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Dietary Cadmium and Risk of Invasive Postmenopausal Breast Cancer in the VITAL Cohort

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Abstract

Purpose—Estimate the association between dietary intake of cadmium, a carcinogenic heavy metal, and risk of invasive breast cancer.

Methods—Study subjects were 30,543 postmenopausal women in the VITamins And Lifestyle (VITAL) cohort who completed a food frequency questionnaire (FFQ) at baseline (2000–2002). Dietary cadmium consumption was estimated by combining FFQ responses with US Food and Drug Administration data on food cadmium content. Incidence of invasive breast cancer was ascertained through linkage of the cohort to the western Washington Surveillance, Epidemiology, and End Results cancer registry through December 31, 2009. Cox regression was applied to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for breast cancer with increasing dietary cadmium intake, adjusted for total energy intake, smoking history, consumption of vegetables, potatoes, and whole grains, multivitamin use, education, race, body mass index, physical activity, age at first birth, postmenopausal hormone use, and mammography.

Results—Vegetables and grains together contributed an average of 66% of estimated dietary cadmium. During a mean of 7.5 years of follow-up, 1,026 invasive postmenopausal breast cancers were identified. Among 899 cases with complete covariate information, no evidence of an association between dietary cadmium intake and breast cancer risk was observed (aHR (95% CI), highest to lowest quartile cadmium: 1.00 (0.72–1.41), P_{trend}=0.95). No evidence was found for interactions between dietary cadmium and breast cancer risk factors, smoking habits, or total intake of calcium, iron, or zinc from diet, supplements, and multivitamins.

Conclusions—This study does not support the hypothesis that dietary cadmium intake is a risk factor for breast cancer. However, non-differential measurement error in the estimate of cadmium intake is likely the most important factor that could have obscured an association.

Keywords

cadmium; breast cancer; food frequency questionnaire; environmental carcinogens; heavy metals; endocrine disruptor

Cadmium is a toxic and carcinogenic heavy metal released into the environment as a result of industrial and agricultural activities[1, 2]. Historically, most research on the health effects of cadmium has focused on occupational exposure[3]. However, chronic non-occupational exposure to cadmium is common. Cadmium is taken up from contaminated soil by tobacco,

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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grains, and a variety of vegetables[4–7]. Cadmium inhaled with cigarette smoke is readily absorbed by lung tissue[8]. Although only approximately 5% of cadmium ingested in food is absorbed, cadmium absorption is potentiated by low iron stores, and it may be in part for this reason that women are consistently observed to have higher average urine and blood cadmium concentrations[9, 10]. Cadmium, once absorbed from the environment, is retained throughout the body, including in breast tissue for decades[8, 11–13].

Multiple mechanisms potentially link cadmium to carcinogenesis including oxidative stress and inflammation[14, 15], interference with DNA repair[16, 17], and alterations of DNA methylation[18]. Intriguing laboratory evidence suggests that cadmium may act on estrogenic signaling pathways[19, 20], stimulating proliferation of breast cancer cells in culture[21], and inducing increased uterus and mammary gland weight in rats[22]. Further evidence specifically shows that low level, long term cadmium can malignantly transform breast cells, albeit through pathways independent of estrogen receptor(α)[23].

Cadmium has been linked to lung cancer in occupational settings[24, 25], although uncertainty remains[26]. In non-occupationally exposed populations, cadmium has also been associated with lung cancer incidence and mortality[27, 28]. Because of the laboratory data potentially linking cadmium with estrogen signaling pathways, cadmium has received increasing attention as a risk factor for hormone-related cancers in women. Prospective studies in Sweden observed an association between dietary cadmium and risk of breast cancer[29] and endometrial cancer[30], but not ovarian cancer[31]. In the United States, two case-control studies observed consistent strong associations between urine cadmium and breast cancer risk[32, 33].

This report describes our prospective study of dietary cadmium intake and postmenopausal, invasive breast cancer risk in the VItamins And Lifestyle (VITAL) cohort.

METHODS

VITAL cohort recruitment (Women)

Study participants were female members of the VITAL cohort; the details of the study methods have been reported previously [34]. Briefly, VITAL was designed to prospectively investigate the associations of vitamins, mineral, and specialty supplements with cancer risk. Men and women were eligible to join the cohort if they were aged 50–76 and lived in the 13-county area in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry[34]. Because this paper is limited to women, we describe here recruitment of women. Using names purchased from a commercial mailing list, we mailed 168,953 baseline questionnaires to women, followed by a post-card reminder after 2 weeks. Recruitment was conducted from October 2000–December 2002, during which time 41,157 (24.4%) questionnaires were returned. Of these, 40,337 passed eligibility and questionnaire quality control checks.

For this analysis we excluded 9 women who were diagnosed after enrollment with rare breast cancer histologies (sarcoma, lymphoma, or phyllodes), 1 diagnosed from a death certificate only, and 3,160 women with a self-reported history of breast cancer prior to enrollment or unknown breast cancer history. An additional 3,948 women were excluded because missing food frequency questionnaire responses precluded estimation of dietary cadmium, or because they reported <600 kcal or >4000 kcal daily energy intake. Women reporting no periods in the year before baseline, had ever used hormone replacement therapy (HRT), reported prior bilateral oophorectomy, or were ≥60 years old at baseline were assumed postmenopausal; an additional 2,676 pre-and perimenopausal women, and women for whom menopausal status was not known were therefore excluded. The final analytical

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cohort included 30,543 postmenopausal women. Of these, 26,801 had complete information on all covariates in the fully adjusted risk model. Descriptive analysis showed no important differences between excluded and included women with respect to smoking or breast cancer risk factors, aside from age and menopausal status.

Data collection

Data collection was accomplished at baseline using a 24-page self-administered, sex-specific, optically scanned questionnaire that covered diet, supplement use, lifestyle, demographics, and health history, as detailed previously[34].

Diet—Diet was assessed with a food frequency questionnaire (FFQ) that captured usual intakes of 120 food, food group, and beverage items over the past one year, and included adjustment questions on types of foods and preparation techniques. This was an adaptation of FFQs developed for the Women's Health Initiative and other studies and previously described in detail [35–37]. The measurement properties of an earlier version of this questionnaire has been published [38]. The FFQ analytic program calculates average annual servings of each FFQ food item, adjusted to sex-specific portion sizes, and estimated nutrient intakes based on the Minnesota Nutrient Data System.

Dietary cadmium—To estimate dietary cadmium intake, we adapted methodology commonly used for dietary micronutrient estimates[39]. We relied on cadmium content of foods determined by the United States Food and Drug Administration (US FDA) as part of the Total Diet Study (TDS), described previously [40, 41]; data are accessible online[42]. Briefly, market baskets of 285 or 290 foods were typically purchased each year (1991–2008) from three locations in each of four regions of the US. These foods were sent to a central laboratory (Lexana, Kansas) for preparation according to predetermined recipes, and analysis for content of a number of contaminants including cadmium[41]. Cadmium was determined with graphite furnace atomic absorption spectroscopy; detection limits depended on the food item and ranged from 0.001 to 0.007 mg/kg[41].

Each of 343 food and beverage line items on the VITAL FFQ was matched to one or more foods analyzed by US FDA based on the food names provided by US FDA. When FFQ line items comprised several foods (*e.g.*, "Muffins, scones, croissants, and biscuits"), we matched each component food to the TDS data and combined them using the same weights employed for other micronutrient analysis of VITAL data, derived from the design of the FFQ. For 32 foods on the FFQ for which no obviously closely similar food was analyzed by US FDA, we relied on food mapping created by the US FDA for the TDS[42]. The arithmetic mean of cadmium content (mg/kg prepared weight) reported by US FDA for all samples of each food, 1991–2008, was assigned as the cadmium concentration for each food. Reported cadmium levels for food items below the limit of detection were assigned values of zero.

Reproductive history and hormone therapy—Each woman reported her age at menarche, age at first birth, and the total number of pregnancies longer than six months. Women were asked about use of prescription estrogen and/or progestin as pills or patches, excluding oral contraceptives, including years of use by formulation.

Other variables—Dietary supplements were a focus of the VITAL study and the assessment methods have been described in detail[34, 43]. Briefly, supplement use covered the 10 years prior to baseline and included use of multivitamins and 16 individual vitamin and mineral supplements; assessment was validated with in-depth interviews in a subset of participants[44]. For analysis, the nutrient content of multivitamins is based on information

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from the PDR for Non-Prescription Drugs [45] and from direct inquiry to manufacturers to determine composition of multivitamins in the past 10 years. Total intake of iron, zinc, and calcium was calculated by summing intake from diet, multivitamins and individual supplements.

The remaining parts of the questionnaire covered personal identifiers for tracking, demographic characteristics, health history, physical activity over the 10 years prior to baseline, cancer screening practices, and other potential cancer risk factors. Body mass index (BMI) was calculated from self-reported height and weight. Physical activity was assessed with a one-page validated questionnaire and converted to metabolic equivalent task hours (MET-h)[46]. To assess smoking, women reported whether they had ever smoked cigarettes regularly, defined as at least one cigarette per day for at least a year. Those who said yes were asked to report the age when they started smoking, the usual number of cigarettes they smoked during the time they smoked, the number of years smoked, and whether they smoked currently. Based on this information each woman was designated as a never-smoker, current smoker, or former smoker.

Follow-up for cancer and censoring

Participants were monitored from date of enrollment to December 31, 2009 for incidence of breast cancer. Cases were ascertained by linkage to the western Washington SEER cancer registry based on multiple identifying characteristics including name, social security number and date of birth as has been described for the VITAL cohort[34]. Tumor estrogen receptor (ER) status was retrieved from SEER. During a mean of 7.5 years follow-up, a total of 1,026 incident invasive breast cancers were diagnosed in the VITAL cohort and met inclusion criteria for this study. Of these, 899 had complete covariate information for adjusted analyses.

Women not diagnosed with incident invasive breast cancer during follow-up were censored at the earliest of the following: incidence of *in situ* breast cancer (N=273), death (N=1,810), withdrawal from the study (N=10), emigration from the SEER registry catchment (N=1,971), or December 31, 2009 (N=25,453). Death was ascertained by linkage to the Washington State death file, and emigrations were identified through the National Change of Address System and active follow-up[34].

Statistical analyses

Multivariable Cox proportional hazards regression with age in days as the time variable was applied to estimate adjusted breast cancer hazard ratios (aHRs) with 95% confidence intervals (95% CIs). Reported P values are two-sided, and P values for linear trend (P_{trend}) were calculated by modeling dietary cadmium as a continuous variable. Interaction P values are from Wald tests of a multiplicative term added to the fully adjusted model, in which linear continuous dietary cadmium was multiplied by the dichotomous effect modifier variable. Graphical inspection of log-log survival plots did not suggest substantial violations of the proportional hazards assumption. Additional models in which dietary cadmium as a continuous variable interacted with time since study enrollment, or with age, did not show statistically significant interactions (P>0.8 in each model for the interaction term). For analyses specific to tumor ER status, separate survival analyses were conducted in which women diagnosed with ER+ were considered incident cases and ER− cases were censored at time of diagnosis, or vice-versa; these analyses result in separate aHRs for ER+ and ER− cancer. To test for the difference in association of cadmium with ER+ and ER− tumors, the dataset was reformulated as a case-control study. Logistic regression was then applied to calculate P values (P-difference) for the difference in adjusted odds ratio comparing ER+ cases to ER− cases.

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We selected confounders based on knowledge of breast cancer risk factors, and sources of cadmium exposure (*e.g.*, cigarette smoking). Multivariable models were adjusted for age, energy intake (kcal, in quartiles), race (white, non-white), education (high school diploma or less; some college or post-secondary education; college degree or more), BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2, ≥30.0 kg/m^2), alcohol consumption (continuous, g/d), physical activity (continuous, MET-hrs/week), years of combined estrogen plus progesterone HRT, age at first birth (nulliparous, ≤19 y, 20–24 y, 25–29 y, ≥30 y), mammography in the two years prior to baseline (yes/no), regular multivitamin use (never, former, or current), cigarette smoking history (never, former, current), and servings per day of vegetables excluding potatoes.

RESULTS

Estimated dietary cadmium intake ranged from 0.5 μg to 55.7 μg per day, with an arithmetic mean (standard deviation, SD) of 10.9 (4.9) μg per day. Dietary cadmium intake was higher among women who consumed more calories and who ate more servings of vegetables on average (Table 1). Women in the highest quartile of estimated dietary cadmium ingestion were younger, more highly educated, consumed more alcohol, had higher total energy intake, and reported higher physical activity than women in the lower quartiles. Zinc, iron, and calcium intake from both dietary and supplementary sources also was higher among women in the upper quartiles of dietary cadmium intake, but much of this likely reflects higher total energy intake. Other personal characteristics were not related to dietary cadmium.

Vegetables, including potatoes, contributed a mean (± SD) of 44% ± 14% of dietary cadmium. Among vegetables, white potatoes contributed an average of 11% ± 8% of total daily dietary cadmium, and leafy greens including salads 22% ± 13%. Aside from vegetables, other important contributors to dietary cadmium were pasta, breads, grains and cereals including rice (22% ± 10%). Legumes and beans including peanut and soybean products (4% ± 4%); seafood (3% ± 2%), fruits (3% ± 3%), and beverages excluding milk (3% ± 3%) were minor sources of dietary cadmium. Meats and dairy products (<1%) contributed very little dietary cadmium on average.

No evidence of an association between dietary cadmium and risk of invasive breast cancer was observed, in either age-and energy-adjusted analysis or in analysis further adjusted for smoking, vegetable consumption, multivitamin use and certain breast cancer risk factors (Table 2). This result held for all tumors regardless of estrogen receptor expression (Table 3). No evidence of effect modification by cigarette smoking history, HRT use, BMI, multivitamin or supplement use, parity, or intake of zinc, iron, or calcium from dietary and supplementary sources was found (Table 3).

DISCUSSION

Dietary cadmium exposure was not associated with risk of postmenopausal breast cancer in this cohort of women residing in the Puget Sound region of Washington State. In addition, no interaction of dietary cadmium with breast cancer risk factors, smoking, or intake of calcium, zinc, or iron through diet and supplements was observed.

Occupational exposure to cadmium has been associated with lung cancer, resulting in cadmium's classification as a human carcinogen by the World Health Organization[3]. Non-occupational exposure to cadmium occurs predominantly through tobacco smoke and food[1], and the association between environmental cadmium exposure and risk of various cancers has recently received increasing attention. Prospective epidemiological studies have

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observed higher rates of total cancer mortality, and mortality from some specific cancers, associated with cadmium exposure, although breast cancer mortality was not associated with cadmium in prior studies[27, 28, 47].

The apparent action of cadmium as an endocrine disruptor or "xeno-estrogen" has stoked interest in it as a potential environmental carcinogen, specifically in relation to hormone-driven cancers[48]. In contrast to our results, a prospective study of postmenopausal women in the Swedish Mammography Cohort observed increased risk of postmenopausal breast cancer with elevated dietary cadmium[29]; earlier studies in the same Swedish cohort found an association of dietary cadmium exposure with endometrial cancer [30] but not ovarian cancer[31]. Like our study, these studies combined food frequency questionnaire responses with analytical data from a national market-basket survey on the cadmium content of foods. Perhaps consistent with an estrogenic mode of action, elevated levels of dietary cadmium were reported to be most strongly associated with breast and endometrial cancer risk among women with lower BMI [29, 30].

Two retrospective case-control studies reported increased risk of breast cancer associated with elevated cadmium exposure [32, 33], also in contrast to our results. These studies assessed cadmium exposure through measurement of urine cadmium, an objective marker of cadmium absorption over decades, [49, 50], and this methodological difference may explain the discrepant results in comparison to our study. However, because of the retrospective design of these studies[32, 33], it is also possible that cancer treatment increased cadmium excretion, leading to a non-causal association of urine cadmium with breast cancer. To our knowledge there is no extant published data examining how cancer treatments including surgery, radiation, and chemotherapy influence urinary heavy metal excretion. Moreover, the modest number of cases in each of these studies precluded detailed investigation of potential modification of the association between urine cadmium and breast cancer risk, such as smoking, BMI, and diet.

The large size of the study allowed us to investigate whether the association between cadmium and breast cancer risk might differ between subgroups of women defined by personal characteristics, and between tumors based on estrogen receptor expression. We focused on three areas. First, motivated by the hypothesis that cadmium acts on estrogen signaling pathways[48], we examined whether hormone-related breast cancer risk factors including parity, BMI, and postmenopausal HRT modified the association between cadmium and breast cancer risk. Furthermore, we conducted separate analyses restricted to estrogen-receptor positive or negative tumors. We found very little evidence supporting an association of cadmium with breast cancer risk in any subgroup examined. Second, we hypothesized that other dietary components could modulate uptake of dietary cadmium, or mitigate the carcinogenic potential of cadmium. Because cadmium competes with iron, zinc, and calcium for binding sites on cellular proteins[51–54], we hypothesized that the cadmium-breast cancer association would be strongest among women with low levels of zinc, iron, or calcium intake. We found no evidence supporting this notion. More generally, we did not observe evidence that the total amount of vegetables consumed mitigated risk of cancer associated with cadmium, in contrast to an earlier report from a study of endometrial cancer[30]. Third, cigarette smoking is an important source of cadmium that could mask an effect of dietary cadmium[30, 55, 56]. Therefore we investigated whether smoking history acted as a modifier of the dietary cadmium-breast cancer association, but found no difference between ever-and never-smokers.

An important limitation of our study that may partly explain our inability to observe an association was our method of exposure assessment. We relied on food frequency questionnaire responses of participants to assess the usual intake of foods. These were

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combined with market-basket studies, conducted by the US FDA as part of the Total Diet Study [40, 41], that determined the average cadmium content of foods. Thus, our methodology was patterned on nutritional epidemiological studies of micronutrients and cancer risk which use a food frequency questionnaire. Such studies are subject to numerous sources of measurement error including social desirability bias and poor recall. Specifically, the FFQ we used in this study was validated for intake of many micronutrients by comparison to daily food records, and the mean correlation between the two methods was ~0.5[38]. This measurement error would be non-differential in a prospective cohort study and likely have substantial bias towards a finding of no association [57, 58].

Another possibility is that limited variation in dietary cadmium exposure among the VITAL study participants could explain our finding of no association with breast cancer risk. We noted that estimated dietary cadmium intake was lower, and exhibited less variation, for VITAL women than for women in the Swedish Mammography Cohort studied previously[29, 30]. Although this could partly reconcile the results of our study with those of the Swedish Mammography Cohort study[29], approximately 12% of all women in the VITAL cohort would have been categorized in the upper tertile of dietary cadmium intake in the Swedish Mammography Cohort. Thus, we would have expected to observe a trend in breast cancer risk with higher cadmium intake comparable to that reported for the Swedish Mammography Cohort, if it existed in our data.

Our methodology may have introduced misclassification of estimated dietary cadmium from multiple sources in addition to problems inherent to FFQs. Our FFQ asked about diet in the year prior to enrollment in the VITAL cohort, and therefore responses may not reflect long term dietary patterns or exposure to cadmium. Even if FFQ responses accurately capture food intake, variation in the cadmium content of food items is likely to be another important sources of measurement error, because the amount of cadmium absorbed by crops depends on details of growing location and conditions as well as crop varietals[4, 6, 59, 60]. We used the arithmetic mean cadmium content of food items measured by US FDA between 1991 and 2008 from cities across the US in our cadmium database. Furthermore, participants in our study resided in western Washington State but we used national average values of food cadmium. We chose this method because, although we noted that cadmium concentration in relatively cadmium-rich individual food items varied several fold between market basket years and locations, we did not observe systematic secular trends or regional differences in average cadmium content of foods within the data reported by the US FDA, perhaps because many vegetables, and processed or packaged foods, are nationally distributed, diminishing regional differences in cadmium content. Thus, our estimation of dietary cadmium for an individual reflects the average cadmium content of foods across years and geographical locations, rather than the actual cadmium content of foods consumed by each participant, as might be measured by urinary assays.

Our estimates of mean dietary cadmium compare well to previous estimates for US women of similar age reported from the US FDA TDS[40]. US FDA employs a sex-and age-specific standard diet to routinely estimate dietary intake of hazardous substances including cadmium; most recently they estimated 60–65 year old women ingest an average of 9.39 μg cadmium per day, 40% of which came from vegetables and 27% from grains[40]. Because we used the food cadmium values from the US FDA it is reassuring that when applied to VITAL participant dietary data, our average dietary cadmium intake estimate and the relative sources were similar to US FDA's. Estimates of dietary intake of cadmium vary between populations, and with the method of diet assessment and with the cadmium database applied. Our estimates are generally somewhat lower than estimates from studies based on the (US) National Health and Nutrition Examination Survey[61], or in a comparable population of Swedish postmenopausal women[30]. We compared the cadmium

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levels detected in Swedish foods [62–64] with US foods [40–42] but could not find systemic differences that might explain different estimates in dietary cadmium intake, although comparison was hampered by differences in methodology between Swedish and US market basket studies.

Intake measures from an FFQ may not accurately reflect actual absorbed does of a micronutrient or contaminant. Absorption of cadmium from ingested food may vary between individuals because of nutritional status. Low circulating ferritin, for example, is associated with increased uptake of cadmium from food presumably because cadmium shares transport pathways with iron[10, 54, 65]. The bioavailability of cadmium may differ depending on the source food or combinations in which foods are eaten[66]; cadmium is bound to chelating proteins both in plants[67] and animals[52]. However, we attempted to account for some of these variations in absorption by modeling interaction between cadmium intake and intake of calcium, zinc, and iron, as well as total vegetable consumption and multivitamin use. The lack of interactions observed suggests that variation in bioavailability and absorption is a relatively minor source of variation in our study.

Although we could not assess occupational exposure to cadmium in the VITAL cohort, a previous study of the US adult population suggests that elevated cadmium exposure occurs mainly in automotive and electrical repair, mining, metalworking, and similar jobs working directly with metals[68]. Because the participants in our study are women over the age of 50 occupational exposure seems unlikely to be an important in this population. Furthermore, for persons without occupational exposure and who have never smoked, dietary intake is the largest source of cadmium exposure[5, 61, 69]. Therefore our finding of no association between dietary cadmium and breast cancer risk among women with no history of smoking, identical to results among all women in the cohort, suggests that unaccounted-for sources of cadmium are unlikely to explain our results.

Finally, because VITAL cohort members were at least 50 years old, the cohort included a small proportion of pre-or perimenopausal women, whom we excluded from analysis. Among pre-and perimenopausal women, 38 incident breast cancers were observed during the follow up period (not shown). Therefore, we were unable to address potential differences between pre-and postmenopausal breast cancer and our findings are restricted to postmenopausal breast cancer.

Despite these potential limitations our study has important strengths, including its prospective design. We did not observe important systematic differences in estimated cadmium intake between VITAL cohort members with complete covariates and those excluded due to incomplete data; nor did we find differences in breast cancer risk factors between VITAL members with and without complete dietary data used to estimate cadmium intake. Follow-up of participants through an established population-based cancer registry and vital statistics minimized attrition from the cohort through loss to follow-up. Thus, selection resulting from missing data within the cohort, or differential attrition, is unlikely to have biased our results.

In summary, the results of our study do not support the hypothesis that cadmium contamination of food is a risk factor for postmenopausal breast cancer. However, limitations including our ability to accurately assess dietary cadmium may have attenuated our estimates of the risk associated with cadmium exposure. A more valid assessment of cadmium exposure would be a direct measure of cadmium body burden, such as provided by urine cadmium concentration; such an assessment of cadmium exposure could then be tested in relation to breast cancer risk in future studies.

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Table 1

VITAL participant characteristics by quartile of estimated dietary cadmium intake

	Quartiles of estimated dietary cadmium[a]							
	1		2		3		4	
	<7.48 μg/d		7.48–10.05 μg/d		10.06–13.30 μg/d		>13.30 μg/d	
	N=7613		N=7651		N=7621		N=7658	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Dietary cadmium (μg/d)	5.8	1.2	8.8	0.7	11.6	0.9	17.4	4.3
Age (y)	62.2	7.3	61.8	7.2	61.6	7.2	61.3	7.1
Energy (Kcal)	1021	295	1322	341	1605	400	2021	567
BMI (kg/m^2)	27.0	5.7	27.1	5.6	27.3	5.7	27.6	6.1
Physical activity (MET-h/wk)	7.5	10.9	8.6	11.6	9.2	12.1	10.8	13.3
Vegetable consumption (servings/d)[b]	1.1	0.6	1.8	0.8	2.4	1.1	3.7	1.8
Potatoes (servings/d)	0.17	0.15	0.26	0.21	0.34	0.25	0.43	0.35
Whole grains (servings/d)[c]	0.45	0.42	0.62	0.52	0.80	0.61	1.05	0.78
Alcohol consumption (g/d)	4.4	10.0	5.2	10.9	5.3	10.0	6.0	11.2
Zinc intake (mg/d)	15.3	11.2	17.7	11.3	19.2	11.1	22.5	11.9
Iron intake (mg/d)	14.9	9.2	17.8	9.0	20.1	9.3	24.4	10.4
Calcium intake (mg/d)	934	582	1099.1	564.4	1219.1	595.6	1428.7	639.6
	N	%	N	%	N	%	N	%
Cigarette smoking[d]								
Never	4082	54	4169	54	4219	55	4256	56
Current	830	11	633	8	526	7	428	6
Former	2677	35	2822	37	2847	37	2957	39
Education[d]								
Secondary or less	2353	31	1900	25	1631	21	1307	17
Some college	3317	44	3301	43	3117	41	2996	39
College degree	1903	25	2409	31	2832	37	3319	43
Race and ethnicity[d]								
Non-Hispanic white	7105	93	7182	94	7190	94	7069	92

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	Quartiles of estimated dietary cadmium[a]							
	1		2		3		4	
	<7.48 μg/d		7.48–10.05 μg/d		10.06–13.30 μg/d		>13.30 μg/d	
	N=7613		N=7651		N=7621		N=7658	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Other	474	6	435	6	397	5	558	7
Multivitamin use								
Never	2377	31	2135	28	2172	29	2030	27
Former	650	9	655	9	628	8	618	8
Current	4586	60	4861	64	4821	63	5010	65
Age at first childbirth (y)[d]								
Nulliparous	888	12	938	12	893	12	1033	13
≤19	1603	21	1378	18	1303	17	1174	15
20–24	3256	43	3215	42	3130	41	3034	40
25–29	1335	18	1418	19	1554	20	1603	21
≥30	472	6	634	8	679	9	753	10
HRT use (y)[d,e]								
Never	4553	60	4347	57	4295	56	4269	56
1–4	949	12	1042	14	1094	14	1124	15
5–9	765	10	890	12	876	11	924	12
≥10	892	12	938	12	929	12	938	12
Mammography[d,f]								
No	709	9	597	8	587	8	652	9
Yes	6883	90	7031	92	7014	92	6988	91

[a] Based on US FDA Total Diet Study market basket data, 1991–2008.

[b] Excluding potatoes.

[c] The sum of FFQ items: highly fortified cereals; high fiber or bran cereals; granola; cooked cereals and grits; dark breads; and 25% of “rice, noodles, and other grains as side items.”

[d] Numbers do not sum to total because of missing information.

[e] Combined estrogen plus progesterone formulation.

[f] Within the two years prior to study baseline.

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Table 2

Estimated adjusted hazard ratios (aHRs) for invasive breast cancer associated with dietary cadmium intake.

Dietary cadmium	N	Cases	aHR[a]	(95% CI)[a]	P_{trend}	N	Cases	aHR[b]	(95% CI)[b]	P_{trend}
Quartile										
1	7,613	276	Ref			6,576	232	Ref		
2	7,651	248	0.85	(0.71–1.03)		6,691	213	0.91	(0.73–1.15)	
3	7,621	258	0.88	(0.72–1.08)		6,718	230	1.03	(0.79–1.35)	
4	7,658	244	0.84	(0.67–1.06)		6,816	224	1.00	(0.72–1.41)	
per μg/d	30,543	1,026	0.99	(0.97–1.01)	0.29	26,801	899	1.00	(0.98–1.02)	0.95

[a]Adjusted for age and total energy intake.

[b]Adjusted for age, total energy intake, education, race, HRT use (combined estrogen and progesterone), vegetable consumption (excluding potatoes), potato consumption, whole grain consumption, cigarette smoking, BMI, physical activity, alcohol consumption, age at first childbirth, multivitamin use, and mammography.

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Table 3

Association of dietary cadmium intake with breast cancer stratified by smoking, breast cancer risk factors, total intake of zinc, calcium, and iron, and tumor estrogen receptor expression.

	N	Cases	aHR[a,b]	(95% CI)[b]	$P_{interaction}$
Cigarette smoking					
Never	14,787	491	1.01	(0.98–1.04)	
Ever	12,014	408	0.99	(0.96–1.01)	0.07
HRT use[c]					
Never	16,121	487	0.99	(0.97–1.02)	
Ever	10,680	412	1.00	(0.98–1.03)	0.44
BMI (kg/m^2)					
<25	10,903	345	1.01	(0.98–1.03)	
≥25	15,898	554	0.99	(0.97–1.02)	0.27
Parity					
Nulliparous	3,341	128	1.00	(0.97–1.04)	
Parous	23,460	771	1.00	(0.97–1.02)	0.71
Vegetable consumption (servings/d)[d]					
<3	20,217	668	1.02	(0.97–1.04)	
≥3	6,584	231	1.00	(0.97–1.02)	0.65
Regular multivitamin use					
Ever	7,586	272	1.00	(0.97–1.04)	
Never	19,215	627	1.00	(0.97–1.02)	0.82
Zinc (mg/d)[e]					
<10.3	6,484	225	1.02	(0.98–1.07)	
≥10.3	20,317	674	1.00	(0.97–1.02)	0.18
Iron (mg/d)[e]					
<11.7	6,343	224	1.00	(0.94–1.05)	
≥11.7	20,458	675	1.00	(0.98–1.02)	0.91
Calcium (mg/d)[e]					
<706.7	6,516	212	1.00	(0.95–1.04)	

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	N	Cases	aHR[a,b]	(95% CI)[b]	$P_{interaction}$
≥706.7	20,285	687	1.00	(0.98–1.02)	0.95
Tumor estrogen receptor status					P-difference[f]
ER+	26,801	757	1.00	(0.98–1.03)	
ER−	26,801	123	0.94	(0.89–1.01)	0.11

[a]Adjusted for age, total energy intake, education, race, HRT use (combined estrogen and progesterone), vegetable consumption (excluding potatoes), potato consumption, whole grain consumption, cigarette smoking, BMI, physical activity, alcohol consumption, age at first childbirth, multivitamin use, and mammography.

[b]per μg cadmium/day.

[c]Hormone replacement therapy, combined estrogen and progesterone preparations.

[d]Excluding potatoes; cut-off corresponds approximately to lowest quartile among all participants.

[e]Total intake from diet and multivitamins; cut-offs correspond to lowest quartile among all participants.

[f]P-value for difference between ER+ and ER− in association with dietary cadmium, from nested case-control analysis.