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Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study

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BACKGROUND: Experimental data convincingly propose the toxic metal cadmium as a prostate carcinogen. Cadmium is widely dispersed into the environment and, consequently, food is contaminated.

METHODS: A population-based cohort of 41 089 Swedish men aged 45–79 years was followed prospectively from 1998 through 2009 to assess the association between food frequency questionnaire-based estimates of dietary cadmium exposure (at baseline, 1998) and incidence of prostate cancer (3085 cases, of which 894 were localised and 794 advanced) and through 2008 for prostate cancer mortality (326 fatal cases).

RESULTS: Mean dietary cadmium exposure was 19 μg per day $\pm$ s.d. 3.7. Multivariable-adjusted dietary cadmium exposure was positively associated with overall prostate cancer, comparing extreme tertiles; rate ratio (RR) 1.13 (95% confidence interval (CI): 1.03–1.24). For subtypes of prostate cancer, the RR was 1.29 (95% CI: 1.08–1.53) for localised, 1.05 (95% CI: 0.87–1.25) for advanced, and 1.14 (95% CI: 0.86–1.51) for fatal cases. No statistically significant difference was observed in the multivariable-adjusted risk estimates between tumour subtypes ($P_{heterogeneity} = 0.27$). For localised prostate cancer, RR was 1.55 (1.16–2.08) among men with a small waist circumference and RR 1.45 (1.15, 1.83) among ever smokers.

CONCLUSION: Our findings provide support that dietary cadmium exposure may have a role in prostate cancer development.

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The metal cadmium is classified as a human carcinogen based on evidence for increased risk of lung cancer among occupationally exposed (IARC, 2011). Originating mainly from anthropogenic sources, cadmium is, however, also widely dispersed into the environment (Pan *et al*, 2010). Consequently, farmland has become contaminated and thereby food constitutes the main source of exposure in the non-smoking population (Järup and Åkesson, 2009).

Prostate cancer is the leading type of cancer among males in developed countries and the second most common worldwide (Jemal *et al*, 2011). Still, the causes of prostate cancer are largely unknown (Patel *et al*, 2008). The prostate has been shown to be a target organ for the deposition of cadmium (Elinder, 1985; Lindegaard *et al*, 1990; Brys *et al*, 1997) and several experimental studies show that cadmium can act as a prostate carcinogen, inducing tumours and hyperplastic lesions in rat prostate (Waalkes, 2003). At low doses ($\sim 5.0\,\mu$mol Cd kg^{-1}), this induction is dose-dependent, whereas at high doses, there is no typical dose-response pattern as the proliferative response is lost (Waalkes, 2003). Intestinal uptake of cadmium appears to be influenced by micronutrients, such as Zinc (Kippler *et al*, 2009), and a study evaluating total prostate-specific antigen (PSA) levels in relation to urinary cadmium concentrations and dietary zinc intake provided suggestive evidence for an interaction ($P = 0.09$) between zinc intake and cadmium exposure (van Wijngaarden *et al*, 2008). Some earlier epidemiological studies have observed an association between cadmium and prostate cancer among occupationally exposed men, whereas more recent and larger studies did not confirm those findings (Sahmoun *et al*, 2005; IARC, 2011). Whether such an association exists also in environmentally exposed subjects remains unknown and results from case–control studies are inconclusive (West *et al*, 1991; Platz *et al*, 2002; Vinceti *et al*, 2007; Chen *et al*, 2009).

No prospective studies have examined the relationship between dietary exposure to cadmium and prostate cancer risk. Herein we assessed the relation between cadmium exposure via food and prostate cancer incidence and mortality in a large population-based prospective cohort of men.

SUBJECTS AND METHODS

Study population

The Cohort of Swedish Men was established in 1997–1998, when all eligible men aged 45–79 years and residing in Västmanland and Örebro counties in Central Sweden received an invitation to participate in the study along with a self-administrated questionnaire, including almost 350 items on diet and other lifestyle factors. Of those invited, 48 645 returned a complete questionnaire (response rate 49%). This large population-based cohort is

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representative of Swedish males aged 45–79 years, in terms of age distribution, educational level and prevalence of overweight (Norman *et al*, 2002). Incidence rates in 1998 per 100 000 men are almost the same: for example, the incidence rate among men aged 65–69 years was 603 in our cohort and 595 in the entire Sweden (NBHW, 2000; Orsini *et al*, 2009). Ethical approval for the study was granted by the Regional Ethical Review Board in Stockholm, Sweden, and return of the completed questionnaire was considered to imply informed consent.

We excluded from the baseline population those men with incorrect or incomplete national registration numbers and those who were diagnosed with cancer (not including non-melanoma skin cancer) or moved out of the county prior to baseline, based on computerised linkage of the cohort to the National Cancer Registry and the Population Registry. We also excluded those who reported an implausible energy intake (± 3 s.d. of mean log-transformed energy, $n = 567$). We further excluded from the baseline population those diagnosed with diabetes prior to 1998 ($n = 4250$, based on self-reports and the National Hospital Discharge Registry data), as diabetes is associated with decreased risk of prostate cancer and the dietary advice given to diabetics is likely to lead to an increased exposure to cadmium (Giovannucci and Michaud, 2007). Thus, the analytical cohort for the primary analysis consisted of 41 089 men.

Assessment of diet and covariates

Dietary intake was assessed at baseline using a 96-item food frequency questionnaire (FFQ). Participants reported their average frequency of consumption of each food item during the previous year. The frequency of consumption was reported according to eight predefined categories, ranging from never/seldom to more than three times per day. The consumption of bread and dairy products was assessed using open-ended questions. The validity of the FFQ has been assessed in a random population-based sample of 248 men aged between 40–74 years living in the study area, which completed the FFQ and 14 repeated 24-h recalls during a 1-year period. For macronutrients, the mean Spearman's rank correlation coefficient was 0.65, and for the micronutrients calcium and selenium, the coefficients were 0.77 and 0.72, respectively (Messerer *et al*, 2004).

The average daily dietary cadmium exposure was calculated by multiplying the consumption frequencies from the FFQ by age-specific portion sizes and the average cadmium content in each food item. The data on cadmium concentrations in foods were mainly provided by the Swedish National Food Agency. We used the average cadmium content in each food item because there is no detected geographic variation of cadmium content in foods across Sweden (Jorhem and Sundstrom, 1993), and most foods are distributed throughout Sweden by a small number of wholesale companies. Thus, the cadmium concentrations in food used in the database in this study are expected to represent the actual exposure levels in the area. Exposures from other sources, such as drinking water and air, are low and were ignored (Vahter *et al*, 1991; Olsson *et al*, 2002). We obtained questionnaire data on family history of prostate cancer, education, height (at age 20), weight, waist circumference, smoking habits and physical activity. Based on the reported weight and height, we calculated the body mass index (BMI) as weight (kg) divided by height^2 (m^2). The time spent per day at specific activities was multiplied by its typical energy expenditure requirements (expressed in metabolic equivalents (METs) and summarised in MET hours per day (Norman *et al*, 2001)).

Ascertainment of prostate cancer cases

Incident cases of prostate cancer occurring between 1 January 1998 and 31 December 2009 were identified by linkage of the cohort to the National Cancer Registry, close to 100% complete (Mattsson and Wallgren, 1984). Information on tumour (T)–node (N)–metastasis (M) stage, Gleason grade and PSA was ascertained through medical records and the Swedish Prostate Cancer Quality Registry. Incident cases were classified by subtype as localised (T stage <3, Gleason grade $\leqslant 6$ and PSA <10) or advanced (T stage $=4$, N $=1$, M $=1$, Gleason grade >7 or PSA >100). Because of this specific classification (not including Gleason grade 7), only 55% of the prostate cancer cases were classified as either localised or advanced. Information on prostate cancer death was ascertained through linkage to the Swedish Register of Death Causes at the National Board of Health and Welfare. Classification of deaths was based on the International Classification of Diseases (ICD-10, code 61 for prostate cancer).

Statistical analysis

Follow-up was censored at the date of invasive prostate cancer diagnosis, death or 31 December 2009, whichever occurred first. In the case of fatal tumours, end of follow-up was 31 December 2008. We used Cox proportional hazards regression models with attained age (1-year units) as the time scale to estimate rate ratios (RRs) with 95% confidence intervals (CIs) of prostate cancer by tertiles of dietary cadmium exposure. Cadmium intake values were adjusted to the mean energy intake in the cohort (2600 kcal per day) using the residual-regression method (Willett and Stampfer, 1986). In the multivariable analysis, we adjusted for attained age, family history of prostate cancer (yes, no), years of education ($\geqslant 12$, <12 years), BMI (18.5–<25, 25–<30 and $\geqslant 30$ kg m^{-2}), waist circumference (<94, 94–<102 and $\geqslant 102$ cm) (WHO, 2000), MET hours per day (quartiles), smoking status (ever, never), total energy intake (kcal cont.) and alcohol consumption (<0.1, 0.1–<5, 5–<10, 10–<15 and $\geqslant 15$ g per day). Because dietary intake of selenium, lycopene and calcium has been evaluated as probable protective factors for the risk of prostate cancer (World Cancer Research Fund (WCRF), 2007), we also included tertiles of these variables in the multivariable analysis. The Schoenfeld's residual test indicated no violation of the proportional hazard assumption (Grambsch and Therneau, 1994). We formally tested for heterogeneity of prostate cancer subtypes (localised, advanced and fatal) using the Cochran's *Q*-test. Linear trends across categories were tested using the median cadmium values within categories as a continuous variable. We performed stratified analysis by waist circumference (<94 or $\geqslant 94$ cm) in prostate cancer subtypes because associations may differ between lean and obese men (Calle and Kaaks, 2004; Discacciati *et al*, 2011). All reported *P*-values were two-sided and values <0.05 were considered statistically significant. Missing values—treated as a separate 'missing category' in the models—were generally very few ($<2\%$) with the exception of waist circumference and physical activity ($\sim 20\%$). To evaluate a potential effect of missing values on the observed results, we used multiple imputation using chained equations with 30 imputated data sets (White *et al*, 2011). Statistical analysis was performed with Stata, version 11 (StataCorp., College Station, TX, USA).

RESULTS

The mean estimated energy-adjusted cadmium exposure in the 41 089 study participants at baseline was 19 μg per day $\pm$ s.d. 3.7, and only 4% exceeded the tolerable weekly intake (2.5 μg kg^{-1} of body weight) set by the European Food Safety Authority (EFSA, 2009). The major contributors to the dietary cadmium exposure were bread (33%), potatoes (18%), other cereals than bread (15%) and vegetables, including root vegetables (14%), as compared with offal products, meat and shellfish (2%, 4% and 1%, respectively) (Figure 1). Age-standardised characteristics by category of dietary cadmium exposure are shown in Table 1. Men in the highest tertile

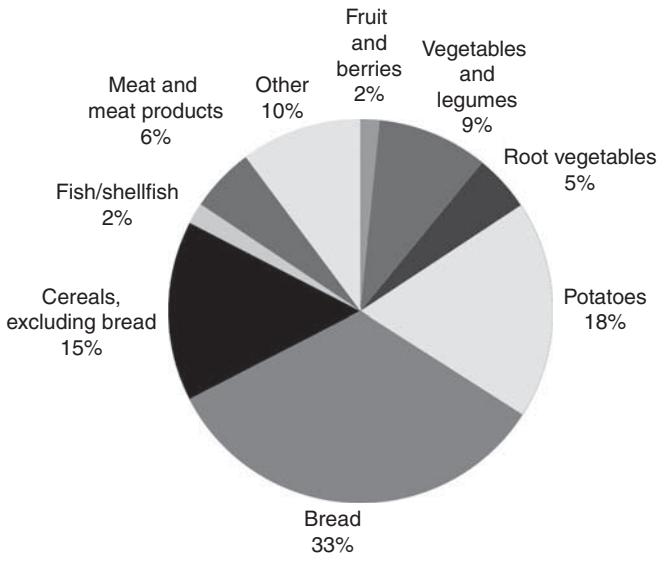

Figure 1 Major sources to dietary cadmium exposure within the Cohort of Swedish Men.

Table 1 Age-standardised baseline characteristics by categories of dietary cadmium exposure in 41 089 men, aged 45–79 years, the Cohort of Swedish Men

	Tertiles of dietary cadmium exposure, μg per day		
	<17	17–20	>20
Characteristics[a]			
Mean cadmium (μg per day)	15	19	23
Age (years)	60	59	60
Family history of prostate cancer (%)	9	10	9
⩾12 years of education (%)	16	17	18
Weight (mean, kg)	81	81	80
Body mass index (mean, kg m^{-2})	26	26	26
Waist circumference (<94 cm, %)	32	35	37
MET (hours per day)	41	41	42
Smoking status (%)			
Ever smoker	67	61	59
Never smoker	33	39	41
Total energy intake (mean, kcal)	2690	2690	2666
Alcohol intake (mean, g per day)	17	14	12
Selenium (mean, μg per day)[b]	38	39	40
Lycopene (mean, μg per day)[b]	2056	2442	2683
Calcium (mean, mg per day)[b]	1627	1441	1309

Abbreviation: MET = metabolic equivalent. [a]All factors, except age were directly standardised to the age distribution of the study participants. [b]Energy adjusted to 2600 kcal.

of dietary cadmium exposure were more likely to never have smoked and to have a lower intake of alcohol and calcium, but a higher intake of lycopene, compared with men in the lowest tertile.

During a mean follow-up of 10.8 years (443 599 person-years), we ascertained 3085 incident cases of prostate cancer (894 localised, 794 advanced and 326 fatal cases). Age and multivariable-adjusted RRs for prostate cancer incidence of overall, localised, advanced and fatal prostate cancers according to dietary cadmium exposure are presented in Table 2. Dietary cadmium exposure was, after multivariable-adjustment, associated with a statistically significant RR of 1.13 (95% CI: 1.03–1.24) of overall prostate cancer, comparing the highest tertile with the lowest (Table 2). Multiple imputation of missing data did not change the results substantially; multivariable-adjusted RR 1.15 (95% CI: 1.05–1.26) for all tumours comparing the highest tertile of dietary cadmium with the lowest. A similar risk estimate (RR 1.13; 95% CI: 1.01–1.26) was also observed when substituting the dietary cadmium exposure by the consumption of foods rich in cadmium (all cereals and vegetables), comparing the highest tertile with the lowest.

In subtypes of prostate cancer tumours, the RR was 1.29 (95% CI: 1.08–1.53) for localised cases, 1.05 (95% CI: 0.87–1.25) for advanced cases and 1.14 (95% CI: 0.86–1.51) for fatal cases. No statistically significant difference was observed in the multivariable-adjusted risk estimates between localised, advanced and fatal tumours ($P_{\text{heterogeneity}} = 0.27$). We did not observe any support for a modification by zinc in the multivariable-adjusted models ($P_{\text{interaction}} = 0.32$ for overall prostate cancer, 0.57 for localised, 0.76 for advanced and 0.69 for fatal prostate cancer).

We explored if central obesity or smoking status modified the risk of prostate cancer. In stratified analyses, the RR for localised tumours was 1.55 (95% CI: 1.16–2.08; $P_{\text{interaction}} = 0.73$) among men with a waist circumference <94 cm and 1.45 (95% CI: 1.15–1.83; $P_{\text{interaction}} = 0.30$) among men reporting to have ever smoked, comparing the highest dietary cadmium exposure tertile with the lowest (Table 3).

DISCUSSION

In this large population-based prospective cohort of men, dietary cadmium exposure was associated with a slightly increased risk of total prostate cancer tumours. For localised prostate cancer tumours, the risk tended to be more pronounced among lean men and among those who reported smoking.

The estimated average dietary cadmium exposure in the studied population of men was in a similar range as that observed both in the United States and elsewhere in Europe (MacIntosh *et al*, 1996; Thomas *et al*, 1999; Larsen *et al*, 2002; Llobet *et al*, 2003; Rose *et al*, 2010). Four studies (West *et al*, 1991; Platz *et al*, 2002; Vinceti *et al*, 2007; Chen *et al*, 2009) have assessed the association between cadmium exposure present in the general non-occupationally exposed populations and prostate cancer risk, with inconsistent results. Only one of them assessed the cadmium exposure through diet (West *et al*, 1991): In a population-based case–control study in Utah, comparing extreme quartiles, an increase in prostate cancer risk for all tumours (OR 1.8; 95% CI: 1.1–3.1) was observed in elderly men (aged 68–74 years), but not in younger (OR 1.1; 95% CI: 0.7–1.9). In an Italian hospital-based case–control study, a 4.7-fold increased risk (95% CI: 1.3–17.5) of prostate cancer was observed, comparing the highest quartile of toenail cadmium with the lowest (Vinceti *et al*, 2007). Our results are in line with those observations. However, no difference was observed in blood cadmium between Taiwanese hospital-based cases and controls, although cases had lower urinary cadmium (Chen *et al*, 2009). In an American nested case–control study, no association was observed between toenail cadmium and the risk of prostate cancer (Platz *et al*, 2002). The validity of toenail cadmium concentration as a marker of cadmium body burden is uncertain as the factors influencing the deposition of cadmium in toenails and the time-course of deposition is unknown (Platz *et al*, 2002).

Cadmium was shown to cause prostate cancer in rodents (Goyer *et al*, 2004) and induces malignant transformation of human prostate epithelial cells (Achanzar *et al*, 2001; Nakamura *et al*, 2002). The prostate is one of the target organs for bioaccumulation of cadmium (Elinder, 1985; Lindegaard *et al*, 1990) and higher accumulation have been observed in prostate cancer patients (Brys *et al*, 1997). The mechanisms involved in cadmium carcinogenesis are unclear, but are proposed to occur via indirect genotoxic mechanisms, such as oxidative stress, inhibition

Table 2 Rate ratios (RRs) and 95% confidence intervals (CIs) of total prostate cancer and its subtypes by tertiles of dietary cadmium exposure, the Cohort of Swedish Men 1998–2009

	Tertiles of dietary cadmium exposure, μg per day (median)			
	<17 (15)	17–20 (19)	>20 (22)	P_{trend}
All invasive tumours				
Number of cases	956	1043	1086	
Person-years	146 885	149 038	147 676	
Age-adjusted RR (95% CI)	1.00	1.10 (1.01, 1.20)	1.09 (1.00, 1.19)	0.05
Multivariable-adjusted RR (95% CI)[a]	1.00	1.11 (1.01, 1.21)	1.13 (1.03, 1.24)	0.01
Localised prostate cancer				
Number of cases	260	304	330	
Person-years	146 885	149 038	147 676	
Age-adjusted RR (95% CI)	1.00	1.16 (0.98, 1.37)	1.21 (1.03, 1.43)	0.02
Multivariable-adjusted RR (95% CI)[a]	1.00	1.18 (1.00, 1.40)	1.29 (1.08, 1.53)	<0.01
Advanced prostate cancer				
Number of cases	249	275	270	
Person-years	146 885	149 038	147 676	
Age-adjusted RR (95% CI)	1.00	1.14 (0.96, 1.36)	1.06 (0.89, 1.26)	0.57
Multivariable-adjusted RR (95% CI)[a]	1.00	1.14 (0.96, 1.36)	1.05 (0.87, 1.25)	0.70
Fatal prostate cancer[b]				
Number of cases	104	103	119	
Person-years	137 015	138 199	136 329	
Age-adjusted RR (95% CI)	1.00	1.02 (0.78, 1.34)	1.11 (0.86, 1.45)	0.41
Multivariable-adjusted RR (95% CI)[a]	1.00	1.04 (0.79, 1.37)	1.14 (0.86, 1.51)	0.35

[a]Adjusted for age (years), family history of prostate cancer (yes, no, unknown), years of education (⩾12, <12 years), body mass index (BMI) (18.5–<25, 25–<30 and ⩾30 kg m^{-2}), waist circumference (<94, 94–102 and ⩾102 cm), metabolic equivalent (MET) hours per day (quartiles), smoking status (ever, never), total energy intake (kcal cont.), alcohol consumption (<0.1, 0.1–<5, 5–<10, 10–<15 and ⩾15 g per day), selenium, lycopene and calcium (mg per day, tertiles). Missing values were treated as a separate 'missing category' in the model. [b]Follow-up 1998–2008.

Table 3 Multivariable-adjusted rate ratios (RRs) and 95% confidence intervals (CIs) of prostate cancer subtypes by tertiles of dietary cadmium exposure stratified by waist circumference and smoking status, the Cohort of Swedish Men 1998–2009

	Tertiles of dietary cadmium exposure, μg per day (median)						
	<17 (15)		17–20 (19)		>20 (22)		
	Number of cases	Ref.	Number of cases	RR (95% CI)	Number of cases	RR (95% CI)	P_{trend}
Localised prostate cancer							
Waist circumference[a]							
<94 cm	81	1.00	118	1.47 (1.10, 1.96)	130	1.55 (1.16, 2.08)	<0.01
⩾94 cm	132	1.00	134	1.03 (0.80, 1.31)	150	1.25 (0.97, 1.60)	0.07
Smoking status[b]							
Never	112	1.00	124	1.00 (0.77, 1.29)	140	1.09 (0.83, 1.42)	0.52
Ever	143	1.00	174	1.31 (1.05, 1.65)	184	1.45 (1.15, 1.83)	<0.01
Advanced prostate cancer							
Waist circumference[a]							
<94 cm	82	1.00	89	1.05 (0.78, 1.43)	113	1.18 (0.88, 1.60)	0.26
⩾94 cm	125	1.00	136	1.11 (0.87, 1.42)	120	0.97 (0.75, 1.27)	0.81
Smoking status[b]							
Never	82	1.00	110	1.24 (0.92, 1.65)	107	1.05 (0.77, 1.42)	0.90
Ever	163	1.00	165	1.12 (0.90, 1.40)	160	1.06 (0.84, 1.34)	0.64
Fatal prostate cancer[c]							
Waist circumference[a]							
<94 cm	32	1.00	29	0.88 (0.53, 1.46)	40	1.12 (0.68, 1.82)	0.61
⩾94 cm	51	1.00	59	1.20 (0.82, 1.75)	61	1.23 (0.83, 1.82)	0.33
Smoking status[b]							
Never	35	1.00	42	1.14 (0.72, 1.80)	45	1.09 (0.68, 1.75)	0.74
Ever	66	1.00	60	1.03 (0.72, 1.46)	72	1.21 (0.85, 1.73)	0.28

Adjusted for age (years), family history of prostate cancer (yes, no, unknown), years of education (⩾12, <12 years), body mass index (BMI) (18.5–<25, 25–<30 and ⩾30 kg m^{-2}), metabolic equivalent (MET) hours per day (quartiles), total energy intake (kcal cont.), alcohol consumption (<0.1, 0.1–<5, 5–<10, 10–<15 and ⩾15 g per day), selenium, lycopene and calcium (mg per day, tertiles). Missing values were treated as a separate 'missing category' in the model. [a]Additionally adjusted for smoking status (ever, never). [b]Additionally adjusted for waist circumference(<94, 94–102 and ⩾102 cm). [c]Follow-up 1998–2008.

of DNA repair, stimulation of cell proliferation, blockage of apoptosis or through epigenetic mechanisms (Hartwig, 2010). Because oestrogen receptors are found in the prostate, and cadmium is suggested to have oestrogenic properties (Johnson *et al*, 2003), direct receptor-mediated effects of oestrogens on the prostate are plausible. There is experimental evidence to support a role of too much or untimely exposure to estrogens in the development of prostate cancer (Härkönen and Mäkelä, 2004). In human prostate epithelial cells, cadmium increased proliferation through an oestrogen receptor-dependent mechanism and promoted androgen independence of the tumours (Benbrahim-Tallaa *et al*, 2007). Of interest is to note that we have previously observed, in a large prospective cohort of women, statistically significant positive associations between dietary cadmium exposure and risk of endometrial (Åkesson *et al*, 2008) and breast cancer (Julin *et al*, 2012), but not ovarian cancer (Julin *et al*, 2011). In the present study, there were indications of stronger associations with high dietary cadmium exposure among lean men and ever smokers. We can only speculate that endogenous sex-hormone profiles differ, depending on the amount of body fat (Calle and Kaaks, 2004), and that this may influence any potential effect of cadmium on prostate cancer risk.

To date, no single dietary factor has been shown to be conclusively associated to the risk of prostate cancer. Fibre-rich foods and vegetables—foods in general considered healthy, but at the same time being the major sources to dietary cadmium exposure—have, however, been hypothesised to have protective effects. In the present study, we observed similar increased risk for dietary cadmium as for the major food sources of the metal, similar to the slightly positive association (RR 1.13; 95% CI: 1.03–1.24) reported in the Health Professionals follow-up study between dietary intake of whole grains and total prostate cancer (Nimptsch *et al*, 2011). Results from a Danish prospective study of middle-aged men did not observe any association between intakes of total or specific whole-grain products and risk of prostate cancer (Egeberg *et al*, 2011).

This study has several limitations. Most important is that whether the estimated intake of cadmium provides a valid measure of exposure. Dietary assessments are always subjected to misclassification due to the difficulty of reporting diet correctly and, although the used mean concentrations of cadmium in specific foods in some cases were based on several hundred measurements, we may not account for all the variability in cadmium content in the reported food. We did not have the possibility to assess the relationship between the FFQ-based cadmium-exposure estimates and a biomarker in this cohort of men. However, among women of approximately the same age and from the same geographical region as the men, we observed an $r = 0.2$ between FFQ-estimated dietary cadmium exposure and urinary cadmium concentrations, indicating misclassification of the exposure. Because of the prospective design of this study, the misclassification is most likely non-differential. Accounting for this misclassification suggested a likely underestimation of the true exposure-risk association (Julin *et al*, 2012). Our study was observational and may therefore be subjected to residual confounding.

The major strengths of this study include its population-based and prospective study design, which eliminates recall and selection bias. Although the response rate was 49%, the incidence rate of prostate cancer in the cohort was almost the same as in the whole male population of Sweden, and the cohort participants were considered representative in terms of age distribution, educational level and prevalence of overweight (Norman *et al*, 2002). Further, we were able to ascertain a relatively large number of cases, and the case ascertainment was highly complete, thanks to matching of the cohort with the national and regional cancer registers. We also assessed the association in subtypes of prostate cancer based on their aggressiveness. As information on exposure was collected prospectively, any non-differential misclassification of dietary cadmium would probably bias our observed relative risks toward the null rather than exaggerate the true association between dietary cadmium exposure and prostate cancer.

In conclusion, our findings based on prospective, population-based data provide support that dietary cadmium exposure has a potential harmful role in prostate cancer development.

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Conflict of interest

The authors declare no conflict of interest.

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