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Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women

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ABSTRACT

Osteoporosis and its main health outcome, fragility fractures, are large and escalating public health problems. Cadmium, a widespread food contaminant, is a proposed risk factor; still the association between estimated dietary cadmium exposure and bone mineral density (BMD) has never been assessed. Within a sub-cohort of the Swedish Mammography Cohort, we assessed dietary cadmium exposure based on a food frequency questionnaire (1997) and urinary cadmium (2004–2008) in relation to total-body BMD and risk of osteoporosis and fractures (1997–2009) among 2676 women (aged 56–69 years). In multivariable-adjusted linear regression, dietary cadmium was inversely associated with BMD at the total body and lumbar spine. After further adjustment for dietary factors important for bone health and cadmium bioavailability—calcium, magnesium, iron and fiber, the associations became more pronounced. A 32% increased risk of osteoporosis (95% CI: 2–71%) and 31% increased risk for any first incident fracture (95% CI: 2–69%) were observed comparing high dietary cadmium exposure (≥13 μg/day, median) with lower exposures (<13 μg/day). By combining high dietary with high urinary cadmium (≥0.50 μg/g creatinine), odds ratios among never-smokers were 2.65 (95% CI: 1.43–4.91) for osteoporosis and 3.05 (95% CI: 1.66–5.59) for fractures. In conclusion, even low-level cadmium exposure from food is associated with low BMD and an increased risk of osteoporosis and fractures. The partial masking of the associations by essential nutrients indicates important interplay between dietary factors and contaminants present in food. In separate analyses, dietary and urinary cadmium underestimated the association with bone effects.

1. Introduction

Cadmium, a ubiquitous environmental pollutant may possess a wide range of negative effects on human health [1]. Food is the main source of exposure, but smokers are additionally exposed as a result of the high cadmium content of tobacco leaves and the relative high absorption of cadmium in the lung. In areas with cadmium-contaminated soils, house dust is potentially an important route of exposure to the metal [2]. In food, the highest concentrations are present in mollusks and crustaceans, offal products and certain seeds [3]. Plant food generally contains higher concentrations than meat, dairy products, and fish. Among plant foods, the highest concentrations are generally present in cereals such as wheat (especially whole grain) and rice, leafy green vegetables and in potatoes and root vegetables [3–5]. Thus, cereals and vegetables—important dietary sources of minerals, antioxidants and fiber—contribute to ~80% of dietary cadmium exposure [4–6].

In a public health context, the association between cadmium exposure and osteoporosis and fractures observed in the general population [7–12] is of particular concern. With one exception [12], all studies are based on measurements of urinary cadmium, a biomarker of long-term cadmium exposure from all sources [13]. Thus, it is not known to what extent dietary cadmium per se is associated with low bone mineral density (BMD) and with osteoporosis.

We assessed the associations between questionnaire-based estimates of dietary cadmium exposure and BMD and risk of osteoporosis and fractures in the same sub-cohort of women from a well-characterized population-based prospective cohort, where we previously observed clear associations between urinary cadmium and bone effects [11]. We also assessed whether the associations were affected by the co-presence of dietary factors, both those beneficial for bone health and those affecting the bioavailability of cadmium. Thirdly, we evaluated the suitability of the two exposure markers used in relation to effects on bone.

2. Material and methods

2.1. Study population

The Swedish Mammography Cohort (SMC) was established in 1987–1990, when all 90,303 women residing in two counties

Abbreviations: Cr, Creatinine; EFSA, European Food Safety Authority; FFQ, Food frequency questionnaire; ICPMS, Inductively coupled plasma mass spectrometry; TWI, Tolerable weekly intake.

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(Uppsala and Västmanland) in central Sweden and born between 1914 and 1948, received a mailed invitation to be screened by mammography. Enclosed with this invitation was a six-page questionnaire covering diet, body size, education and parity and 66,651 (74%) of the women completed the questionnaire. In the autumn of 1997 a second questionnaire (baseline in the present study) was sent to all 56,030 participants who were still alive and living in the study area to update dietary data and to collect information on several life-style factors and medical history of certain diseases (response rate 70%).

Between 2003 and 2009, all women (n = 8311, aged 54–85 years) in the cohort residing in Uppsala town were randomly invited to complete a detailed questionnaire, to undergo total-body BMD (dual energy X-ray absorptiometry; DXA) and weight and height measurements, and to provide first voided morning urine sample (from 2004). During this period, 5022 women underwent BMD measurements and 4276 women provided urine samples. As previously described in detail [11], we selected all women below 70 years of age to avoid an inverse effect of old age on kidney cadmium accumulation. Women with diabetes (n = 132; based on self-reports and on computerized linkage of the cohort to the National Patient Registry) were excluded because they have an increased risk of fractures that might not be explained by low BMD, and that the dietary advice given to diabetics include consumption of foods high in cadmium. For the present study we additionally excluded women with implausible values for energy intake (three standard deviations from the mean value of $\log_e$-transformed energy intake; n = 12), leaving 2676 women to be included in this study. These women had similar mean dietary cadmium exposure (13 μg/day) as the women in the main cohort in 1997.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden, and written informed consent was obtained from each participant.

2.2. Assessment of diet and covariates

At baseline the women completed a 96-item food frequency questionnaire (FFQ). The FFQ has previously been validated against weighted food records; Pearson correlation coefficients ranged from 0.5 to 0.8 for vegetables, potatoes and bread (Wolk, unpublished data). A food-cadmium database was constructed based on the cadmium content of all foods available on the Swedish market as previously reported [6,14]. The data were provided by the National Food Administration [15–17] except for a few items where Finnish and Danish data were used [18–20]. The average cadmium concentration was used for each food item because there is no detected geographic variation of cadmium content in foods across Sweden, and most foods are distributed throughout Sweden by few wholesale companies [17]. The exposure from drinking water is low (0.2% of total cadmium intake [21]) and was ignored. Cadmium intake calculated by multiplying the frequency of consumption of each food type (from the 1997 FFQ) by its cadmium content using age-specific portion sizes (based on 5922 weighted food records kept by 213 randomly selected women from the study area). From the FFQ, we also assessed the dietary intake of calcium, magnesium, iron and fiber. Calcium, magnesium, iron and fiber are important for bone health [22–25]; iron and fiber affect the bioavailability of cadmium [26]. The intakes was adjusted to total energy intake of 1700 kcal (mean in the cohort) using the residual method [27].

We also obtained information on level of education and on the type and amount of alcoholic beverages consumed. We categorized smoking status into "never" or "ever smoking", and use of postmenopausal hormones as "never" or "ever use". The total daily physical activity (multiples of the metabolic equivalent, MET, kcal/kg × h) was estimated by the reported duration of predefined activities with varying degrees of assigned intensity. The estimates of total physical activity had reasonable validity, deattenuated concordance correlations comparing the questionnaire to activity records was 0.6 and with accelerometers 0.4 [28]. Information on history of inflammatory joint diseases (10th revision of the International Classification of Disease, ICD: M05–M14) was based on self-reported information and on computerized linkage of the cohort to the National Patient Registry.

2.3. Assessment of bone mineral density, osteoporosis and fractures

As previously described in detail [11], BMD was measured at the total body (n = 2661), femoral neck (n = 2636) and lumbar spine (vertebrae L_2–L_4) (n = 2674) using DXA (DPX Prodigy, Lunar corp., Madison, WI, USA). When applicable, measurements from both extremities were used in the calculation (in 1.6% of the women only one-sided measurement of the femoral neck was available). The precision of the DXA BMD measurements was high [11]. Osteoporosis was defined as a *T*-score < −2.5; i.e. 2.5 SD [29] below the mean values of the reference population provided by the manufacturer. Information on all fractures (ICD 10 codes S12, S22, S32, S42, S52, S62, S72, S82 and S92) was obtained from mid-September 1997 (baseline) throughout March 2009 by computerized linkage of the cohort by the individual personal registration number provided to all Swedish citizens to the regional hospital diagnosis registries and to the National Patient Registry covering both outpatient and inpatient treated fractures.

2.4. Biomarker assessment

Urine sampling and the analysis of urinary cadmium have previously been described in detail [11]. In summary, cadmium concentrations (first voided morning urine) were measured using inductively coupled plasma mass spectrometry with collision cell to minimize interferences (ICPMS; Agilent 7500ce, Agilent Technologies, Waldbronn, Germany). A rigorous quality control program was applied to minimize the risk of contamination of urine and to ensure high analytical precision. Urinary cadmium (limit of detection: 0.002 μg/L) was adjusted to creatinine (cr) excretion (μg/g cr). The median concentration of urinary cadmium was 0.34 (5–95th percentile: 0.15–0.79) μg/g cr [11].

2.5. Statistical analyses

Univariate associations were assessed using Spearman's rank correlation coefficient (r_s). Associations between the estimated dietary cadmium exposure (in 1997)—rescaled to 10 μg/day-increment—and BMD were assessed using multiple linear regression analysis (BMD as a continuous dependent variable). Residual analyses indicated no major deviation from a linear pattern. We assessed the risk of osteoporosis (*T*-score < −2.5) and fractures using binary logistic regression with dietary cadmium included either as a continuous variable (rescaled to 10 μg/day-increment) or categorized into 2 groups: below (low) or above (high) the median of 13 μg/day. Possible multicollinearity was checked with tolerance (>0.1) and with variance inflation factor (VIF) (<10), and goodness-of-fit with Hosmer & Lemeshow test (>0.05). Non-linear association was tested by further adjustment for squared dietary cadmium. The combined effect of high dietary (baseline 1997) and urinary cadmium (2004–2008) was assessed by combining the high dietary cadmium category with that of urinary cadmium (≥0.50 μg/g cr). Women having a low dietary cadmium exposure (<13 μg/day) and urinary cadmium <0.50 μg/g cr constituted the reference category, while the remaining women were categorized into the intermediate category.

We examined the association between dietary cadmium exposure and the different outcomes, adjusting for age (Model 1), and additionally for body mass index, education, use of postmenopausal hormones, total physical activity, smoking status, alcohol consumption and inflammatory joint diseases based on data obtained in 1997