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Dietary cadmium exposure and kidney stone incidence: A population-based prospective cohort study of men & women

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ABSTRACT

Cadmium exposure is associated with increased urinary calcium excretion. Hypercalciuria is recognised as a major risk factor for kidney stone formation. Increased prevalence of kidney stones among those occupationally exposed to cadmium has previously been suggested. Food is the main source of cadmium exposure in the general population with tobacco representing an important additional source among smokers.

We aimed to assess the association between dietary cadmium exposure and kidney stone incidence in two large population-based, prospective cohorts of men (Cohort of Swedish Men; COSM) and women (The Swedish Mammography Cohort; SMC). Those with a history of kidney stones were excluded.

At baseline 1997, men (45–79 yrs) and women (48 to 83 yrs), completed a self-administered questionnaire on diet and lifestyle. During 12 years of follow-up, we ascertained 707 cases of kidney stones in men and 290 in women through linkage of the cohorts to the national inpatient and outpatient registers. Individual dietary cadmium exposure was estimated using dietary data and concentrations of cadmium in food. Hazard ratios (HR) were calculated using the Cox proportional hazards regression models with adjustment for other risk factors.

Estimated dietary cadmium exposure was not associated with increased kidney stone incidence among men HR 0.97 (95% confidence interval (CI): 0.77–1.23) or women HR 0.99 (95% CI: 0.89–1.43), comparing the highest tertile with the lowest. In conclusion, our results do not support a strong association between dietary cadmium and kidney stone risk at the exposure levels seen in the general population.

1. Introduction

Kidney stones cause severe pain and are highly recurrent (Moe, 2006). The prevalence of kidney stones is increasing (Romero et al., 2010; Stamatelou et al., 2003) suggesting that changes in nutritional or environmental factors may be important. Increased urinary calcium is recognised as a major risk factor for kidney stone formation (Curhan et al., 2001; Moe, 2006). Cadmium is a nephrotoxic metal present in food. Exposure to cadmium is associated with increased urinary calcium excretion (Buchet et al., 1990; Engstrom et al., 2011; Schutte et al., 2008); proposed to be a result of increased bone resorption and/or resorptive dysfunction caused by damage to the kidney tubule (Jarup and Akesson, 2009).

Occupational studies dating back 60 years have suggested that kidney stones may be more common among cadmium-exposed workers (Elinder et al., 1985; Scott et al., 1982), with one study reporting a significantly increased risk and dose-response among cadmium battery workers in Sweden (Jarup and Elinder, 1993). Cadmium in food is the main source of exposure in the general population, however, the kidney stone risk associated with long-term low-level cadmium exposure, such as that from the diet, has remained largely unexplored. Tobacco represents an important additional source among smokers. One previous cross-sectional study among a representative sample of the US population (NHANES III) showed a higher prevalence (odds ratio (OR) 1.40 95% CI: 1.06–1.86) of self-reported kidney stones among women with urinary cadmium levels >1 μg/g compared to those with ≤1 μg/g, however, no statistically significant association was observed among men (OR 0.89 95% CI: 0.67–1.19) (Ferraro et al., 2011).

In this study we aimed to assess the association between dietary cadmium exposure and kidney stone incidence in two large population-based prospective cohorts of men and women (Cohort of Swedish Men (COSM), Swedish Mammography Cohort (SMC)). The analysis was conducted with and without stratification by smoking status (ever/never). In both cohorts we have previously observed an increased risk of fracture in relation to dietary cadmium exposure (Engstrom et al., 2012; Thomas et al., 2011) as well as increased risks of breast (Julin et al.,

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; OR, odds ratio; SD, standard deviations; TWI, tolerable weekly intake.

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2012a), endometrial (Åkesson et al., 2008) and prostate cancers (Julin et al., 2012c).

2. Material & methods

2.1. Study populations

The study population is taken from two population-based prospective cohorts of men and women from central Sweden. The Cohort of Swedish Men (COSM) was formed in 1997. All men born between 1918 and 1952 and living in Örebro and Västmanland counties were invited to participate (response rate 49%). The Swedish Mammography Cohort (SMC) was formed between 1987–1990. All women born between 1914 and 1949 and living in Uppsala and Västmanland counties were invited to participate (response rate 74%). Those women who were still alive and living in the study area were sent a second questionnaire in 1997 (response rate 70%). In the current study, the 1997 questionnaire was used as baseline in both cohorts. The Regional Ethical Review Board in Stockholm, Sweden granted ethical approval for the study and return of the completed questionnaire was considered to imply informed consent.

From the baseline population (men n = 48,850; women n = 39,227), we excluded those with incorrect or incomplete national registration numbers, those who reported an implausible energy intake (±3 Standard deviations (SD) of mean log transformed energy) and those with pre-baseline diagnosis of cancer (not including non-melanoma skin cancer) through linkage to the National Cancer Register. Those with a pre-baseline diagnosis of diabetes were also excluded based on self-report and register data. In addition, we excluded those who were diagnosed with kidney stones prior to baseline, based on both register (men n = 1385; women n = 428) and self-report (men n = 4153; women n = 1290) data. Thus, the analytical cohorts for the primary analysis consisted of 35,545 men and 33,050 women.

2.2. Assessment of dietary intake and covariates

The self-administered questionnaires completed by both cohorts at baseline in 1997 included nearly 350 items on diet and other lifestyle factors. Dietary intake was assessed using a 96 item food frequency questionnaire (FFQ). Cadmium is present in food in its inorganic form, both as salts and bound to protein molecules. Dietary cadmium exposure was calculated using data from the FFQ and a database of the cadmium content of all food available on the Swedish market, as previously described (Åkesson et al., 2008). The database was constructed using data provided mainly by the National Food Administration. In calculating dietary cadmium intake we have used the national average cadmium concentration in each food item as most foods in Sweden are distributed throughout the country by a few wholesale companies (Jorhem, 1993) and there is no known industrial cadmium contamination of agricultural soil in any of the three counties covered by our study. Moreover the exposure from air (<1% of total exposure) (Vahter et al., 1991) and from drinking water (0.2% of total cadmium intake) (Olsson et al., 2002) is low and was ignored. Daily intakes of cadmium and nutrients were estimated by multiplying the frequency of consumption of each food type by its specific content using age specific portion sizes. Values were then adjusted to the mean energy intake in the cohorts (men 2600 kcal/day; women 1700 kcal/day) using the residual method (Willett and Stampfer, 1986). Cadmium is mainly absorbed from the gut in its ionic form by the DTM 1 transporter (Tallkvist et al., 2001) with approximately 3–5% (dependent on the body iron stores) (Åkesson et al., 2002; Berglund et al., 1994) of ingested cadmium being absorbed.

The method for estimating dietary cadmium exposure has been validated in a sample of 680 non-smoking women from the Swedish Mammography Cohort. Cross classification of FFQ-estimated dietary cadmium and urinary cadmium concentrations gave a sensitivity of 51% and a specificity of 58%. The Pearson's correlation coefficient between measured and modeled urinary cadmium (based on dietary cadmium) was 0.2 when accounting for within person variability (Julin et al., 2012b). The validity and reproducibility of the FFQ-derived nutrient intake have been assessed in a random population-based sample of 248 men aged between 40 and 74 years living in the study area. Each of the 248 men completed the FFQ, and 14 repeated 24-hour recall interviews carried out over the space of a year. Validation of the FFQ against 24 h recall data gave Spearman's rank correlation coefficients of: 0.65 for macronutrients, 0.77 for calcium, 0.38 for iron, 0.73 for magnesium, 0.65 for vitamin B6 and 0.81 for vitamin C intakes (Messerer et al., 2004). Data on height, weight, alcohol consumption, cigarette use, tea and coffee consumption, use of vitamin C supplements, diabetes, and hypertension, were also collected.

2.3. Case ascertainment

First incident cases of kidney stones (International Statistical Classification of Disease, Revision 10 (ICD-10) code N20) were ascertained from the 1st of Jan 1998 to the 31st of December 2010 by linkage of the study populations to the National Hospital Discharge Register, the Day Surgery Register (covering 1998–2000) and the Outpatient Register (covering 2001–2010) (Thomas et al., 2013). Information on date of death was obtained from the Swedish Death Register.

2.4. Statistical analysis

Men and women were categorised separately into tertiles of dietary cadmium exposure. The Cox proportional hazards regression model, using attained age (in years) as the timescale, was used to estimate hazard ratios and 95% confidence intervals (CI). Those in the lowest tertile of dietary cadmium exposure were used as the reference. Follow-up was censored at date of kidney stone diagnosis, death or end of follow-up, whichever occurred first. The Schoenfeld's residual test indicated no violation of the proportional hazard assumption. In the multivariable analysis, we adjusted for BMI (body mass index), alcohol, cigarette use and dietary intake of calcium, iron, magnesium, potassium, vitamin B6 and vitamin C. Calcium and magnesium complex with oxalate in the gut thereby reducing its absorption and have previously been associated with reduced kidney stone risk (Curhan et al., 1993; Taylor et al., 2004). Dietary iron was used as a proxy for iron status (Åkesson et al., 2002). Potassium decreases calcium excretion and may therefore reduce the risk of kidney stones (Lemann et al., 1991). Vitamin B6 is a cofactor in oxalate metabolism thereby reducing urinary oxalate excretion, and has previously been associated with decreased kidney stone risk (Curhan et al., 1999).

The analysis for men and women was carried out separately as there are known to be significant differences between the sexes both in terms of kidney stone incidence and cadmium absorption. As tobacco is a significant source of cadmium among smokers, we also performed the analysis stratified by smoking status (ever/never).

Statistical significance was taken as $p < 0.05$. All analyses were carried out using Stata software (Stata version 12; Stata Corp., College Station, TX, USA).

3. Results

During an average of 13 years of follow-up we ascertained 707 incident cases of kidney stones among men (in 421,611 person-years) and 290 cases among women (in 403,575 person-years). The mean estimated dietary cadmium exposure in the cohort of men was 19 μg/day ± standard deviation 3.7 (range of central 98% 11–29 μg/day) and 13 μg/day ± standard deviation 3.1 among women (range of central