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Blood levels of cadmium and lead in relation to breast cancer risk in three prospective cohorts

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Abstract

Cadmium and lead have been classified as carcinogens by the International Agency for Research on Cancer. However, their associations with breast cancer risk are unknown despite their persistence in the environment and ubiquitous human exposure. We examined associations of circulating levels of cadmium and lead with breast cancer risk in three case–control studies nested within the Cancer Prevention Study-II (CPS-II) LifeLink Cohort, European Prospective Investigation into Cancer and Nutrition – Italy (EPIC-Italy) and the Northern Sweden Health and Disease Study (NSHDS) cohorts. Metal levels were measured in stored erythrocytes from 1,435 cases and 1,433 controls using inductively coupled plasma-mass spectrometry. Summary relative risks (RR) and 95% confidence intervals (CI) were calculated using random-effects models with each study result weighted by the within- and between-study variances. I^2 values were calculated

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to estimate proportion of between study variation. Using common cut-points, cadmium levels were not associated with breast cancer risk in the CPS-II cohort (continuous RR = 1.01, 95% CI 0.76–1.34), but were inversely associated with risk in the EPIC-Italy (continuous RR = 0.80, 95% CI 0.61–1.03) and NSHDS cohorts (continuous RR = 0.73, 95% CI 0.54–0.97). The inverse association was also evident in the meta-analysis (continuous RR = 0.84, 95% CI 0.69–1.01) with low between-study heterogeneity. Large differences in lead level distributions precluded a meta-analysis of their association with breast cancer risk; no associations were found in the three studies. Adult cadmium and lead levels were not associated with higher risk of breast cancer in our large meta-analysis.

Keywords

cadmium; lead; breast cancer

Introduction

Breast cancer is the most frequently diagnosed cancer in women, accounting for 25% of diagnoses worldwide, with nearly 50% of the diagnoses occurring in Europe and North America.[1] Evidence from studies of migrants moving from a low-risk to a high-risk country and studies of twins suggest nongenetic factors contribute substantially to breast carcinogenesis.[2,3] Public concerns exist about the health effects of broad, low-level exposure to environmental pollutants worldwide, yet the role of the environmental pollutants in breast carcinogenesis is poorly understood.[4,5] Nonessential metals, such as cadmium and lead, are ubiquitous and persistent environmental contaminants contributing to the exposure of nonoccupational populations.[6,7] The biological half-lives of these metals result in bio-accumulation over the lifetime such that older adults have the highest body burden.[4,5] Women are prone to higher levels of these metals due to lower levels of iron,[4,5] and cadmium and lead have been found in breast tissue.[8–10]

Cadmium is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, based primarily on its association with higher risk of lung cancer.[7] It has been hypothesized to be associated with breast cancer risk, potentially through its inhibition of DNA repair, promotion of oxidative stress, stimulation of cell proliferation and/or as an endocrine disruptor.[7] However, epidemiologic studies have produced mixed results. Dietary studies primarily report no association with breast cancer risk, which could be explained by the nondifferential misclassification inherent with assigning a single value to foods with highly variable cadmium levels.[11] In a 2015, a meta-analysis of seven studies with 1,416 cases and 5,083 controls found that higher urinary cadmium levels were positively associated with breast cancer risk (summary odds ratio (OR) = 2.2, 95% CI 1.5–3.3).[12] Only two[13,14] of the seven studies[15–19] in the meta-analysis had prospectively collected blood samples and each had fewer than 50 breast cancer deaths in each study. All of the case–control studies reported direct associations, but the two prospective studies found no associations,[12] as did two much larger cohort studies (508 cases in a US cohort[20] and 900 cases in a Danish cohort[21]) published more recently.

IARC has classified lead as probably carcinogenic to humans (Group2A), based on associations with cancers of the stomach, brain, kidney and lung.[6] Lead might facilitate the carcinogenetic effects of other exposures by impairing DNA repair.[22] In the only population-based breast cancer case–control study (246 cases and 254 controls) with retrospective urine collection, no association was found between urinary lead levels and breast cancer risk after excluding cases taking aromatase inhibitors at the time of urine collection.[23]

Additional studies with larger sample sizes and prospectively collected biological samples are warranted given the persistent and ubiquitous exposure to environmental levels of cadmium and lead. In this study, we provide results on the associations of circulating levels of cadmium and lead with breast cancer risk in 1,435 cases and 1,433 controls from three studies with prospective blood collection. In one of the studies, we examined for potential confounding and stratified on estrogen receptor (ER) status. The metals were measured in erythrocytes, which provide markers of the body burden of cadmium[24,25] and lead.[26,27]

Materials and Methods

Study populations

The pooled analysis is based on nested case–control data from nonoccupationally exposed subjects free of diagnosed cancer at the time of blood draw of three cohort studies with prospective blood collections: the Cancer Prevention Study-II (CPS-II) LifeLink Cohort[28,29] in the United States, European Prospective Investigation into Cancer and Nutrition – Italy (EPIC-Italy),[30] and the Northern Sweden Health and Disease Study (NSHDS)[31] (Table 1). These studies were approved by Emory University, the Florence Health Unit Local Ethical Committee, the Regional Ethical Review Board in Umeå, respectively, and in accordance with the Declaration of Helsinki of the World Medical Association. All participants provided written consent at recruitment.

The CPS-II LifeLink cohort includes 21,963 women who provided a blood specimen among the 97,783 women in the CPS-II Nutrition Cohort. Enrollment in the Nutrition Cohort occurred during 1992–1993, at which time participants completed a mailed baseline questionnaire. Follow-up surveys were sent to participants every 2 years starting in 1997 to update exposure information and to ascertain newly diagnosed cancer outcomes. From 1998 through 2001, participants in the CPS-II Nutrition Cohort were invited to provide a blood sample at a medical facility in their community. All participants completed a brief questionnaire about risk factors and parameters related to the blood collection. Nonfasting blood samples, including two EDTA tubes and a serum separator tube, were provided. Blood samples were shipped chilled overnight to a central repository where they were fractionated and placed in liquid nitrogen freezers for long-term storage. Cancers incident to blood draw diagnosed through June 30, 2011 were self-reported on follow-up questionnaires and subsequently verified by obtaining medical records or through linkage with state registries when complete medical records could not be obtained.[28] Deaths were obtained through linkage of the cohort with the National Death Index.[32]

In EPIC-Italy, 32,579 female volunteers were recruited at five centers in Varese, Florence, Turin, Naples and Ragusa between 1993 and 1998.[30] At enrollment, participants completed

a detailed dietary and lifestyle questionnaire and a nonfasting blood sample was drawn. Blood samples were collected in citrate tubes and processed by centrifugation on the same day of collection. Aliquots were stored in liquid nitrogen tanks at −196 °C until processing. Newly identified cancer cases were identified through automated linkages to cancer and mortality registries, municipal population offices and hospital discharge systems. In Naples, follow-up information was collected through periodic personal contact.

The NSHDS cohort contains three sub-cohorts, of which samples were used in the current project from only the Vasterbotten Intervention Program (VIP).[31] The VIP cohort is an open cohort recruiting both men and women aged 40, 50 and 60 years old. Up to the end of 2007, 40,256 women had been recruited. At enrollment, the participants completed a self-administered questionnaire to collect demographic, medical and lifestyle information as well as a separate food frequency questionnaire. During a medical examination, blood specimens were collected and processed by centrifugation and separation, and frozen at −80 °C within 1 h of collection. For the present study, we used erythrocytes from blood collected in heparin tubes. Newly identified cancer cases were identified through linkage with the Swedish Cancer Registry and the local Northern Sweden Cancer Registry.

Subject selection

Breast cancer cases with blood specimens included 816 cases from CPS-II, 294 from EPIC-Italy and 325 from NSHDS. Each case was paired with one control. Eligible controls were selected among those who were alive and cancer-free at the time of the case's diagnosis and matched on race (CPS-II), birthdate (within 6 months in CPS-II and within 2.5 years in EPIC-Italy and NSHDS), menopausal status (NSHDS, EPIC-Italy), study center (EPIC-Italy) and blood draw date (within 6 months in CPS-II and within the same year in EPIC-Italy and NSHDS). More than 90% of participants had the same fasting status at blood extraction as their matched control.

Laboratory assays

Cadmium and lead levels were measured in stored erythrocytes. Blood cadmium can be used for exposure assessment, although it mainly reflects current exposure, during the most recent months and only to some extent reflects accumulated body burden.[33,34] While whole blood is the biomarker of choice for measuring chronic exposure to environmental lead,[35] nearly all lead in blood is bound to erythrocytes.[27,36] Generally, blood lead levels reflect recent exposure,[35] but can be reflective of past exposures due to mobilization of lead from bones back into blood.[26]

Cadmium and lead levels were determined by inductively coupled plasma-mass spectrometry (ICP-MS)[37] at RTI International for the CPS-II samples and at Lund University Hospital, Lund, Sweden for the EPIC- Italy and NSHDS samples. The limit of detection, calculated as three times the standard deviation of a blank, was 0.03 μg/L for cadmium and 0.15 μg/L for lead in CPS-II samples, and 0.03 μg/L for cadmium and 0.09 μg/L for lead in EPIC-Italy and NSHDS samples. Molybdenum concentrations were monitored for all samples to ensure that measured cadmium data were free from background interference. Multiple aliquots of a National Institute of Standards and Technology (NIST)

standard reference material (SRM; 955c, Levels I and II, Toxic Elements in Caprine Blood), laboratory blanks, and lead and cadmium fortified method blanks were processed with each batch of samples at RTI International to continuously assess data quality. Analytical accuracy was checked against a human blood reference (the Centre de Toxicologie du Quebec, International Comparison Program, Canada) at the Lund University Hospital with coefficient of variation of 5% and 4%. For quality control purposes, replicate samples equal to 5% of the total number of samples were included in CPS-II, and all samples were run in duplicate for EPIC- Italy and NSHDS. Between-batch coefficient of variation (CV) was 5% for cadmium and 6.3% for lead in CPS-II, and 5% for cadmium and 3% for lead in EPIC-Italy and NSHDS. The identity of the samples, including quality control replicates and case–control status, were blinded to the laboratory personnel. Each case and her matched control(s) were assayed in the same batch to minimize technically induced variation.

Statistical analyses

The cut-point selection strategy was based on the distribution of values for the three cohorts (Table 1). Cut-points for cadmium values (in μg/L) were manually selected based on the distributions of the controls from each cohort; the categories were 0–0.49, 0.50–0.99, 1.00–1.49, 1.50–1.99 and ≥2.00. There was little overlap in the lead value (in μg/L) distributions by cohort, so they were categorized separately for each cohort based on quintiles of the control distribution. Distributions of education, smoking status at blood draw and season of blood draw were compared in the highest and lowest categories of metal values using the chi-square test. For each cohort, relative risks (RR) and 95% confidence intervals (CI) were estimated using logistic regression models, adjusted for the study-specific matching factors. Linear trend tests were conducted by modeling the median values of each category. Evaluating the influence of pre-diagnostic disease on cadmium and lead levels was considered; however, a minimal number of cases were diagnosed <2 years after blood draw (CPS-II: $n = 190$, EPIC-Italy: $n = 5$, NSHDS: $n = 4$). To evaluate the influence of current smoking on the association between heavy metals and breast cancer risk, sensitivity analyses were conducted among the never smoking women.

Summary RR (95% CI) estimates were calculated for the associations between cadmium and breast cancer risk using a random-effects model with each study result weighted by the within- and between-study variances.[38] I^2 values were calculated to estimate the proportion of between study variation.[39]

In CPS-II, we additionally evaluated for potential confounding of known or suspected breast cancer risk factors. Body mass index, age at first birth, education, personal history of benign breast disease, and family history of breast cancer were not related to levels of cadmium or lead (data not shown). However, the variables associated with the exposure and outcome, including race, blood draw date, age, cigarette smoking initiation relative to first birth, cigarette smoking status, iron/multi-vitamin use, alcohol consumption, HRT use and season of blood draw, were included in fully adjusted models. Associations were evaluated for subgroups defined by estrogen receptor (ER) status from medical records or state cancer registry data using models to predict risk for one subgroup while censoring for the other subgroups. The Wald p-value for tumor heterogeneity was estimated from an unconditional

nominal polytomous logistic regression model using the model-based variance–covariance matrix estimate.[40]

Results

In all studies, the highest category of cadmium levels had a greater proportion of cigarette smokers than the lowest category (Table 2). The distributions of age at blood draw, attained education, and season of blood draw were similar for the highest and lowest categories of cadmium levels except for slightly older women in the highest cadmium category. In the EPIC-Italy study, the highest category of lead levels had older and less educated women (Supplemental Table 1). In the CPS-II and NSHDS studies, current smoking was more common in the highest, compared to the lowest, category of lead.

Cadmium levels were not associated with breast cancer risk in the CPS-II cohort, but were inversely associated with risk in the EPIC- Italy and NSHDS cohorts (Table 3). The inverse association was also evident in the meta-analysis of the three cohorts, totaling 1,435 cases and 1,433 controls (continuous RR = 0.84, 95% CI 0.69–1.01) with little evidence of between study heterogeneity (I^2 = 27.0%). The inverse association was nearly identical (continuous RR = 0.85, 95% CI 0.55–1.31; data not in tables) among never smokers (731 cases and 803 controls). Lead levels were not associated with breast cancer risk in any of the cohorts (Supplemental Table 2) nor among never smokers (data not shown).

In further analysis of CPS-II data, no evidence of confounding was observed when comparing the fully adjusted model to the minimally adjusted models for cadmium and lead (Supplemental Table 3). ER status, including 668 ER+ cases and 90 ER- cases, was available for the CPS-II cases only. No differences in the association were found for risk of ER+ and ER- cancer for cadmium (ER+: multivariable-adjusted RR of continuous levels = 0.89, 95% CI 0.62–1.27; ER-: RR = 0.96, 95% CI 0.44–2.09; *p*-value for tumor heterogeneity = 0.84) or lead (ER+: RR = 1.00, 95% CI 0.99–1.01; ER-: RR = 0.99, 95% CI 0.97–1.02; p-value for tumor heterogeneity = 0.82).

Discussion

In the largest prospective studies to-date of cadmium and lead levels and risk of breast cancer, no dose response associations were found between these metals and risk of breast cancer. However, women with cadmium levels that were 2 μg/L or higher had a lower risk of breast cancer than women with the lowest levels of cadmium.

Across the three cohorts, there was a wide range of cadmium levels, but the distributions were similar enough to allow for the use of common cut-points in each cohort. Our results for cadmium are consistent with prior studies with prospectively collected urine samples.[13,14,20,21] The inconsistency with the prior case–control studies, using retrospectively collected bloods, might be due to treatment effects on cadmium levels, as proposed by Adams and colleagues for other metals.[13] In our study, the lower risk of breast cancer observed in the highest, compared to lowest, level of cadmium was unexpected based on its role in promoting chromosomal damage and genomic instability and as an endocrine-disrupting chemical.[7] The strong correlation between cadmium levels and cigarette smoking

is unlikely to explain this association given the direct association between cigarette smoking and breast cancer risk.[41] Two studies of postmenopausal women found higher cadmium levels were associated with lower levels of estradiol,[42,43] which would suggest a lower risk of breast cancer.[44] Together these data support the inverse association between higher cadmium levels and lower breast cancer risk observed in our study. Prospective studies with measured cadmium and estradiol would be needed to better understand a possible inverse association with breast cancer risk.

The ranges of lead levels across the studies were not congruent and were not combined in a meta-analysis. The lack of association between lead and breast cancer observed in these three cohorts is consistent with the prior population-based case–control study.[23]

Our study benefited from relatively large number of cases in each of the individual studies and the large range of exposure levels across the three studies. Although the metal levels were measured in two different laboratories and the distribution of levels varied across the cohorts, the higher levels of lead in the Italians compared to Americans have been previously documented.[45,46] We expect laboratory differences had little effect on metal levels since associations were estimated within individual studies, and we found little evidence of between-study heterogeneity in the meta-analysis. We were limited in the interpretation of our results to only adult metal levels, and adult levels could lead to a misclassification of exposure if an earlier window of susceptibility existed. Although we were unable to evaluate for confounding in two of the cohorts, we did fully evaluate confounding in CPS-II, but found no evidence that the observed associations were biased by other factors. While unmeasured confounding could theoretically exist, the lack of strong risk factors for breast cancer limits this possibility. Thus, our results provide strong evidence that high levels of cadmium and lead in adulthood are not associated with breast cancer risk.

Beyond breast cancer, cadmium and lead have been shown overall to have negative consequences on health and the environment, leading to industrial limits in many countries. While decreases in lead exposure have led to limited decreases in blood concentrations, blood cadmium levels have been stable.[34] The persistence of these metals in the environment warrants continued research on their adverse health effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

CI	confidence interval
CPS-II	Cancer Prevention Study-II
EPIC-Italy	European Prospective Investigation into Cancer and Nutrition—Italy
ER	estrogen receptor
NSHDS	Northern Sweden Health and Disease Study
OR	odds ratio
RR	relative risk

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What's new?

Do cadmium and lead cause breast cancer? These two notorious toxic metals tend to linger in the body, and both are classified as carcinogens. Ubiquitous environmental contaminants, they accumulate in women particularly, due to their lower iron levels. Yet no definitive link has been demonstrated between cadmium or lead and breast cancer. Here, the authors analyzed three case–control studies. Across the three studies, a wide range of exposure levels was represented, and each study included a large number of participants. The meta-analysis revealed no association between high levels of cadmium or lead and breast cancer risk.

Table 1.

Study characteristics of the three prospective studies used to examine the association of blood levels of cadmium and lead with breast cancer risk

	Cancer Prevention Study-II Lifelink (CPS-II)	European Prospective Investigation into Cancer and Nutrition - Italy (EPIC-Italy)	Northern Sweden Health and Disease Study (NSHDS)
N (Case/ Control)	816/ 816	292/ 294	325/ 325
N of female cohort	21,956	32,578	40,256
Age range (median) at blood draw	47–85 (68)	35–70 (52)	30–61 (50)
Matching factors (among living and cancer-free at case's diagnosis date)	Race, birth date (±6 months), blood draw date (±6 months)	Center, birth date (±2.5 years), blood draw date year), menopausal status	Birth data (±2.5 years), blood draw date (year), menopausal status
Years of blood draw	1998–2001	1993–1998	1990–2006
Distribution of cadmium values (μg/L) (25th, 50th, 75th percentile)	0.42, 0.57, 0.79	0.47, 0.71, 1.12	0.38, 0.55, 1.00
Distribution of lead values (μg/L) (25th, 50th, 75th percentile)	18.51, 25.34, 34.42	68.1, 87.8, 112.1	28.63, 38.97, 52.88

Table 2.

Highest and lowest cadmium level quintiles by age, education, smoking status and season of blood draw in the highest and lowest exposure categories in three studies with prospective blood collection

Variable	Cancer Prevention Study-II Lifelink (CPS-II) Cadmium Levels (μg/L)			European Prospective Investigation into Cancer and Nutrition - Italy (EPIC-Italy) Cadmium Levels (μg/L)			Northern Sweden Health and Disease Study (NSHDS) Cadmium Levels (μg/L)		
	0–0.49	**2.00 +**	**p-value**	**0–0.49**	**2.00 +**	**p-value**	**0–0.49**	**2.00 +**	**p-value**
Age at blood draw, mean (SD)	67.8 (5.72)	68.8 (5.33)	0.008	51.36 (8.15)	50.62 (7.40)	0.25	52.24 (7.71)	51.54 (7.68)	0.79
Education, *N* (%)									
Primary	6 (0.9)	0 (0)	0.84	80 (49.1)	24 (47.1)	0.98	77 (28.4)	24 (32.4)	0.03
Technical/ professional	32 (5)	1 (4.3)		19 (11.7)	6 (11.8)		68 (25.1)	20 (27.0)	
Secondary	194 (30.1)	7 (30.4)		39 (23.9)	10 (19.6)		49 (18.1)	14 (18.9)	
University/ college	408 (63.4)	15 (65.2)		24 (14.7)	11 (21.6)		71 (26.2)	15 (20.3)	
Unknown	4 (0.6)	0 (0)		1 (0.6)	0 (0.0)		6 (2.2)	1 (1.4)	
Smoking status at blood draw, *N* (%)									
Never	439 (68.2)	2 (8.7)	<0.001	115 (70.6)	3 (5.9)	<0.001	187 (69.0)	1 (1.4)	<0.001
Former	202 (31.4)	5 (21.7)		35 (21.5)	3 (5.9)		71 (26.2)	6 (8.1)	
Current	3 (0.5)	16 (69.6)		13 (8.0)	45 (88.2)		5 (1.8)	66 (89.2)	
Missing	0 (0)	0 (0)		0 (0.0)	0 (0.0)		8 (3.0)	1 (1.4)	
Season of blood draw, *N* (%)									
Winter	89 (13.8)	4 (17.4)	0.38	26 (16.0)	6 (11.8)	0.95	83 (30.6)	16 (21.6)	0.35
Spring	138 (21.4)	3 (13)		48 (29.4)	18 (35.3)		80 (29.5)	25 (33.8)	
Summer	217 (33.7)	5 (21.7)		38 (23.3)	9 (17.6)		14 (5.2)	8 (10.8)	
Fall	200 (31.1)	11 (47.8)		51(31.3)	18 (35.3)		94 (34.7)	25 (33.8)	

Table 3.

Minimally [1] adjusted relative risks (RR) and 95% confidence intervals (CI) for the association of circulating levels of cadmium with breast cancer risk in a meta-analysis of in three studies with prospective blood collection

	Cadmium (μg/L)					
	0–0.49	**0.50–0.99**	**1.00–1.49**	**1.50–1.99**	**2.00 +**	**Continuous**
Cancer Prevention Study-II Lifelink (CPS-II)						
Case *N*	310	395	78	23	10	816
Control *N*	334	365	87	17	13	816
RR (95% CI)	1.00	1.16 (0.94–1.43)	0.96 (0.68–1.35)	1.40 (0.73–2.7)	0.80 (0.35–1.87)	1.01 (0.76–1.34)
p for trend						0.96
European Prospective Investigation into Cancer and Nutrition - Italy (EPIC-Italy)						
Case *N*	88	119	45	23	19	294
Control *N*	75	118	48	19	32	292
RR (95% CI)	1.00	0.87 (0.58–1.32)	0.76 (0.45–1.30)	1.00 (0.50–2.04)	0.52 (0.26–1.00)	0.80 (0.61–1.03)
p for trend						0.08
Northern Sweden Health and Disease Study (NSHDS)						
Case *N*	145	110	24	16	30	325
Control *N*	126	106	26	23	44	325
RR (95% CI)	1.00	1.03 (0.62–1.73)	0.67 (0.28–1.58)	0.42 (0.16–1.05)	0.56 (0.26–1.17)	0.73 (0.54–0.97)
p for trend						0.026
Meta-analysis						
Case *N*	543	624	147	62	59	1435
Control *N*	535	589	161	59	89	1433
RR (95% CI)	1.00	1.09 (0.91–1.30)	0.87 (0.66–1.15)	0.90 (0.48–1.71)	0.59 (0.39–0.91)	0.84 (0.69–1.01)
I^2	NA	0.0%	0.0%	52.9%	0.0%	27%

[1] Models were adjusted for matching factors, which included race (CPS-II), birthdate (within 6 months in CPS-II and within 2.5 years in EPIC-Italy and NSHDS), menopausal status (NSHDS, EPIC-Italy), study center (EPIC-Italy) and blood draw date (within 6 months in CPS-II and within the same year in EPIC-Italy and NSHDS).