to Environmental Chemicals showed 4.77 (μg/g of creatinine) (median) among women (Centers for Disease control and Prevention (CDC), 2014). In a Spain female population, the urinary cesium level was 8.0 (μg/g of creatinine) (median) (Fort et al., 2014). In the present study, the level of urinary cesium in the control group was 19.29 (μg/g of creatinine) (median), which is the first report in China, higher than that in other populations. This difference may be attributed to the variation in diet compositions and natural environment among different areas. It was reported that cesium daily dietary intake in Chinese (13 μg/day) was higher than that in Americans (10 μg/day) and in the Canadians (6.6 μg/day) with a Market Basket Method approach (Wang et al., 2002; Akhter et al., 2003). Taking body mass into consideration, this difference is even bigger. Furthermore, given that cesium has an anticancer efficacy, higher levels of cesium in Chinese population may be one of the reasons why the incidence of breast cancer is much lower in China than in the USA (McCracken et al., 2007; Fan et al., 2014; Liu et al., 2014). The present results show that the higher urinary cesium levels were, the more breast cancer risk decreases, indicating that the levels of cesium in Chinese population are still in the beneficial range.

One of the strengths in this study is that the possibility of a differential measurement error is very low because cesium exposures were evaluated in urine and so did not depend on women's reports, and the laboratory assessment was blind in relation to case/control status. Moreover, in all the cases, the urine samples for cesium determination were obtained immediately after their admission to hospitals before treatment began, so the metal exposures in them were not influenced by treatment or change in lifestyles due to disease status. Furthermore, although breast cancer may cause change in the physiological function, no obvious evidence is available suggesting that the breast cancer status would change the absorption, metabolism, and excretion of cesium.

A main limitation of this study is the fact that this case-

control study is hospital-based; thus the patients might not be a representative sample of the entire patient population in Guangzhou area. However, the selection bias may be reduced because the hospital-based controls had similar probability to be seen at the same hospitals as the cases who were diagnosed with breast cancer (Wacholder et al., 1992; Wacholder et al., 2002). Furthermore, there is no reason to suspect that women who visit the recruited hospitals are more or less exposed and sensitive to cesium than those visiting other hospitals in Guangzhou area. Moreover, a focused hospital-based case-control study can enhance the response rates, which is another strength of this study, and can better facilitate the collection of urines before any treatment as well as patients' awareness of their disease status than a population-based case-control study (Wacholder et al., 2002). Another limitation of this study is that external exposures were not considered, such as dietary and occupational factors, which are related to urinary levels of cesium. However, the urinary concentration is an integral internal measurement of external exposure through multiple sources and routes. Nevertheless, because this is a small-scale retrospective study and we cannot determine whether the altered distribution of urinary cesium is a cause or a consequence of breast cancer, larger and prospective studies are required.

In conclusion, the present results showed for the first time that exposure to cesium, as assessed by urinary concentration, was significantly associated with a decrease in breast cancer risk. This association was more evident in women with ER-positive or localized clinical stage. These findings suggest that cesium may have anticancer efficacy and urinary cesium have potential to be a biomarker for breast cancer risk assessment, but warrant further study on the biological mechanisms. Larger population studies, particularly prospective follow-up studies, are deserved.

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