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Dietary intake and urinary level of cadmium and breast cancer risk: A *meta*-analysis

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ABSTRACT

Cadmium, a human carcinogenic heavy metal, has been reported to be associated with breast cancer risk; however, the results from the epidemiological studies are not always consistent. The objective of this study was to quantitatively summarize the current evidence for the relationship between cadmium exposure and breast cancer risk using *meta*-analysis methods. Six studies determining the dietary cadmium intake level and five studies evaluating the urinary cadmium level were identified in a systematic search of MEDLINE and PubMed databases, and the associations between these levels and breast cancer risk were analysed. The pooled estimates under the random-effects model suggested that higher urinary cadmium levels were associated with an increased risk for breast cancer (highest versus lowest quantile, pooled odds ratio [OR] = 2.24, 95% confidence interval [95%CI] = 1.49–3.35) and a 1 μg/g creatinine increase in urinary cadmium led to a 1.02-fold increment of breast cancer (pooled OR = 2.02, 95%CI = 1.34–3.03); however, pooled estimates for dietary cadmium intake found no significant association between cadmium exposure and breast cancer risk (highest versus lowest quantile, pooled relative risk [RR] = 1.01, 95%CI = 0.89–1.15). These results suggest that cadmium exposure may lead to an increased risk of breast cancer, and urinary cadmium levels can serve as a reliable biomarker for long-term cadmium exposure and may predict the breast cancer risk.

1. Introduction

Breast cancer is one of the most prevalent cancers in women around the world. It was estimated that 39,510 women and 410 men globally died from breast cancer in 2012 [1]. Risk factors – including genetic factors, alcohol intake, smoking, obesity, low physical activity, menstrual history, and pregnancy history etc. – that may contribute to breast cancer development have been identified [2]. It has been proposed that estrogen-mimicking contaminants may also contribute to the increased risk of breast cancer [3]. The heavy metals, which are usually dispersed into the environment through industrial emission, waste incineration, and combustion of fossil fuels, were found to have estrogenic activities. Cadmium, one of the most common food- and water-borne heavy metals, accumulates in the human body with age. Cadmium may induce cancer through several mechanisms, such as aberrant gene expression, inhibition of DNA damage repair, induction of oxidative stress, and inhibition of apoptosis [3]. In vitro molecular studies have shown that cadmium acts like estrogen in breast cancer cell lines, forming a high-affinity complex with the hormone-binding domain of the estrogen alpha receptor (ERα) and stimulating its downstream signaling pathways [4]. Exposure to cadmium leads to the increased formation of side branches and alveolar buds of the mammary glands in female rats, and the female offspring of the rats showed an earlier onset of puberty, an increase in the epithelial area, and an increase in the number of terminal end buds in the mammary gland, suggesting that cadmium mimics the effects of estrogen in vivo [5]. High concentrations of cadmium in food is found in shellfish, offal products and certain seeds; however, due to a comparatively high accumulation of cadmium in agricultural crops and the high level of consumption of these products, the main sources of dietary cadmium exposure (~80%) are bread and other cereals, potatoes, root crops, and vegetables [6]. Tobacco is another major source of cadmium, with almost half the daily cadmium intake being inhaled from smoking in heavy smokers [7].

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In humans, cadmium has an elimination half-life of 12–30 years [6,8]. Compared to other common heavy metal pollutants, the urinary cadmium level has been suggested as a stable biomarker for individual lifetime exposure, providing a possible method for assessing the lifetime body burden of cadmium [9,10]. To date, several epidemiological studies have evaluated the associations between the dietary cadmium intake, the urinary cadmium level, and the breast cancer risk; however, the results were always conflicting and inconsistent [11–21]. For example, Julin et al. reported a significant association between the dietary cadmium intake and postmenopausal breast cancer risk [14], while other studies that have determined the association between dietary cadmium intake level and breast cancer risk found no such association [13,16–18,21]. Epidemiological studies have also evaluated the association between the urinary cadmium level and breast cancer risk; some of them came to the conclusion that women with higher urinary cadmium levels showed an increased risk for breast cancer, but with different amplitude [11,12,15,19]. In addition, the concentration of cadmium was found to be higher in the breast cancer tissues than it was in the adjacent normal or benign breast tissue, suggesting that cadmium exposure may contribute to breast tumorigenesis [22,23]. Thus, the aim of the current study was to systematically review the evidence for the tumorigenic activities of cadmium in breast cancer from the observational epidemiological studies, and to quantitatively evaluate the associations between dietary cadmium intake level, urinary cadmium exposure level, and the risk of breast cancer using *meta*-analysis methods.

2. Materials and methods

2.1. Identification of eligible studies

We conducted a search of MEDLINE/PubMed and Scopus databases with the keywords “cadmium” OR “cadmium compounds” OR “cadmium poisoning” AND “breast neoplasms” OR “breast cancer” to identify the published eligible studies (updated to March 2016) that have evaluated associations between dietary cadmium intake and urinary cadmium levels and the breast cancer risk. The titles and abstracts of the identified studies were initially assessed; and the whole reports were checked when necessary. References in the included studies and the reviews were also checked to identify any studies missing from the database search.

2.2. Study inclusion and exclusion

Studies included in the *meta*-analysis should provide information on any association between the dietary intake level or/and urinary cadmium level and the breast cancer risk. Eligible studies were those providing sufficient data about cadmium exposure level (including dietary intake and/or urinary level) in quantiles with the corresponding risk estimates [relative risk (RR) or odds ratio (OR)] and their 95% confidential intervals (95%CIs); or those providing the estimates and the corresponding 95%CIs for the highest quantile in contrast with the lowest quantile; or those providing sufficient data that could be used to calculate the risk estimate and its 95%CI for the highest quantile relative to lowest quantile of cadmium exposure. The eligible study types were case–control, cohort, and cross-sectional studies.

2.3. Data extraction

The information extracted included the last name of the first author, publication year, the country in which the study was performed, population size for cases and controls, dietary cadmium in quantiles or urinary cadmium in quantiles, the estimated risks and the corresponding 95%CIs that reflected the most complete degree of adjustment for potential confounders, the adjusted confounders. Features of individual studies are summarized in Table 1 and the working flowchart is shown in Fig. 1.

2.4. Study quality assessment

We followed the Newcastle–Ottawa quality scale protocol to assess the quality of the evidence on the association between the dietary cadmium intake level/urinary cadmium level and breast cancer risk [24]. For each case–control or cohort study, a total of nine points was designated based on the characteristics of the studies, including: (1) the selection of the comparison groups with a total score of 4; (2) the comparability between the groups with a total score of 2; and (3) the quality of the measurement of the exposure and the outcomes with a total score of 3. The quality score for the eligibility ranged between 5 and 8, and we deemed that those with a score $\geq$7 were higher quality studies.

2.5. Statistical analysis methods

To assess the relationship between breast cancer risk and exposure to cadmium, the pooled estimates were synthesized with a standard inverse-variance weighting method under the random-effects model, which considers the heterogeneity between and within studies [25]. To establish the appropriate weighting for each study, the standard error (SE) for each logarithm odds ratio (OR) or relative risk (RR) was calculated, and it was recognized as the estimated variance of the logOR/RR. The assessment of heterogeneity between the studies was performed using Cochrane’s Q test in combination with the I^2 statistic. Publication bias was assessed using Egger’s test, in which a regression model was established, using the standardized estimate of size effect as a dependent variable and the inverse of the standard error as an independent variable [26]. The sensitivity analysis was performed to identify individual studies that may significantly affect the pooled estimates through calculating the pooled estimates of the remaining studies after the exclusion of individual studies repeatedly. To assess the dose–response effects between urinary cadmium level (μg cadmium/g creatinine) and the breast cancer risk, we normalized the risk estimate OR for 1 μg increment of cadmium/g creatinine with the generalized least square estimated trend (GLST) analysis methods proposed by Orsini et al. [27]. All of the statistical analyses were performed with R software and the Meta package (www.r-project.org). All the tests were two-sided, and a *P* value of less than 0.05 for any test was considered to be statistically significant.

3. Results

3.1. Data selection

In total 189 studies were identified through a systematic search of the PubMed and MEDLINE databases. We excluded 166 manuscripts by checking the titles and abstracts. Ten studies were excluded from the final analysis as they did not determine the dietary intake level or urinary level of cadmium and the breast cancer risk. Eleven studies fully met the inclusion criteria and were included in the *meta*-analysis [11–21]. Of these, six have determined the association between the dietary cadmium intake level and the breast cancer risk [13,14,16–18,21] and five have determined the urinary cadmium level and the breast cancer risk [11,12,15,19,20]. Four studies were performed in the United States, four in Japan, and one in China (Table 1). The working flowchart is shown in Fig. 1.