BRIEF COMMUNICATIONS

Cadmium Exposure and Breast Cancer Risk

Jane A. McElroy, Martin M. Shafer, Amy Trentham-Dietz, John M. Hampton, Polly A. Newcomb

Cadmium, a highly persistent heavy metal, has been categorized as a probable human carcinogen by the U.S. Environmental Protection Agency. Primary exposure sources include food and tobacco smoke. We carried out a population-based case–control study of 246 women, aged 20–69 years, with breast cancer and 254 age-matched control subjects. We measured cadmium levels in urine samples by inductively coupled plasma mass spectrometry and conducted interviews by telephone to obtain information on known breast cancer risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer by creatinine-adjusted cadmium levels were calculated by multivariable analysis. Statistical tests were two-sided. Women in the highest quartile of creatinine-adjusted cadmium level (≥0.58 μg/g) had twice the breast cancer risk of those in the lowest quartile (<0.26 μg/g; OR = 2.29, 95% CI = 1.3 to 4.2) after adjustment for established risk factors, and there was a statistically significant increase in risk with increasing cadmium level (P_{trend} = .01). Based on this study, the absolute risk difference is 45 (95% CI = 0 to 77) per 100 000 given an overall breast cancer rate of 124 per 100 000. Whether increased cadmium is a causal factor for breast cancer or reflects the effects of treatment or disease remains to be determined. [J Natl Cancer Inst 2006;98:869–73]

Cadmium is a toxic, bioaccumulating, nonessential, and highly persistent heavy metal with a variety of known adverse health effects. It has been designated as a probable human carcinogen by the U.S. Environmental Protection Agency, which means that the weight of evidence of carcinogenocity based on animal studies is sufficient and the weight of the evidence based on epidemiologic studies is limited *(1)*. For nonoccupationally exposed women who do not smoke, food is the largest source of cadmium intake, whereas for smokers, inhalation of tobacco smoke is the predominant source of exposure *(2)*. Only a small fraction of inhaled or ingested cadmium is excreted, resulting in increased body burden over time *(3)*. In vitro studies provide provocative evidence that cadmium is associated with human breast cancer through several mechanisms *(4–10)*. For example, cadmium may act like an estrogen, forming high-affinity complexes with estrogen receptors *(10–13)*.

Past studies suggest that values from urine samples give an indication of lifetime cadmium exposure, whereas values from serum samples represent recent exposure *(2)*. From September 2004 through February 2005, we collected urine samples from 246 women with breast cancer aged 20–69 years to determine whether higher body burden levels of cadmium as measured in urine are associated with risk of breast cancer. Women who were asked to contribute a urine sample were part of an ongoing population-based case–control study of breast cancer. Only women who had been diagnosed with breast cancer within the 24 months preceding the interview and whose cancers had been reported to Wisconsin's mandatory statewide cancer reporting system, the Wisconsin Cancer Reporting System, were eligible for enrollment in the parent study. Information on stage of disease and reported treatment(s) for all participating case participants was obtained from the Wisconsin Cancer Reporting System. Community control subjects were randomly selected women from State of Wisconsin driver's license lists who did not have a personal history of breast cancer. Control subjects were matched to case participants within 5-year age strata to yield an age distribution similar to that of the case participants. We collected urine samples from 254 community control subjects from September 2004 through February 2005. The participation proportions—i.e., the percentage of participants eligible to participate in the parent study who actually completed the interview—was 75% for case patients and 71% for control subjects. Of those who completed the interview and agreed to participate in the substudy, the participation proportion for the sequential sample returning the urine specimen was 90% for both case patients and control subjects. The study was approved by the University of Wisconsin–Madison Health Sciences Human Subjects Committee. Oral informed consent was obtained for the interview, and written informed consent was obtained for the urine specimen collection.

All participants were interviewed by telephone by trained interviewers. The 35-minute interview asked about physical activity, reproductive history, alcohol consumption, height and weight, use of oral contraceptives and hormone replacement therapy, personal and family medical history, demographic factors, a limited set of dietary components, and smoking history. Women collected urine samples in their homes. Urine collection kits and detailed photoessay instructions were carefully designed to minimize trace element contamination during specimen collection and handling. Samples were processed at the Wisconsin State Laboratory of Hygiene, a laboratory that is specially designed for and dedicated to trace element analysis and is subject to high-efficiency particulate air filtration. Urine samples contacted only Teflon or polyethylene materials and sample containers were exhaustively cleaned using multistep acid leachings. Cadmium was quantified by using inductively coupled plasma mass spectrometry *(2)*. Trace metal analyses were performed from November 2004 to August 2005 (a 2- to 6-month lag from collection time). A comprehensive quality-control program

Affiliations of authors: University of Wisconsin Comprehensive Cancer Center, Madison, WI (JAM, ATD, JMH, PAN); Environmental Chemistry & Technology Program (MMS), Department of Population Health Sciences (ATD), University of Wisconsin, Madison, WI; Fred Hutchinson Cancer Research Center, Cancer Prevention Program, Seattle, WA (PAN).

Correspondence to: Jane A. McElroy, PhD, University of Wisconsin Comprehensive Cancer Center, Room 307 WARF, 610 Walnut St., Madison, WI 53726 (e-mail: jamcelroy@wisc.edu).

See "Notes" following "References."

DOI: 10.1093/jnci/djj233

Table 1. Characteristics of participants with breast cancer and control subjects

Characteristic	Case patients ($N = 246$)		Control subjects ($N = 254$)		Odds ratio*	95% CI†
	n	%	*n*	%		
Parity						
0–1	69	28	45	18	1.00	
2	95	39	100	39	0.61	0.4 to 1.0
3 or more	81	33	107	42	0.45	0.3 to 0.7
Age at first full term pregnancy (years)						
<20	36	15	43	17	1.00	
20–24	80	33	105	41	0.87	0.5 to 1.5
25–29	55	22	54	21	1.26	0.7 to 2.3
30+	36	15	21	8	2.17	1.1 to 4.4
Nulliparous	39	16	31	12	1.58	0.8 to 3.0
Family history of breast cancer						
Absent	187	76	218	86	1.00	
Present	52	21	30	12	2.01	1.2 to 3.3
Unknown	7	3	6	2	1.35	0.5 to 4.1
Recent alcohol consumption (drinks/week)						
None	46	19	50	20	1.00	
1–6	173	70	178	70	1.07	0.7 to 1.7
7+	27	11	25	10	1.15	0.6 to 2.3
Body mass index (kg/m^2)‡						
<22.5	34	23	27	18	1.00	
22.5–25.0	30	20	30	20	0.75	0.4 to 1.6
25.1–28.8	35	24	41	27	0.68	0.3 to 1.4
28.9+	48	33	52	34	0.74	0.4 to 1.4
Age at menarche						
<12.0	59	24	51	20	1.00	
12.0–12.9	51	21	58	23	0.75	0.4 to 1.3
13.0–13.9	60	24	72	28	0.71	0.4 to 1.2
≥14.0	67	27	65	26	0.89	0.5 to 1.5
Unknown	9	4	8	3	1.06	0.4 to 3.0
Menopausal status						
Postmenopausal	147	60	152	60	1.00	
Premenopausal	67	27	75	30	0.97	0.5 to 1.8
Unknown	32	13	27	11	1.24	0.6 to 2.5
Age at menopause (years)‡						
<45	25	17	43	28	1.00	
45–49	38	26	37	24	1.84	0.9 to 3.6
50–54	50	34	33	22	2.69	1.4 to 5.3
55+	22	15	22	14	1.64	0.8 to 3.6
Unknown	12	8	17	11	1.18	0.5 to 2.9
Type of postmenopausal hormone therapy‡						
Never	52	35	61	40	1.00	
Estrogen only	32	22	37	24	1.01	0.6 to 1.9
Estrogen and progestin only	47	32	37	24	1.49	0.8 to 2.6
Other combination	9	6	10	7	1.05	0.4 to 2.8
Unknown	7	5	7	5	1.13	0.4 to 3.5
Smoking status						
Never	135	55	155	63	1.00	
Former	77	31	65	26	1.37	0.9 to 2.1
Current	33	13	31	13	1.23	0.7 to 2.1
Education						
No high school diploma	4	2	13	5	0.28	0.1 to 0.9
High school diploma	103	42	97	38	1.00	
Some college	60	24	69	27	0.84	0.5 to 1.3
College degree	77	31	72	28	1.04	0.7 to 1.6
Unknown	2	1	3	1	0.64	0.1 to 3.9
Marital status						
Never married	17	7	7	3	2.46	1.0 to 6.1
Married/living as married	199	81	201	79	1.00	
Separated/widowed	28	11	43	17	0.64	0.4 to 1.1
Unknown	2	1	3	1	0.67	0.1 to 4.1
Annual income, US dollars						
<15 000	9	3.7	8	3.1	1.38	0.5 to 3.8
15 001–30 000	28	11.4	28	11.0	1.22	0.7 to 2.3
30 001–50 000	66	26.8	81	31.9	1.00	
50 001–100 000	87	35.4	95	37.4	1.13	0.7 to 1.8
>100 000	30	12.2	19	7.5	1.94	1.0 to 3.8
Unknown	26	10.6	23	9.1	1.42	0.7 to 2.7

*Adjusted for age.

†CI = confidence interval.

‡Postmenopausal women only.

Table 2. Multivariable-adjusted odds ratio of breast cancer associated with creatinine-adjusted cadmium level*

Cadmium concentration level	Case patients (n = 246)		Control subjects (n = 254)					
	n	%	*n*	%	OR†	95% CI	OR‡	95% CI†
All participants								
Q1	43	17	63	25	1.00		1.00	
Q2	61	25	64	25	1.46	0.9 to 2.5	1.53	0.9 to 2.7
Q3	60	24	64	25	1.44	0.8 to 2.5	1.42	0.8 to 2.6
Q4	82	33	63	25	2.05	1.2 to 3.6	2.29	1.3 to 4.2
Continuous (per 1.0 μg/g increase)					1.59	1.0 to 2.6	2.09	1.2 to 3.8
P value						0.07		0.01
Stratified by stage§								
Localized								
Q1	27	17	63	25	1.00		1.00	
Q2	41	26	64	25	1.46	0.8 to 2.7	1.53	0.8 to 3.0
Q3	37	24	64	25	1.27	0.7 to 2.4	1.25	0.6 to 2.5
Q4	50	32	63	25	1.75	0.9 to 3.3	1.99	1.0 to 4.0
Continuous (per 1.0 μg/g)					1.48	0.9 to 2.5	2.04	1.1 to 3.9
P value						0.14		0.03
Regional/distant								
Q1	14	18	63	25	1.00		1.00	
Q2	16	20	64	25	1.40	0.6 to 3.2	1.57	0.6 to 3.9
Q3	21	26	64	25	1.94	0.9 to 4.4	1.95	0.8 to 4.9
Q4	29	36	63	25	3.14	1.4 to 7.1	3.92	1.6 to 9.9
Continuous (per 1.0 μg/g)					1.95	1.0 to 4.0	3.24	1.2 to 8.6
P value						0.07		0.02
Stratified by treatment‖								
Surgery and/or radiation only								
Q1	25	18	63	25	1.00		1.00	
Q2	33	24	64	25	1.36	0.7 to 2.6	1.65	0.8 to 3.5
Q3	28	20	64	25	1.14	0.6 to 2.2	1.08	0.5 to 2.3
Q4	51	37	63	25	2.19	1.1 to 4.2	3.18	1.5 to 6.8
Continuous (per 1.0 μg/g)					1.67	1.0 to 2.9	3.07	1.4 to 7.0
P value						0.07		0.01
Chemotherapy and/or hormonal therapy								
Q1	10	17	63	25	1.00		1.00	
Q2	15	25	64	25	1.58	0.6 to 3.9	1.54	0.6 to 4.3
Q3	17	28	64	25	1.82	0.7 to 4.5	2.11	0.7 to 6.0
Q4	18	30	63	25	2.03	0.8 to 5.1	2.08	0.7 to 6.2
Continuous (per 1.0 μg/g)					1.28	0.6 to 2.8	1.24	0.4 to 3.5
P value						0.54		0.68

*Quartile (Q) of cadmium concentration (in μg/g): Q1 = <0.263; Q2 = 0.263–0.395; Q3 = 0.396–0.579; Q4 = ≥0.580. OR = odds ratio; CI = confidence interval.

†Adjusted for age.

‡Adjusted for age, parity, age at first birth, family history of breast cancer, recent alcohol consumption, body mass index, age at menarche, menopausal status, age at menopause, type of postmenopausal hormone use, education, and marital status.

§For 11 case participants, stage was reported as unknown.

‖For 16 case participants, treatment was not reported to the cancer registry.

incorporating numerous methods including bottle blanks, monitoring of multiple cadmium isotopes, internal and external controls, and routine inclusion of National Institute of Standards and Technology (NIST) standard reference materials ensured high-quality data. A method reporting level of 0.010 μg/L cadmium enabled metal levels in every urine sample to be quantified. Urine creatinine level was also measured to control for kidney function *(14)*.

Case participants were older at first full-term pregnancy, were more likely to have a family history of breast cancer, had fewer children, reported higher income, and were more likely to have never married than similarly aged control subjects (Table 1). Creatinine-adjusted cadmium levels ranged from 0.02 to 4.55 μg/g in case participants (excluding one subject whose level was 30.95 μg/g) and from 0.08 to 2.64 μg/g in control subjects. The creatinine-adjusted cadmium values for each 10-year age group in the control subjects were similar to those reported from a national age-stratified sampling of the general population of Caucasian women in the National Health and Nutrition Examination Survey (NHANES III) (data not shown) *(15)*.

We used multivariable analysis to compute odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer by quartile of cadmium level, as defined by levels in control subjects. After adjustment for age, women in the highest quartile (Q4) had twice the risk of breast cancer as those in the lowest quartile (Q1) (OR = 2.05, 95% CI = 1.2 to 3.6; P = .02, P_{trend} = .07) (Table 2). After adjustment for age, parity, age at first birth, family history of breast cancer, recent alcohol consumption, body mass index, age at menarche, menopausal status, age at menopause, type of postmenopausal hormone use, education, and marital status, the odds ratio for women in Q4 as compared with Q1 rose slightly to 2.29 (95% CI = 1.3 to 4.2; P = .01, P_{trend} = .02). For every 0.1 μg/g increase in cadmium, we observed an 8% increase in breast cancer risk (95% CI = 1.02 to 1.14; P = .01). Adding smoking status (three categories—never, former, and current) to the models did not change the risk estimates (data not shown).

We carried out several exploratory stratified analyses. In one, we stratified

by smoking status (never versus former or current). All of the odds ratios were higher than 1.0 for every quartile in relation to the lowest quartile, as we had observed in the full models. However, the estimates were unstable and had very large confidence intervals due to the very small numbers of smokers (data not shown). We also stratified by median age (56 years) of study participants. In age-adjusted analyses, younger women had an increased risk of breast cancer with increased cadmium level (OR for Q4 versus Q1 = 2.34, 95% CI = 1.1 to 5.0; P = .58, P_{trend} = .06). However, among older women the relationship between cadmium level and breast cancer risk was not statistically significant (OR for Q4 versus Q1 = 1.36, 95% CI = 0.5 to 3.4; P = .08, P_{trend} = .12). Similar patterns were observed when stratifying by menopausal status (data not shown). We also evaluated breast cancer risk associated with intake of a limited number of foods that are potentially high in cadmium (canned fish, liver, kidney, and crustaceans); however, we did not observe any associations (data not shown). The breast cancer participant with very high creatinine-adjusted cadmium levels (30.95 μg/g) had only one established risk factor (low parity) and no evidence of occupational exposure to cadmium. However, she was a heavy smoker who also reported heavy consumption of crustaceans.

Finally, we considered whether the disease process per se or treatment may have altered cadmium levels by stratifying by disease stage (localized versus regional/distant) and by treatment (surgery and/or radiation only versus chemotherapy and/or hormonal therapy). Similar results in the multivariable analysis were observed among participants with localized breast cancer (OR for Q4 versus Q1 = 1.99; 95% CI =1.0 to 4.0; P = .03, P_{trend} = .10) and among participants with regional/distant breast cancer (OR = 3.92; 95% CI = 1.6 to 9.9; P = .02, P_{trend} = .004) (Table 2). We also analyzed differences in odds ratios by stage using the Wald test in polytomous logistic regression models and found no statistically significant differences in odds ratios (data not shown). In analyses by treatment, breast cancer risk increased with increasing cadmium level among those treated by surgery and/or radiation only (OR for Q4 versus Q1 = 3.18; 95% CI = 1.5 to 6.8; P = .01, P_{trend} = .01). However, among those treated with chemotherapy the association of risk with cadmium level was not statistically significant (OR for Q4 versus Q1 = 2.08; 95% CI = 0.7 to 6.2; P = .68, P_{trend} = .16) (Table 2). There were no differences in odds ratios when participants were stratified by treatment (surgery/radiation only versus chemotherapy) using the Wald test in polytomous logistic regression models (data not shown).

Our finding of an association of breast cancer risk with cadmium level is provocative, although whether the association reflects an effect of cadmium on the initiation or promotion of tumor growth or possible effects of treatment or the disease itself on cadmium levels (reverse causation) is unclear. Studies of smoking—a major cadmium source—and breast cancer have yielded mixed results *(16,17)*. If cadmium were a cause of breast cancer, then a positive association of smoking with breast cancer would be expected. More research is needed to examine the relation of cadmium exposure to breast cancer risk, including additional research on potential interactions between treatment or disease status and cadmium release from tissue stores as well as the influence of smoking (with its concomitant high cadmium exposure potential) on breast cancer risk, particularly with regard to polymorphisms in detoxification enzymes.

The results of this population-based case–control study indicate a statistically significant twofold increased breast cancer risk for women in the highest quartile of cadmium level compared with those in the lowest quartile. If cadmium exposure is causal—which one epidemiology study cannot determine—the population attributable risk, using our point estimates, could account for 45 of the 124 annual breast cancer cases per 100 000. However, due to the small sample size, the absolute risk calculation has considerable uncertainty. If we used 95% confidence limits for each quartile, the population attributable risk for cadmium exposure would range from 0 to 77 of the 124 annual breast cancer cases per 100 000. Laboratory data also support a relation between high cadmium levels and increased breast cancer risk *(4–8,10–13)*. Given the ubiquitous exposure of the general population to cadmium, the mode of the association between cadmium exposure and breast cancer risk warrants further study.

References

(1) Environmental Protection Agency. Cadmium. Washington (DC): Environmental Protection Agency; 1987.

(2) Centers for Disease Control and Prevention. Third national report on human exposure to environmental chemicals. Atlanta (GA): Centers for Disease Control and Prevention; 2005.

(3) Klaassen CD. Pharmacokinetics in metal toxicity. Fundam Appl Toxicol 1981;1:353–7.

(4) Abshire MK, Buzard GS, Shiraishi N, Waalkes MP. Induction of c-myc and c-jun proto-oncogene expression in rat L6 myoblasts by cadmium is inhibited by zinc preinduction of the metallothionein gene. J Toxicol Environ Health 1996;48:359–77.

(5) Jin P, Ringertz NR. Cadmium induces transcription of proto-oncogenes c-jun and c-myc in rat L6 myoblasts. J Biol Chem 1990; 265:14061–4.

(6) Shimada H, Shiao YH, Shibata M, Waalkes MP. Cadmium suppresses apoptosis induced by chromium. J Toxicol Environ Health A 1998;54:159–68.

(7) Fan LZ, Cherian MG. Potential role of p53 on metallothionein induction in human epithelial breast cancer cells. Br J Cancer 2002;87: 1019–26.

(8) Meplan C, Mann K, Hainaut P. Cadmium induces conformational modifications of wild-type p53 and suppresses p53 response to DNA damage in cultured cells. J Biol Chem 1999;274:31663–70.

(9) Nagata C, Nagao Y, Shibuya C, Kashiki Y, Shimizu H. Urinary cadmium and serum levels of estrogens and androgens in postmenopausal Japanese women. Cancer Epidemiol Biomarkers Prev 2005;14:705–8.

(10) 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.

(11) 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.

(12) Choe SY, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H, et al. Evaluation of estrogenicity of major heavy metals. Sci Total Environ 2003; 312:15–21.

(13) Stoica A, Katzenellenbogen BS, Martin MB. Activation of estrogen receptor-α by the heavy metal cadmium. Mol Endocrinol 2000; 14:545–53.

(14) Elinder C-G. Normal values for cadmium in human tissues, blood, and urine in different countries. In Friberg L, Elinder C-G, Kjellstrom T, Nordberg GF, editors. Cadmium and health: a toxicological and epidemiological appraisal Vol 1: Exposure, dose, and metabolism. Boca Raton (FL): CRC Press; 1985. p. 81–102.

(15) Paschal DC, Burt V, Caudill SP, Gunter EW, Pirkle JL, Sampson EJ, et al. Exposure of the U.S. population aged 6 years and older to cadmium: 1988–1994. Arch Environ Contam Toxicol 2000;38:377–83.

(16) Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. Br J Cancer 2002;87:1234–45.
(17) Li CI, Malone KE, Daling JR. The relationship between various measures of cigarette smoking and risk of breast cancer among older women 65–79 years of age (United States). Cancer Causes Control 2005;16:975–85.

NOTES

This study was supported by National Institutes of Health grants R03 CA110796 and R01 CA47147. The study sponsor had no role in the study design, data collection, analysis, or interpretation of the data.

We thank Dr. Henry Anderson and Laura Stephenson for support and assistance with the cancer data. The authors are appreciative of the staff of the Wisconsin Women's Health Study and the State Laboratory of Hygiene for data collection and laboratory support on this project. We are especially grateful to the study participants, whose generosity made this research possible.

Manuscript received October 11, 2005; revised April 6, 2006; accepted April 10, 2006.