Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

Dietary Cadmium Exposure and Risk of Postmenopausal Breast Cancer: A Population-Based Prospective Cohort Study

Bettina Julin1, Alicja Wolk1, Leif Bergkvist3, Matteo Bottai2,4, and Agneta Åkesson1

Authors' Affiliations: *Divisions of [1]Nutritional Epidemiology and [2]Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Surgery and Centre for Clinical Research, Central Hospital, Västerås, Sweden; and [4]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina*

Corresponding Author:
Agneta Åkesson, Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, Stockholm 17177, Sweden. Phone: 468-524-87542; Fax: 468-33-6981; E-mail: Agneta.Akesson@ki.se

Abstract

The ubiquitous food contaminant cadmium has features of an estrogen mimetic that may promote the development of estrogen-dependent malignancies, such as breast cancer. However, no prospective studies of cadmium exposure and breast cancer risk have been reported. We examined the association between dietary cadmium exposure (at baseline, 1987) and the risk of overall and estrogen receptor (ER)–defined (ER^+ or ER^-) breast cancer within a population-based prospective cohort of 55,987 postmenopausal women. During an average of 12.2 years of follow-up, 2,112 incident cases of invasive breast cancer were ascertained (1,626 ER^+ and 290 ER^-). After adjusting for confounders, including consumption of whole grains and vegetables (which account for 40% of the dietary exposure, but also contain putative anticarcinogenic phytochemicals), dietary cadmium intake was positively associated with overall breast cancer tumors, comparing the highest tertile with the lowest [rate ratio (RR), 1.21; 95% confidence interval (CI), 1.07–1.36; $P_{trend} = 0.02$]. Among lean and normal weight women, statistically significant associations were observed for all tumors (RR, 1.27; 95% CI, 1.07–1.50) and for ER^+ tumors (RR, 1.25; 95% CI, 1.03–1.52) and similar, but not statistically significant associations were found for ER^- tumors (RR, 1.22; 95% CI, 0.76–1.93). The risk of breast cancer increased with increasing cadmium exposure similarly within each tertile of whole grain/vegetable consumption and decreased with increasing consumption of whole grain/vegetables within each tertile of cadmium exposure ($P_{interaction} = 0.73$). Overall, these results suggest a role for dietary cadmium in postmenopausal breast cancer development. *Cancer Res; 72(6); 1459–66. ©2012 AACR.*

Introduction

Breast cancer is the most prevalent malignancy and the leading cause of death from cancer among women (1). Many of the established risk factors for breast cancer are linked to lifetime exposure of estrogens (2). Therefore it is proposed that estrogen-mimicking contaminants contribute to the high breast cancer incidence in Western populations, although data in humans are scarce (3). The food contaminant cadmium was recently discovered to possess estrogen-mimicking effects *in vivo* (4). In line with these findings, we observed in a large population-based prospective cohort of women, a statistically significant positive association between dietary cadmium exposure and risk of endometrial cancer (5), the cancer form most strongly related to estrogen exposure (6).

Cadmium has been widely dispersed into the environment through industrial emission, waste incineration, and combustion of fossil fuels. Even in industrially nonpolluted areas, farmland may become contaminated by atmospheric deposition and by the use of cadmium-containing fertilizers and sewage sludge (7). The highest concentration of cadmium in food is found in shellfish, offal products, and certain seeds; however, because of a comparatively high accumulation of cadmium in agricultural crops and a high consumption of these products, the main sources of dietary cadmium exposure (80%) are bread and other cereals, potatoes, root crops, and vegetables (8). Cadmium has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC, Lyon, France) and administration of the metal to animals results in tumors of multiple organs and tissues (9). Cadmium may induce cancer by several mechanisms, such as aberrant gene expression, inhibition of DNA damage repair (10), induction of oxidative stress (11, 12), and inhibition of apoptosis (13). In addition, both *in vitro* and *in vivo* studies provide evidence that cadmium may act as a metalloestrogen (4, 14–18). Estrogen-mimicking effects of cadmium on mammary gland, showed at environmentally relevant doses in ovariectomized rats, include increased formation of side branches and alveolar buds and an induction of a secretory differentiation (4). Mechanistically, cadmium has been shown to bind the nuclear estrogen receptor (ER)-α and appears to interact with its hormone-binding domain (19, 20). Recently, cadmium was shown to activate membrane-bound estrogen receptors (21, 22), indicating an alternative way of action even in the absence of nuclear ERs. The hypothesized role of cadmium in the development of breast cancer has been supported by a few small case–control studies where urinary cadmium was positively associated with risk of breast cancer (23, 24). Recently, a cross-sectional study lent further support to this hypothesis by observing an association between urinary cadmium and mammographic density (25). Because risk factors, especially reproduction-related exposures and postmenopausal obesity, differ by ER status of the tumor (26), examining the association between cadmium exposure and these subtypes may provide further insights on possible hormone disruption by cadmium.

The aim of the present study was to assess whether dietary cadmium exposure is associated with increased risk of overall and specific hormone-dependent subtypes of postmenopausal breast cancer, defined by ER status (+ or −) of the tumor. The associations were examined in a large population-based prospective cohort of Swedish women.

Methods

Study population

The Swedish Mammography Cohort was established in 1987 to 1990 in Västmanland and Uppsala counties in central Sweden when all women born between 1914 and 1948 were invited to a mammography screening (n = 90,303). A mailed, self-administered questionnaire concerning diet, lifestyle, and reproductive factors was completed by the participants; response rate being 74%. Information on history of oral contraceptive use, postmenopausal hormone use, and age at menarche and menopause was obtained from a supplemental questionnaire from the women in Uppsala county (54% of the cohort). In 1997, a second questionnaire was sent to all cohort members to gain information on smoking status and details on reproductive factors; response rate

being 70%. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. Obtained written information about the study and a returned completed questionnaire were considered to imply informed consent.

Women with incorrect or missing national registration number, those who reported implausible values for energy intake (mean ± 3 SD value of $\log_e$-transformed energy intake), and those with a previous cancer diagnosis before baseline were excluded. Because diabetes may increase the risk of breast cancer (27) and the dietary advice given to diabetics includes high consumption of foods high in cadmium, we excluded 2,543 women with diabetes mellitus from the cohort. Because a potential estrogenic effect of cadmium could be masked by the effect of endogenously produced estrogens from the ovaries, we restricted our analyses to postmenopausal women. Thus, enrollment, that is, time at risk was counted from baseline (1987–1990) for participants who were postmenopausal at that time (n = 30,825), otherwise enrollment was counted from the date of self-reported cessation of menstruation during follow-up, given that they remained at risk (n = 27,705). If menopausal status was not reported, we classified women as postmenopausal if they had had bilateral oophorectomy (information from the National Hospital Discharge Registry) or were 55 years old or older (approximately 90% of the cohort were menopausal before that age). Hence, the analytic cohort for the primary analyses consisted of 55,987 postmenopausal women.

Assessment of dietary cadmium and covariates

Dietary intake was assessed by a 67-item food frequency questionnaire (FFQ) at baseline, 1987–1990. The average frequency of consumption of each food item was reported using 8 predefined frequency consumption categories, ranging from never/seldom to 4 times a day. The consumption of bread and milk was assessed by open-ended questions. In a validation study of 129 women randomly selected from the cohort, Pearson correlation coefficients (r) between the FFQ and the mean of four 1-week weighted diet records ranged from 0.5 to 0.8 for the main cadmium-contributing food items (r = 0.5 for whole grain bread, r = 0.6 for breakfast cereals, r = 0.5 for potatoes, r = 0.5 for root crops, r = 0.8 for cabbage, and r = 0.6 for spinach).

We estimated the average daily exposure to dietary cadmium by multiplying the frequency of consumption by the age-specific portion sizes (based on 5,922 weighed food records kept by 213 randomly selected women from the study area) and the average cadmium content in each food item (based on national screening data). For the vast majority of foods, the National Food Administration provided us with data on the food cadmium content (28–30). For pepper, spinach, leek, and citrus fruits, we used Finnish and Danish data (31–33). Exposure from air contributes to less than 1% (34) and community-provided tap water and water from private wells contribute on average with 0.2% (35) of the total cadmium exposure and was thus ignored. On the basis of the reported weight and height, we calculated the body mass index (BMI) as weight (kg) divided by height^2 (m^2).

The link between long-term dietary cadmium intake and urinary cadmium concentrations, reflecting the long-term kidney accumulation of the metal (36), has been established in 680 never-smoking women from the Swedish Mammography Cohort using a toxicokinetic model (8). Cross-classification of FFQ-estimated dietary cadmium and urinary cadmium concentration resulted in 51% sensitivity and 58% specificity. The Pearson correlation coefficient was 0.1 when accounting for within-person variability in the FFQ-based estimates of cadmium but not for the exponential shape of the elimination rate (see Supplementary Material).

Identification of breast cancer cases and follow-up of the cohort

Histologically confirmed cases of invasive breast cancer were identified by linkage of the cohort to the National Cancer Registry, close to 100% complete (37). Information about ER status of the tumor was obtained from pathology logs at the Uppsala University Hospital, Uppsala, Sweden (1987–1994) and from the Quality Registry at the Regional Oncology Centre in Uppsala (1994–

2008). Prior to 1998, all classification of ER status was made with an Abbott immunoassay; cases with ≥0.1 fmol/μg cytosol DNA were considered ER^+. Thereafter, an immunohistochemical method was used; a proportion of positive cells more than 10% was defined as ER^+.

All incident cases of invasive breast cancer were ascertained from start of follow-up through December 31, 2008. However, start of follow-up differed between the two counties (1987–1990 in Uppsala county and January 1, 1998, in Västmanland county) because routine assessment of tumor subtypes was introduced in Västmanland county first during 1997. Dates of death were ascertained by linkage to the Swedish Death Registry.

Statistical analysis

Rate ratios (RR) and 95% confidence intervals (CI) were estimated with Cox proportional hazards regression models with attained age (1-year units) as the timescale. Follow-up was censored at date of invasive breast cancer diagnosis, death, or December 31, 2008, whichever occurred first. The estimated daily cadmium intake was adjusted for total energy intake of 1,700 kcal (mean of the cohort) using the residual regression method (38) and then categorized into tertiles. In the multivariable analysis, we adjusted for attained age, height, BMI, education, use of oral contraceptives and postmenopausal hormones, age at menarche and menopause, parity, age at first birth, alcohol consumption, glycemic load, and total energy intake. We further adjusted for whole grains and vegetables, foods that could possibly attenuate the observed association. The Schoenfeld's residual test indicated no violation of the proportional hazard assumption. Linear trends across categories were tested using the median cadmium values within categories as a continuous variable. Missing values—treated as a separate “missing category” in the models—were generally very low with the exception of use of oral contraceptives and postmenopausal hormones and age at menarche (∼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 (39).

We next conducted a probabilistic sensitivity analysis (40, 41) to assess the impact of exposure misclassification on the observed RRs. The sensitivity and specificity of the exposure ranged from 50% to 60% (Supplementary Material). Therefore, on the basis of 10,000 simulations, we specified uniform distributions with equally probable values between 50% and 60% for both sensitivity and specificity (nondifferential exposure misclassification).

Models were stratified by categories of BMI and use of postmenopausal hormones as sources of endogenous and exogenous estrogens. We also examined the association between cadmium and breast cancer by strata of total whole grain and vegetable consumption as well as the association between tertiles of dietary cadmium, total whole grain and vegetable consumption, and breast cancer risk.

All reported *P* values are 2-sided; *P* values below 0.05 were considered statistically significant. All statistical analyses were conducted using STATA software version 10 (StataCorp).

Results

During an average of 12.2 years of follow-up (712,075 person-years), we ascertained 2,112 incident cases of breast cancer among the 55,987 postmenopausal women. Information on ER status was available for 1,916 cases (1,626 ER^+ and 290 ER^-). The mean estimated energy-adjusted cadmium intake in the cohort was 15 μg/d ± 3.2 (SD). The major contributors to the dietary cadmium intake were whole grain foods (31%), refined grain (20%), potatoes (18%), and vegetables including root vegetables (12%), as compared with offal products, meat, and shellfish (4%, 4%, and 3%, respectively). Women in the highest tertile of cadmium intake were more likely to have a postsecondary education and had about a 2-fold higher consumption of whole grain and vegetables than those in the lowest tertile of cadmium intake (Table 1). Women in the highest tertile (37%)

were also slightly more likely to be never-smokers than women in the lowest tertile (31%; based on information from 1997).

Table 1.
Baseline age-standardized characteristics of 55,987 postmenopausal women, by estimated cadmium exposure, Swedish Mammography Cohort 1987–1990

	Tertiles of cadmium intake, µg/d		
	<13	**13–16**	**>16**
Nondietary characteristics			
Age, mean, y	52	53	54
Height, mean, cm	164	164	164
BMI, mean, kg/m^2	25	25	25
Postsecondary education (%)	13	15	16
Ever use of oral contraceptives (%)[a]	42	44	44
Ever use of postmenopausal hormones (%)[a]	34	36	37
Age at menarche < 13 y (%)	21	22	22
Age at menopause ≥ 51 y (%)	28	31	31
Number of children (%)			
Nulliparous	11	10	11
≥3	32	33	33
Age at first birth ≥ 31 y (%)	14	15	15
Current alcohol consumption (%)			
Nondrinker	28	27	30
≥10 g/d	5	5	4
Dietary characteristics			
Glycemic load, mean	168	170	169
Whole grains, mean,[b] g/d	116	160	211
Vegetables, mean[b], g/d	62	82	117

- [a]On the basis of 80% of the cohort participants with complete information from a supplementary questionnaire in 1987 or from 1997.
- [b]Whole grains include whole meal bread, crisp bread, and oatmeal. Vegetables include carrot, beetroot, spinach, cabbage, lettuce, tomato, and cucumber.

The incidence rate difference comparing the highest with the lowest tertile of dietary cadmium exposure was 19 per 100,000 person-years (Table 2). Dietary cadmium intake was, after full multivariable adjustment, associated with a statistically significant RR of 1.21 (95% CI, 1.07–1.36; P_{trend} = 0.02) of overall invasive breast cancer, comparing the highest tertile with the lowest (Table 2). The corresponding results for ER^+ and ER^- tumors were 1.19 (95% CI, 1.03–1.36) and 1.33 (95% CI, 0.95–1.87), respectively. Dietary cadmium was, per continuous 5 µg/d increment, associated with RR of 1.18 (95% CI, 1.08–1.29) for overall breast cancer. Additional adjustment of the models for smoking status (never, former, current) or by multiple imputation of missing data did not change the results (data not shown). In the probabilistic sensitivity analysis conducted to quantify the likely impact of the estimated exposure misclassification of dietary cadmium, we observed a median RR of 2.88 for all breast cancer cases, comparing the highest tertile with lowest.

Table 2.
RRs and 95% CIs of breast cancer incidence among all postmenopausal women according to tertiles of dietary cadmium exposure, Swedish Mammography Cohort, 1987–2008

	Tertiles of cadmium intake (median), μg/d			
	<13 (12)	**13–16 (15)**	**>16 (17)**	P_{trend}
Person-years	233,546	228,121	230,981	
All invasive tumors				
No. of cases	677	691	744	
Rate (per 100,000 person-years)	303	304	322	
Age-adjusted RR (95% CI)	1.00	1.00 (0.90–1.11)	1.06 (0.95–1.17)	0.25
Multivariable adjusted RR (95% CI)[a]	1.00	1.00 (0.90–1.11)	1.05 (0.95–1.17)	0.26
Multivariable adjusted RR (95% CI)[b]	1.00	1.06 (0.95–1.18)	1.21 (1.07–1.36)	0.02
Multivariable adjusted RR (95% CI)[c]	1.00	1.04 (0.93–1.17)	1.21 (1.06–1.37)	0.02
ER^+ tumors				
No. of cases	538	520	568	
Rate (per 100,000 person-years)	241	228	246	
Age-adjusted RR (95% CI)	1.00	0.94 (0.84–1.07)	1.01 (0.90–1.14)	0.27
Multivariable adjusted RR (95% CI)[a]	1.00	0.94 (0.84–1.07)	1.01 (0.90–1.14)	0.26
Multivariable adjusted RR (95% CI)[b]	1.00	1.01 (0.89–1.15)	1.19 (1.03–1.36)	0.02
ER^- tumors				
No. of cases	83	101	106	
Rate (per 100,000 person-years)	37	44	46	
Age-adjusted RR (95% CI)	1.00	1.21 (0.90–1.62)	1.27 (0.95–1.70)	0.58
Multivariable adjusted RR (95% CI)[a]	1.00	1.19 (0.89–1.60)	1.24 (0.93–1.66)	0.64
Multivariable adjusted RR (95% CI)[b]	1.00	1.22 (0.90–1.66)	1.33 (0.95–1.87)	0.60

- [a]Adjusted for attained age in years, adult height (140–<160, 160–<164, 164–<168, ≥168 cm), BMI (18.5–<25, 25–30, ≥30 kg/m^2), >12 years of education (yes, no), use of oral contraceptives (yes, no), use of postmenopausal hormones (yes, no), age at menarche (<13, 13, >13 years), age at menopause (>51, ≤51 years), parity (nulliparous, 1–2, >2 children), age at first birth (nulliparous, <26, 26–31, ≥ 31 years), alcohol consumption (nondrinker, <3.4, 3.4–10, ≥ 10 g/d), glycemic load, and total energy intake.
- [b]Additionally adjusted for intake (g/d) of whole grain and vegetables in tertiles.
- [c]Excluding 196 cases with no information on ER status of the tumor.

In postmenopausal women, adipose tissue is a source of endogenous estrogen production. Therefore, to restrict the influence of endogenous estrogen on the observed association, we conducted analyses stratified by BMI. In lean and normal weight women (BMI, 18.5–25 kg/m^2), we observed, in the fully adjusted model, a statistically significant RR of 1.27 (95% CI, 1.07–1.50) of overall invasive breast cancer, comparing the highest tertile of cadmium with the lowest (Table 3). Likewise, we observed a RR of 1.25 (95% CI, 1.03–1.52) for the ER^+ subtype, and a similar, but not statistically significant, association for ER^- subtype (RR, 1.22; 95% CI, 0.76–1.93). Among overweight and obese women (BMI ≥ 25 kg/m^2), point estimates were in general lower and not statistically significant except for ER^- tumors where the point estimate was higher (full multivariable adjusted RR and 95% CI for the highest tertile of cadmium: 1.10, 0.91–1.33 for

overall tumors; 1.09, 0.88–1.36 for ER^+; and 1.50, 0.89–2.53 for ER^-). We also stratified women by postmenopausal hormone use. We did not observe differences in never-users (full multivariable adjusted RR and 95% CI for the highest tertile of cadmium: 1.16, 0.95–1.41 for overall tumors; 1.15, 0.92–1.44 for higER$^+$; and 1.37, 0.84–2.26 for ER^-) or ever-users (full multivariable adjusted RR and 95% CI for the hest tertile of cadmium: 1.21, 1.00–1.47 for overall tumors; 1.21, 0.97–1.51 for ER^+, and 1.28, 0.74–2.23 for ER^-) of hormones.

Table 3.
RRs and 95% CIs of breast cancer incidence among lean and normal weight (BMI, 18.5–25 kg/m^2) postmenopausal women according to tertiles of dietary cadmium exposure, Swedish Mammography Cohort, 1987–2008

	Tertiles of cadmium intake, µg/d			
	<13	**13–16**	**>16**	**P_{trend}**
All invasive tumors				
No. of cases	370	379	379	
Age-adjusted RR (95% CI)	1.00	1.02 (0.89–1.18)	1.05 (0.91–1.21)	0.65
Multivariable adjusted RR (95% CI)[a]	1.00	1.12 (0.97–1.30)	1.27 (1.07–1.50)	0.15
Multivariable adjusted RR (95% CI)[b]	1.00	1.13 (0.96–1.32)	1.25 (1.05–1.49)	0.23
ER^+ tumors				
No. of cases	290	291	288	
Age-adjusted RR (95% CI)	1.00	1.00 (0.85–1.18)	1.02 (0.86–1.20)	0.83
Multivariable adjusted RR (95% CI)[a]	1.00	1.11 (0.94–1.32)	1.25 (1.03–1.52)	0.20
ER^- tumors				
No. of cases	47	55	53	
Age-adjusted RR (95% CI)	1.00	1.17 (0.79–1.73)	1.16 (0.79–1.73)	0.95
Multivariable adjusted RR (95% CI)[a]	1.00	1.19 (0.79–1.79)	1.22 (0.76–1.93)	0.95

- [a]Adjusted for attained age in years, adult height (140–<160, 160–<164, 164–<168, ≥168 cm), BMI (kg/m^2, cont.), >12 years of education (yes, no), use of oral contraceptives (yes, no), use of postmenopausal hormones (yes, no), age at menarche (<13, 13, >13 years), age at menopause (>51, ≤51 years), parity (nulliparous, 1–2, >2 children), age at first birth (nulliparous, <26, 26–31, ≥31 years), alcohol consumption (nondrinker, <3.4, 3.4–10, ≥10 g/d), glycemic load, and total energy intake and intake (g/d) of whole grain and vegetables in tertiles.
- [b]Excluding 104 cases with no information on ER status of the tumor.

Because dietary cadmium was correlated with the consumption of whole grain and vegetables (r = 0.41 with whole grain, r = 0.49 with vegetables, and r = 0.59 with total whole grain and vegetable consumption), we examined the joint relationship between cadmium exposure, whole grain and vegetable consumption, and breast cancer risk. The risk of postmenopausal breast cancer increased with increasing cadmium intake within each tertile of total whole grain and vegetable consumption: For overall breast cancer, the RR per 5 µg/d increment in dietary cadmium intake was 1.17 (95% CI, 1.01–1.36) in the lowest, 1.21 (95% CI, 1.03–1.41) in the middle, and 1.15 (95% CI, 1.02–1.29) in the highest tertile of whole grain and vegetable consumption. In further analyses based on tertiles of both cadmium exposure and whole grain and vegetable consumption (Fig. 1), we observed an increased risk of breast cancer with increasing dietary cadmium exposure and with decreasing consumption of whole grain and vegetables. The RR for overall breast cancer was 1.60 (95% CI, 1.28–2.00) among those within both the highest tertile of cadmium intake and lowest tertile of whole grain and vegetable consumption compared with the reference (low intake of cadmium and high consumption of whole grain and

vegetables). There was no interaction on a multiplicative scale ($P_{interaction}$ = 0.73). Similar results were observed for ER^+ tumors, whereas the interpretation of the results for ER^- tumors was limited by the small number of cases.

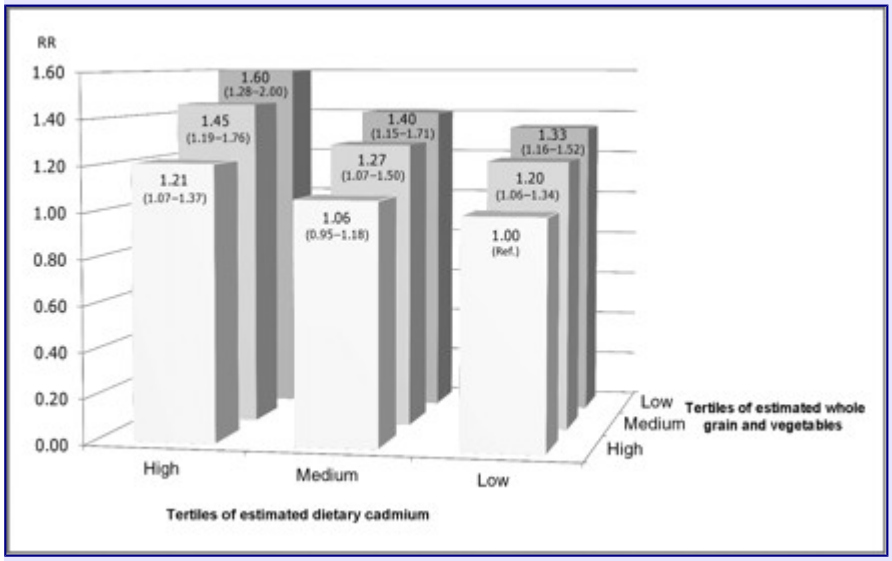

Figure 1.

Overall breast cancer according to tertiles of estimated dietary cadmium exposure and whole grain and vegetable consumption jointly, Swedish Mammography Cohort, 1987–2008. Multivariable adjusted RRs (with 95% CIs) of overall breast cancer according to tertiles of dietary cadmium exposure (<14, 14–16, ≥16 μg/d) and whole grain and vegetable consumption (<187, 187–287, ≥287 g/d). Adjustments were made for attained age in years, height, BMI, education, use of oral contraceptives and postmenopausal hormones, age at menarche and menopause, parity, age at first birth, alcohol consumption, glycemic load, and total energy intake. In the lowest tertile of whole grain and vegetable intake, the daily consumption corresponded to, on average, 1.5 servings of whole grain and 1 serving of vegetables, whereas the corresponding consumption in the highest tertile was 3.5 servings of whole grain and 2.5 servings of vegetables. $P_{interaction}$ = 0.73.

Discussion

In this large population-based prospective cohort of postmenopausal women, estimated dietary cadmium was associated with an increased breast cancer incidence. Results by ER subtype were fairly similar, although not statistically significant for ER^-. The associations were more pronounced when taking the consumption of whole grain and vegetables into account, foods that account for about 40% of the dietary cadmium exposure, but that are also important sources of phytochemicals with proposed anticarcinogenic properties.

We undertook several steps in the analysis to reveal the possible estrogenic effects of cadmium. First, we restricted the analysis to include only postmenopausal women to avoid the effect of ovary-produced estrogens. Second, because estrogen is mainly produced in adipose tissue after menopause and estrogen-related exposures such as BMI are associated specifically with ER^+ tumors (42–44), the analysis was stratified by BMI. This stratification revealed a slight increase in point estimates for ER^+ tumors in normal weight women but not for ER^- tumors.

Some of the major contributors to dietary cadmium (whole grain and vegetables) are also the major dietary sources of fiber, phytoestrogens, and antioxidants, proposed to have anticarcinogenic properties (26) and inversely associated with breast cancer in some studies (45–48), but not all (26, 49, 50). It could be hypothesized that the observed association between dietary cadmium exposure

and breast cancer in the present study may partly be masked by the consumption of whole grain and vegetables, as adjusting the models for these foods resulted in a considerable increase of the risk estimates for dietary cadmium intake. Stratified analysis revealed, within each tertile of total whole grain and vegetable consumption, a clear dose-dependent increased risk of postmenopausal breast cancer with increasing cadmium exposure, supporting that our results were not due to collinearity. When we examined the risk in tertiles of cadmium and whole grain and vegetable intake jointly, we observed the highest risk of breast cancer in relation to diets high in cadmium and low in whole grain and vegetables, whereas the lowest risk was observed for diets low in cadmium and high in whole grain and vegetables.

Two previous reports of case–control studies have assessed the risk of breast cancer among pre- and postmenopausal women in relation to cadmium exposure, assessed as the cadmium concentration in urine (23, 24). McElroy and colleagues observed in the study of 246 cases, a multivariable adjusted OR of 2.29 (95% CI, 1.3–4.2) comparing the highest quartile of urinary cadmium versus the lowest. The second study, conducted by Gallagher and colleagues, examined the association between cadmium and breast cancer in 2 case–control samples from the United States, consisting of 100 and 98 cases, respectively. In both samples, increased ORs were observed (2.69; 95% CI, 1.07–6.78 and 2.5; 95% CI, 1.11–5.63, respectively) comparing the highest quartile of urinary cadmium with the lowest. Information on hormone receptor subtype was however not available in any of the above mentioned studies.

The strengths of our study include the prospective, population-based design, a large number of cases, detailed information on diet, and data on ER status of the breast tumors. Furthermore, we restricted the analysis to postmenopausal women and were able to adjust for many potential confounders. The prospective design excluded risk for differential recall bias affecting estimates of cadmium intake. The nearly complete follow-up of the study population through linkage with various population-based registers (37) minimized the possibility that our results could be affected by differential loss to follow-up.

Several limitations may be present in this study. Most important is whether the estimated intake of cadmium provides a valid measure of exposure. Dietary cadmium was estimated using national data on cadmium content in foods and a self-administrated FFQ. Such assessment of the cadmium exposure leads to nondifferential misclassification of the exposure. Indeed, when we compared the FFQ-estimated dietary cadmium intake with urinary cadmium concentration, reflecting the long-term kidney accumulation of the metal (36), the observed correlation was low. However, our sensitivity analyses, taking into account the misclassification of the exposure, indicated that the observed associations are likely biased toward the null, so that the true association is even stronger.

We observed positive associations between estimated dietary cadmium and breast cancer which remained after controlling for possible dietary confounders such as glycemic load, speaking against that the estimated cadmium intake represented some other aspect of diet. Although controlling for several breast cancer risk factors, like all studies, this study could be subject to unmeasured confounding. Despite a large study population, the low number of cases after stratifications led to restricted statistical power and less precise risk estimates in some analyses.

In conclusion, in line with previous case–control studies (23, 24) based on biomarker of cadmium exposure, we observed in this large population-based prospective cohort a positive association between dietary cadmium exposure and risk of postmenopausal breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Grant Support

The study was supported by The Swedish Cancer Society and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (to A. Åkesson) and by the Swedish Research Council/Research Infrastructures (to A. Wolk).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Acknowledgments

The authors thank L. Jorhem, J. Engman, and B. Sundström from the Swedish National Food Agency for providing food cadmium data.

Footnotes

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Received March 4, 2011.
Revision received January 12, 2012.
Accepted January 14, 2012.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global burden of disease and risk factors. Washington, DC: The International Bank for Reconstruction and Development/The World Bank/Oxford University Press; 2006.

2. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001;**2**:133–40. CrossRefMedline

3. Safe S. Clinical correlates of environmental endocrine disruptors. *Trends Endocrinol Metab* 2005;**16**:139–44. CrossRefMedline

4. Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, et al. Cadmium mimics the *in vivo* effects of estrogen in the uterus and mammary gland. *Nat Med* 2003;**9**:1081–4. CrossRefMedline

5. Akesson A, Julin B, Wolk A. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. *Cancer Res* 2008;**68**:6435–41. Abstract/FREE Full Text

6. Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. *Ann N Y Acad Sci* 2001;**943**:296–315. Medline

7. Jarup L, Akesson A. Current status of cadmium as an environmental health problem. *Toxicol Appl Pharmacol* 2009;**238**:201–8. CrossRefMedline

8. Amzal B, Julin B, Vahter M, Johanson G, Wolk A, Åkesson A. Population toxicokinetic modeling of cadmium for health risk assessment. *Environ Health Perspect* 2009;**117**:1293–301. CrossRefMedline

9. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Summary of data reported and evaluation. IARC Monogr Eval Carcinog Risks Hum World Health Organization

(WHO), International Agency for Research on Cancer (IARC). Volume 58. [cited February 7, 2012]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol58/volume58.pdf.

10. Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, et al. Cadmium is a mutagen that acts by inhibiting mismatch repair. *Nat Genet* 2003;**34**:326–9. CrossRefMedline

11. Shih CM, Ko WC, Wu JS, Wei YH, Wang LF, Chang EE, et al. Mediating of caspase-independent apoptosis by cadmium through the mitochondria-ROS pathway in MRC-5 fibroblasts. *J Cell Biochem* 2004;**91**:384–97. CrossRefMedline

12. Joseph P, Muchnok TK, Klishis ML, Roberts JR, Antonini JM, Whong WZ, et al. Cadmium-induced cell transformation and tumorigenesis are associated with transcriptional activation of c-fos, c-jun, and c-myc proto-oncogenes: role of cellular calcium and reactive oxygen species. *Toxicol Sci* 2001;**61**:295–303. Abstract/FREE Full Text

13. Templeton DM, Liu Y. Multiple roles of cadmium in cell death and survival. *Chem Biol Interact* 2010;**188**:267–75. CrossRefMedline

14. Safe S. Cadmium's disguise dupes the estrogen receptor. *Nat Med* 2003;**9**:1000–1. CrossRefMedline

15. Brama M, Gnessi L, Basciani S, Cerulli N, Politi L, Spera G, et al. Cadmium induces mitogenic signaling in breast cancer cell by an ERalpha-dependent mechanism. *Mol Cell Endocrinol* 2007;**264**:102–8. CrossRefMedline

16. Zang Y, Odwin-Dacosta S, Yager JD. Effects of cadmium on estrogen receptor mediated signaling and estrogen induced DNA synthesis in T47D human breast cancer cells. *Toxicol Lett* 2009;**184**:134–8. CrossRefMedline

17. Garcia-Morales P, Saceda M, Kenney N, Kim N, Salomon DS, Gottardis MM, et al. Effect of cadmium on estrogen receptor levels and estrogen-induced responses in human breast cancer cells. *J Biol Chem* 1994;**269**:16896–901. Abstract/FREE Full Text

18. Ali I, Penttinen-Damdimopoulou PE Makela SI, Berglund M, Stenius U, Akesson A, et al. Estrogen-like effects of cadmium in vivo do not appear to be mediated via the classical estrogen receptor transcriptional pathway. *Environ Health Perspect* 2010;**118**:1389–94. CrossRefMedline

19. Stoica A, Katzenellenbogen BS, Martin MB. Activation of estrogen receptor-alpha by the heavy metal cadmium. *Mol Endocrinol* 2000;**14**:545–53. Abstract/FREE Full Text

20. Enmark E, Gustafsson JA. Oestrogen receptors - an overview. *J Intern Med* 1999;**246**:133–8. CrossRefMedline

21. Yu X, Filardo EJ, Shaikh ZA. The membrane estrogen receptor GPR30 mediates cadmium-induced proliferation of breast cancer cells. *Toxicol Appl Pharmacol* 2010;**245**:83–90. CrossRefMedline

22. Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. *J Steroid Biochem Mol Biol* 2006;**102**:175–9. CrossRefMedline

23. McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. Cadmium exposure and breast cancer risk. *J Natl Cancer Inst* 2006;**98**:869–73. Abstract/FREE Full Text

24. Gallagher CM, Chen JJ, Kovach JS. Environmental cadmium and breast cancer risk. *Aging (Albany N Y)* 2010;**2**:804–14. Medline

25. Adams SV, Newcomb PA, Shafer MM, Atkinson C, Bowles EJ, Newton KM, et al. Sources of cadmium exposure among healthy premenopausal women. *Sci Total Environ* 2011;409:1632–7. CrossRefMedline

26. World Cancer Research Fund (WCRF). Food, nutrition and the prevention of cancer: a global

perspective. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research; 2007.

27. Grote VA, Becker S, Kaaks R. Diabetes mellitus type 2 - an independent risk factor for cancer? *Exp Clin Endocrinol Diabetes* 2010;**118**:4–8. CrossRefMedline

28. Becker W, Kumpulainen J. Contents of essential and toxic mineral elements in Swedish market-basket diets in 1987. *Br J Nutr* 1991;**66**:151–60. CrossRefMedline

29. Jorhem L, Sundstrom B, Engman J. Cadmium and other metals in Swedish wheat and rye flours: longitudinal study, 1983–1997. *J AOAC Int* 2001;**84**:1984–92. Medline

30. Jorhem L, Sundstrom B. Levels of lead, cadmium, zinc, copper, nickel, chromium, manganese, and cobalt in foods on the Swedish market, 1983–1990. *J Food Compos Anal* 1993;**6**:223–41. CrossRef

31. Tahvonen R, Kumpulainen J. Lead and cadmium contents in Finnish breads. *Food Addit Contam* 1994;**11**:621–31. Medline

32. Tahvonen R, Kumpulainen J. Lead and cadmium in some berries and vegetables on the Finnish market in 1991–1993. *Food Addit Contam* 1995;**12**:263–79. Medline

33. Larsen EH, Andersen NL, Moller A, Petersen A, Mortensen GK, Petersen J. Monitoring the content and intake of trace elements from food in Denmark. *Food Addit Contam* 2002;**19**:33–46. CrossRefMedline

34. Vahter M, Berglund M, Slorach S, Friberg L, Saric M, Zheng XQ, et al. Methods for integrated exposure monitoring of lead and cadmium. *Environ Res* 1991;**56**:78–89. Medline

35. Olsson IM, Bensryd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. Cadmium in blood and urine–impact of sex, age, dietary intake, iron status, and former smoking–association of renal effects. *Environ Health Perspect* 2002;**110**:1185–90. Medline

36. Orlowski C, Piotrowski JK, Subdys JK, Gross A. Urinary cadmium as indicator of renal cadmium in humans: an autopsy study. *Hum Exp Toxicol* 1998;**17**:302–6. Abstract/FREE Full Text

37. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;**23**:305–13. Medline

38. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;**124**:17–27. FREE Full Text

39. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. CrossRefMedline

40. Orsini N, Bellocco R, Bottai M, Wolk A, Greenland S. A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies. *Stata J* 2008;**8**:29–48. Search Google Scholar

41. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. *Int J Epidemiol* 2005;**34**:1370–6. Abstract/FREE Full Text

42. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1558–68. Abstract/FREE Full Text

43. Rosenberg LU, Einarsdottir K, Friman EI, Wedren S, Dickman PW, Hall P, et al. Risk factors for hormone receptor-defined breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:2482–8. Abstract/FREE Full Text

44. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status–a meta-analysis. *Int J Cancer* 2009;**124**:698–712. CrossRefMedline

45. Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Adlercreutz H, Wolk A. Dietary fiber intake and risk of postmenopausal breast cancer defined by estrogen and progesterone receptor status–a prospective cohort study among Swedish women. *Int J Cancer* 2008;**122**:403–12. CrossRefMedline

46. Suzuki R, Rylander-Rudqvist T, Saji S, Bergkvist L, Adlercreutz H, Wolk A. Dietary lignans and postmenopausal breast cancer risk by oestrogen receptor status: a prospective cohort study of Swedish women. *Br J Cancer* 2008;**98**:636–40. CrossRefMedline

47. Larsson SC, Bergkvist L, Wolk A. Dietary carotenoids and risk of hormone receptor-defined breast cancer in a prospective cohort of Swedish women. *Eur J Cancer* 2010;**46**:1079–85. CrossRefMedline

48. Mattisson I, Wirfalt E, Johansson U, Gullberg B, Olsson H, Berglund G. Intakes of plant foods, fibre and fat and risk of breast cancer–a prospective study in the Malmo Diet and Cancer cohort. *Br J Cancer* 2004;**90**:122–7. CrossRefMedline

49. Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB. Diet and breast cancer: a review of the prospective observational studies. *Cancer* 2007;**109**:2712–49. CrossRefMedline

50. Cade JE, Burley VJ, Greenwood DC. Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. *Int J Epidemiol* 2007;**36**:431–8. Abstract/FREE Full Text

«Previous | Next Article»
Table of Contents

This Article

doi: 10.1158/0008-5472.CAN-11-0735 *Cancer Res* March 15, 2012 72; 1459

Abstract Figures Only» **Full Text** Full Text (PDF) Supplementary Data

- Classifications

Prevention and Epidemiology

- Services

Email this article to a colleague Alert me when this article is cited Alert me if a correction is posted
Similar articles in this journal Similar articles in PubMed Download to citation manager

+ Citing Articles

+ Google Scholar

+ PubMed

+ Social Bookmarking

:: AACR Publications Home ::

Current Issue

July 15, 2013, 73 (14)

Alert me to new issues of Cancer Research

About the Journal
Instructions for Authors/Editorial Policies
Submit a Manuscript
Author Services Center
Editorial Board
Information for Subscribers
Information for Reviewers
Information for Librarians
Information for Advertisers
Permissions & Reprints
E-mail Alerts & RSS Feeds [Free]
Feedback

Cancer Discovery Clinical Cancer Research Cancer Epidemiology Biomarkers & Prevention
Molecular Cancer Therapeutics Molecular Cancer Research Cancer Prevention Research
Cancer Immunology Research AACR Publications CME Cancer Prevention Journals Portal
Cancer Reviews Online Annual Meeting Education Book Meeting Abstracts Online Help

Most Read Cited

1. Phenylacetate: A Novel Nontoxic Inducer of Tumor Cell Differentiation
2. A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer
3. A Discussion of the Mechanism of Action of Steroid Hormones
4. Genetic Progression Model for Head and Neck Cancer: Implications for Field Cancerization
5. Human Natural Immunoglobulin M Antibodies Induce Apoptosis of Human Neuroblastoma Cells by Binding to a Mr 260,000 Antigen

»View all Most Read articles

Home OnlineFirst Current Issue Past Issues Subscriptions Alerts Feedback AACR Publications
CME AACR Home

Cancer Res Online ISSN: 1538-7445
Cancer Res Print ISSN: 0008-5472
J Cancer Res ISSN: 0099-7013
Am J Cancer ISSN: 0099-7374