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# Dietary cadmium intake and breast cancer risk in Japanese women: A case–control study

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ABSTRACT

Cadmium, an environmental pollutant, may act like an estrogen and be a potential risk factor for estrogen-dependent diseases such as breast cancer. We examined the hypothesis that higher dietary cadmium intake is associated with risk of overall and hormone receptor-defined breast cancer in Japanese women, a population with a relatively high cadmium intake. The study was conducted under a case–control design in 405 eligible matched pairs from May 2001 to September 2005 at four hospitals in Nagano Prefecture, Japan. Dietary cadmium intake was estimated using a food frequency questionnaire. Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer and its hormone-receptor-defined subtypes were calculated by tertile of dietary cadmium intake. We found no significant association between dietary cadmium and risk of total breast cancer in either crude or multivariable-adjusted analysis. Adjusted ORs for tertiles of cadmium intake were 1.00, 1.19, and 1.23 (95% CI, 0.76–2.00; *P* for trend = 0.39) for whole breast cancer. Further, no significant associations were seen across strata of menopausal status, smoking, and diabetes in multivariable-adjusted models except for adjusted OR for continuous cadmium intake in postmenopausal women. A statistically significant association was found for estrogen receptor-positive (ER+) tumors among postmenopausal women (adjusted OR = 1.00, 1.16, and 1.94 [95% CI, 1.04–3.63; *P* for trend = 0.032]). Although the present study found no overall association between dietary cadmium intake and breast cancer risk, higher cadmium intake was associated with increased risk of ER+ breast cancer in postmenopausal women, at least at regular intake levels in Japanese women in the general population. Further studies are needed to confirm this association.



## Introduction

The environmental pollutant cadmium, a toxic and highly bioaccumulative heavy metal, may act like an estrogen. Cadmium has displayed estrogenic properties in both in vitro and in vivo studies (Henson and Chedrese, 2004; Johnson et al., 2003; Safe, 2003; Stoica et al., 2000; Takiguchi and Yoshihara, 2006). Cadmium competes with estradiol in binding to estrogen receptors (ERs), and activates these receptors (Stoica et al., 2000). Accordingly, cadmium may play a role in the development of ER-positive (ER+) breast cancer. Johnson et al. (2003) also reported that cadmium increased uterine weight and promoted hyperplasia of mammary glands in female rats. A positive association between urinary cadmium and serum testosterone among postmenopausal Japanese women has also been reported (Nagata et al., 2005). This hypothesized role of cadmium in the etiology of breast cancer, an estrogen-dependent disease, has recently focused attention on its estrogenic activity (Antila et al., 1996; Gallagher et al., 2010; Julin et al., 2012; McElroy et al., 2006; Sawada et al., 2012).

Humans are exposed to cadmium on a daily basis, mainly via the consumption of environmentally contaminated rice and other foods (Ikeda et al., 2006) and cigarette smoking (Ikeda et al., 2005).

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In particular, Japanese people, who eat rice as their staple food, tend to ingest relatively high levels of cadmium. For example, geometric mean cadmium intake via food in a general population in Japan (25.5 μg/day) (Watanabe et al., 2000) is higher than that in China (9.9 μg/day) (Zhang et al., 1997) and Sweden (mean, 15 μg/day) (Åkesson et al., 2008; Julin et al., 2011, 2012). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) proposed a provisional tolerable monthly intake for cadmium aimed at preventing renal tubular dysfunction of 25 μg/kg body weight/month (WHO, 2011).

Although the association between cadmium exposure and breast cancer has been examined in several epidemiologic studies, findings to date have been inconsistent. Recent population-based case–control and cross-sectional studies in the United States showed that higher urinary levels of cadmium were associated with an increased risk of breast cancer (Gallagher et al., 2010; McElroy et al., 2006), while a cohort study in Sweden reported that dietary cadmium intake evaluated by food frequency questionnaire (FFQ) was associated with an increased risk of postmenopausal breast cancer (Julin et al., 2012). In contrast, a small case–control study in Helsinki found no significant difference in cadmium in breast fat between breast cancer cases and controls (Antila et al., 1996), while a population-based prospective cohort study in Japan found no increased risk of breast cancer in relation to dietary cadmium intake evaluated by FFQ (Sawada et al., 2012). To the best of our knowledge, however, previous case–control and cross-sectional studies have been relatively small (≤246 cases) and have not considered hormone receptor-defined subtype of breast cancer. In fact, only Julin et al. (2012) assessed the association between cadmium exposure and risk of ER-defined breast cancer, but took no account of progesterone receptor (PR) status. ER and PR are widely studied markers in breast tissue, and the clinical, pathologic, and molecular features of breast cancers differ by their ER and/or PR expression profile (Althuis et al., 2004). Because the effects of risk factors of breast cancer, such as reproduction-related exposures and postmenopausal obesity, also differ by ER/PR status (Althuis et al., 2004), assessing the association between cadmium exposure and hormone receptor-defined subtype may provide further insights into its etiology. Further, despite the difference between Western and Asian women in internal hormonal milieu, exposure intensity, and lifestyle, including dietary habits, only one study to date has been conducted in Asian women (Sawada et al., 2012), and that study made no assessment of hormone receptor-defined risk. Thus, epidemiological evidence for the association between cadmium exposure and risk of ER/PR-defined breast cancer is lacking, particularly in Asian women.

Here, we evaluated whether higher dietary cadmium intake was associated with the risk of overall and hormone receptor-defined breast cancer in Japanese women.

## Materials and methods

### *Study subjects*

The subjects of the study have been described in detail elsewhere (Itoh et al., 2009). Briefly, the study was conducted under a multicenter, hospital-based case–control design from May 2001 to September 2005 at four hospitals in Nagano Prefecture, Japan. Case patients were a consecutive series of women aged 20–74 years with newly arising, histologically confirmed invasive breast cancer admitted to any of the four hospitals during the survey period. Of 412 eligible patients, 405 (98%) agreed to participate. Healthy control subjects were selected from among medical checkup examinees in two of the hospitals, who were confirmed to not have cancer, with one control matched with each case by age (within 3 years) and residential area during the study period. Among potential control subjects, one declined to participate, and written informed consent was consequently obtained from 405 matched pairs. The study protocol was approved by the institutional review board of the National Cancer Center (Tokyo, Japan).

### *Data collection*

#### *Questionnaire survey (except FFQ)*

Participants were asked to complete a self-administered questionnaire which included questions on demographic characteristics, anthropometric factors, smoking habits, family history of cancer, physical activity, medical history, and menstrual and reproductive history.

#### *Assessment of cadmium intake by FFQ*

The method used to assess dietary cadmium intake has been described in detail elsewhere (Sawada et al., 2012). Dietary habits were investigated using a 136-item semi-quantitative FFQ which was developed and validated in a Japanese population (Sasaki et al., 2003). The FFQ evaluates average food intake over the last 1 year. The FFQ inquires about the frequency of consumption of individual food items, with the response choices of never or less than once/month, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–6 times/day, and 7 times/day or more; as well as relative sizes compared to standard portions, expressed as small (50% smaller than standard), medium (same as standard), and large (50% larger). These data were then used to calculate consumption for each food group (g/day), nutrients (mg/day), and cadmium (μg/day).

Data on the cadmium content of food was obtained from JECFA and the Committee on Pharmaceutical and Food Sanitation of the Ministry of Health, Labour and Welfare in Japan (Committee on Pharmaceutical and Food Sanitation, 2008; Egan et al., 2006). As described in our previous paper (Sawada et al., 2012), we finally selected the following 6 food groups: rice (3 items: “boiled rice”, “boiled rice cooked with millet or barley”, and “rice cake”), wheat (5 items: “bread”, “Japanese noodles (udon)”, “Chinese noodles”, “biscuits or cookies”, and “cake”), soybeans (6 items: “tofu”, “koyadofu [freeze-dried tofu]”, “aburaage [deep-fried tofu]”, “natto [fermented soybean]”, “soy milk”, and “miso soup”), stem/root vegetables (4 items: “taro”, “carrot”, “Japanese radish”, and “sweet potato”), leafy vegetables (6 items: “komatsuna [Japanese mustard spinach]”, “Chinese cabbage”, “spinach”, “lettuce”, “pickled green vegetables”, and “pickled Chinese cabbage”), and other vegetables or fruits (10 items: “onion”, “cabbage”, “broccoli”, “melon”, “cucumber”, “watermelon”, “pumpkin”, “green pepper”, “pickled cucumber” and “pickled eggplant”). For rice, samples were collected from all over Japan; mean cadmium content varied from 0.04 (Kyushu area) to 0.10 (Hokuriku area) mg/kg (Committee on Pharmaceutical and Food Sanitation, 2008). Such geographical variation for rice was considered in our calculations, as detailed in a previous paper (Sawada et al., 2012). Nagano Prefecture was included in the Kanto area. On the other hand, historical trends in the cadmium content of foods were not considered in our analysis, although concentrations in rice in Japan have changed to some extent over time (Ono et al., 2008). We estimated daily cadmium intake by multiplying the frequency of consumption by portion size and the average cadmium content in each food item (Sawada et al., 2012).

The validity of cadmium intake estimated from the FFQ was evaluated in a subsample of the Japan Public Health Center-based Prospective Study, which includes Nagano Prefecture as one of the study areas (Sawada et al., 2012). Estimated cadmium intake on the basis of the FFQ was compared to 24-h urinary cadmium excretion (μg/day). Spearman’s rank correlation coefficient between