Medical Oncology (2020) 37:1
https://doi.org/10.1007/s12032-019-1328-3

ORIGINAL PAPER

Blood levels of endocrine-disrupting metals and prevalent breast cancer among US women

Yudan Wei[1] · Jianmin Zhu[2]

Received: 5 September 2019 / Accepted: 28 October 2019 / Published online: 8 November 2019

Abstract

A growing body of evidence has pointed to a role of environmental chemical exposures in breast cancer etiology. This study was to examine the association between exposure to the endocrine-disrupting metals, including cadmium (Cd), lead (Pb), and mercury (Hg), and breast cancer in US women. A nationally representative subsample of 9260 women aged ≥ 20 years in the 2003–2012 National Health and Nutrition Examination Survey was analyzed for the association of blood levels of these metals with prevalent breast cancer using multivariate logistic regression models. Of the study participants, 284 women (weighted prevalence, 2.8%) were self-reported being diagnosed with breast cancer during 2003–2012. Breast cancer women showed significantly elevated blood levels of Cd and Pb, but not Hg. After adjusting for potential confounders, we found that women in all of the higher quartiles of blood lead levels (BLLs) had significantly increased odds ratio of prevalent breast cancer compared with those in the lowest quartile. However, a significant association with prevalent breast cancer was not seen with blood levels of either Cd or Hg. Our study demonstrates a potential relationship between lead exposure, measured as BLLs, and female breast cancer. Additional epidemiologic and mechanistic studies would further explore these interactions and elucidate the potential role of lead exposure in breast cancer etiology.

Keywords Breast cancer · Cadmium · Endocrine-disrupting metals · Lead · Mercury · NHANES

Introduction

An increased incidence of female breast cancer has been found in the United States and other industrialized regions [1, 2]. The exact etiology underlying the observed geographic variations of breast cancer incidence is not well understood. Higher levels of exposure to environmental chemicals, such as air pollution, usually occur in urbanized and industrialized areas. There has been increasing concern about the role of environmental chemical exposures in breast cancer development [3–7]. Some of the environmental pollutants are endocrine-disrupting chemicals (EDC) that can mimic or interfere with the actions of endogenous hormones, particularly endogenous estrogens, and mediate epigenetic alterations leading to mammary carcinogenesis [8–10].

Cadmium (Cd), lead (Pb), and mercury (Hg) are toxic non-essential metals that are ubiquitously present in the environment, leading to widespread exposure in the general population mainly through inhalation of contaminated particles in ambient air and ingestion of contaminated food, water and dust, as well as cigarette smoking [11]. Experimental studies using in vitro and animal models have demonstrated endocrine-disrupting potential of these metals [12]. They can exhibit estrogen-like properties through binding to estrogen receptors and subsequently activating estrogen-responsive gene transcription in human breast cancer cells [13, 14], thus representing an emerging class of metalloestrogens with potential to add to the estrogenic burden of the human breast [12–15].

There has been an increasing number of epidemiologic studies investigating human metal exposure and breast cancer risk, among which Cd has been extensively studied, but with inconsistent findings [16–24]. There have been only a small handful of epidemiologic studies investigating the association between Pb and Hg exposure and breast cancer.

✉ Yudan Wei
wei_yd@mercer.edu

[1] Department of Community Medicine, Mercer University School of Medicine, 1550 College St., Macon, GA 31207, USA

[2] Department of Mathematics and Computer Science, Fort Valley State University, Fort Valley, GA 31030, USA

A population-based case–control study that was conducted in Wisconsin, US reported that women in the highest quartile of urinary Pb level had twice increased risk of breast cancer than those in the lowest quartile after adjusting for established risk factors; however, a significant association was not observed when excluding women who were taking nonsteroidal aromatase inhibitor [25]. In addition, workplace exposure to soldering materials that mainly involves Pb exposure was found being associated with an increased risk of premenopausal breast cancer in a study investigating the relationship between workplace chemical exposures and breast cancer risk among women enrolled in the Sister Study, a prospective cohort study of US and Puerto Rican women [6]. Most recently, higher levels of airborne Pb, Cd, and Hg were found to be associated with a higher risk of postmenopausal breast cancer in a US nationwide cohort study [24].

To further explore the relationship between metal exposure and breast cancer, we assessed the association between blood levels of Cd, Pb, and Hg and prevalent breast cancer among US women who participated in the 2003–2012 National Health and Nutrition Examination Survey (NHANES) using multivariate logistic regression models, adjusting for potential confounders. Blood levels of these metals were determined in the participants with and without breast cancer, as well as in different subgroups of the study participants with varying demographic, behavioral, and reproductive health status.

Materials and methods

Study population

Female participants, ≥ 20 years of age, were extracted from the NHANES for a ten-year period of time from 2003 to 2012. The NHANES is a cross-sectional survey to assess the health and nutritional status of the US population, which has been continuously conducted and released in 2-year cycles since 1999 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) [26]. The survey examines a nationally representative sample of about 5000 persons each year, who are located in counties across the country. The survey was approved by the NCHS Research Ethics Review Board and participants provided written informed consents. The unweighted response rates for the 2003–2012 NHANES varied slightly, ranging from 69.5 to 77.4%.

Assessment of metal exposure

Blood levels of metals were used to assess levels of exposure in the study participants. Whole blood was collected from the study participants in a mobile examination center by trained health technicians at the time of interview and physical examination; the samples were then stored at ≤ − 20 °C until analysis. Although blood levels of these metals were measured in a single point of time in the NHANES reflecting recent exposure, they may also represent a long-term exposure, as results of a long biological half-life of these metals [27], their bioaccumulation over a lifetime, and the mobilization from storage sites back into blood [28].

Metal (Cd, Pb, and total Hg) concentrations were determined using inductively coupled plasma dynamic reaction cell mass spectrometer (ELAN® DRC II) (PerkinElmer Norwalk, CT, USA). A detailed method is described in the laboratory procedure manual [29]. Of the study participants, 63.3%, 99.6%, and 81.7% participants had blood levels of Cd, Pb, and Hg at or above the limit of detection (LOD), respectively. For levels below LOD, a value of LOD divided by the square root of two was assigned in the NHANES dataset. Blood metal levels were categorized into quartiles, with the first quartile (Q1) as the reference group.

Evaluation of breast cancer status

Self-reported cancer diagnosis was obtained from the medical conditions questionnaires. Participants were being asked a question "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?'. Participants who answered "yes" were subsequently asked "What kind of cancer was it? Only women who reported "no cancer" diagnosis or a "breast cancer" diagnosis were included in our study population. The study population was categorized into with breast cancer and without breast cancer in the analytical models.

Covariates

We considered the age, race/ethnicity, poverty status, education, BMI, physical activity, cigarette smoking, alcohol consumption, and reproductive health status (including age at menarche, ever been pregnant, oral contraceptive use, and female hormone use) as potential confounders in our analysis. Age was categorized into three groups (20–59 years, 60–74 year, and ≥ 75 years) due to a small number of breast cancer cases in younger ages. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic (Mexican-American and other Hispanic), and other (Asian and other, including multi-racial). The body mass index (BMI) was classified as underweight (< 18.5 kg/m^2), normal weight (18.5 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2). Physical activity was categorized as self-reported moderate or vigorous physical recreational activity versus none. Cigarette smoking (never, current, or past smokers) and alcohol consumption (yes/no) were categorized based on the questionnaire data. Additional

covariates are the questionnaire data on reproductive health, including age at menarche (< 12 years vs. ≥ 12 years), history of pregnancy (yes/no), oral contraceptive use (yes/no), and female hormone use (such as estrogen and progesterone use, yes/no).

Statistical analysis

The statistical software SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analyses. Sample weights were incorporated into the analysis, according to the NHANES guidelines [30], to obtain better estimates as participants in the NHANES are selected using a complex multistage probability sampling design. Descriptive statistics was performed on weighted characteristics of the study population by breast cancer status. Blood levels of metals were determined for the total study population as well as for different demographic, behaviroal, and reproductive health groups. Blood metal levels in women with breast cancer were compared with those without breast cancer. Considering the highly skewed distribution of blood metal concentrations in the study population, weighted geometric means were determined. A multivariate logistic regression model was constructed to examine the association between blood levels of metals and prevalent breast cancer, adjusting for potential confounders.

Results

During the study period of 2003–2012, there were 14,272 women ≥ 20 years of age, of which 13,284 had available breast cancer data. We then excluded women with missing data on blood metal concentrations ($n = 1206$), with missing any of the covariates included in our models ($n = 2287$), and who were pregnant at time of interview and physical examination (531); a total of 9260 participants were included in the analyses.

Of 9260 participants, 284 women (weighted prevalence, 2.8%) were reported having breast cancer during 2003–2012. Table 1 displays weighted characteristics of the study participants by breast cancer status. A different distribution in demographic characteristics was seen between women with breast cancer and without breast cancer. Women with breast cancer were more likely to be older (44% in the age group of 60–74 years and 28.6% in the age group of ≥ 75 years), non-Hispanic white, and have a higher socioeconomic and lower education status, compared to women without breast cancer. There were no significant differences in the distribution between women with and without breast cancer regarding the BMI categories, physical activity, age at menarche, and smoking status. Women with breast cancer were more likely to have pregnant history and female hormone use, but less likely to have oral contraceptive use and alcohol consumption, than women without breast cancer.

Table 1 Weighted characteristics for breast cancer status among women ≥ 20 years of age in the 2003–2012 NHANES ($n = 9260$)

Characteristics	With breast cancer *n* (%)	Without breast cancer *n* (%)
Age at interview (mean age, years)		
20–59 (39)	58 (27.4)	6161 (77.2)
60–74 (66)	134 (44.0)	1985 (16.3)
≥ 75 (80)	92 (28.6)	830 (6.5)
Race/ethnicity		
Non-Hispanic white	187 (83.9)	4158 (70.4)
Non-Hispanic black	50 (8.5)	1979 (11.9)
Hispanic	35 (4.2)	2274 (11.9)
Other	12 (3.5)	564 (5.8)
Family income to poverty ratio		
Below poverty (< 1)	44 (9.0)	1985 (14.8)
Above poverty (≥ 1)	240 (91.0)	6991 (85.2)
Education		
< High school	86 (21.9)	2290 (16.4)
≥ High school	198 (78.1)	6686 (83.6)
Body mass index (kg/m^2)		
Underweight (< 18.5)	6 (2.4)	168 (2.1)
Normal weight (18.5 to < 25)	90 (33.2)	2622 (33.6)
Overweight (25 to < 30)	78 (26.7)	2604 (28.4)
Obese (≥ 30)	110 (37.7)	3582 (35.9)
Physical activity		
Yes	129 (50.9)	4515 (58.2)
No	155 (49.1)	4461 (41.8)
Age at menarche (years)		
< 12	57 (18.1)	1909 (20.5)
≥ 12	227 (81.9)	7067 (79.5)
Ever been pregnant		
Yes	256 (88.2)	7547 (80.8)
No	28 (11.8)	1429 (19.2)
Oral contraceptive use		
Yes	145 (56.7)	6091 (74.4)
No	139 (43.3)	2885 (25.6)
Female hormone use		
Yes	95 (34.4)	1898 (22.6)
No	189 (65.6)	7078 (77.4)
Smoking status		
Never smoker	169 (59.6)	5557 (59.4)
Past smoker	80 (26.8)	1727 (20.7)
Current smoker	35 (13.6)	1692 (19.9)
Alcohol consumption		
Yes	156 (57.6)	5464 (68.1)
No	128 (42.4)	3512 (31.9)

Metal concentrations were determined in the total study participants as well as in the subgroups of participants with

varying demographic, behavioral, and reproductive health characteristics (Table 2). The geometric mean of blood levels of Pb, Cd, and Hg was 1.09 µg/dL, 0.39 µg/L, and 0.94 µg/L, respectively, in the total study population. The median level of Pb, Cd, and Hg was 1.15 µg/dL (range 0.18–25), 0.38 µg/L (0.10–10.8), and 0.90 µg/L (0.10–40.6),

Table 2 Blood metal levels in the total study population as well as by selected variables

Characteristic	N	Lead (µg/dL)	Cadmium (µg/L)	Mercury (µg/L)
Total population	9260	1.09 (1.08, 1.11)	0.39 (0.38, 0.40)	0.94 (0.92, 0.96)
Age (years)				
20–59	6219	0.96 (0.95, 0.98)	0.37 (0.36, 0.38)	0.92 (0.90, 0.95)
60–74	2119	1.57 (1.52, 1.61)[a]	0.43 (0.42, 0.45)[a]	1.05 (1.00, 1.11)[a]
≥ 75	922	1.73 (1.66, 1.79)[a]	0.48 (0.47, 0.51)[a]	0.85 (0.79, 0.90)
Race/ethnicity				
Non-Hispanic white	4345	1.08 (1.06, 1.10)	0.39 (0.38, 0.40)	0.91 (0.88, 0.94)
Non-Hispanic black	2029	1.21 (1.17, 1.24)[a]	0.41 (0.40, 0.43)	1.01 (0.97, 1.05)[a]
Hispanic	2309	1.01 (0.98, 1.05)[a]	0.33 (0.32, 0.34)[a]	0.81 (0.77, 0.84)[a]
Other	577	1.20 (1.14, 1.27)[a]	0.53 (0.49, 0.58)[a]	1.61 (1.46, 1.78)[a]
Family income to poverty ratio				
Below poverty (< 1)	2029	1.11 (1.07, 1.14)	0.47 (0.45, 0.50)[a]	0.68 (0.65, 0.72)[a]
Above poverty (≥ 1)	7231	1.09 (1.07, 1.11)	0.38 (0.37, 0.39)	0.99 (0.97, 1.02)
Education				
< High school	2376	1.31 (1.27, 1.35)[a]	0.49 (0.47, 0.51)[a]	0.72 (0.68, 0.75)[a]
≥ High school	6884	1.05 (1.04, 1.07)	0.37 (0.36, 0.38)	0.99 (0.96, 1.02)
Body mass index (kg/m^2)				
Underweight (< 18.5)	174	1.12 (0.99, 1.25)	0.48 (0.41, 0.56)	0.94 (0.80, 1.11)
Normal weight (18.5 to < 25)	2712	1.11 (1.08, 1.14)	0.41 (0.39, 0.42)	1.07 (1.03, 1.12)
Overweight (25 to < 30)	2682	1.16 (1.13, 1.20)	0.40 (0.38, 0.41)	0.97 (0.92, 1.01)
Obese (≥ 30)	3692	1.03 (1.00, 1.05)	0.37 (0.36, 0.38)	0.81 (0.78, 0.84)
Physical activity				
Yes	4644	1.03 (1.01, 1.05)	0.36 (0.35, 0.37)	1.05 (1.02, 1.09)
No	4616	1.19 (1.16, 1.22)[a]	0.44 (0.43, 0.46)[a]	0.80 (0.78, 0.83)[a]
Age at menarche (years)				
< 12	1966	1.06 (1.03, 1.10)	0.39 (0.37, 0.41)	0.89 (0.84, 0.94)
≥ 12	7294	1.10 (1.08, 1.12)	0.39 (0.38, 0.40)	0.95 (0.93, 0.98)
Ever been pregnant				
Yes	7803	1.16 (1.14, 1.18)[a]	0.41 (0.40, 0.42)[a]	0.94 (0.91, 0.96)
No	1457	0.85 (0.82, 0.89)	0.31 (0.30, 0.32)	0.95 (0.90, 1.01)
Oral contraceptive use				
Yes	6236	1.04 (1.02, 1.06)	0.38 (0.37, 0.39)	0.95 (0.92, 0.98)
No	3024	1.26 (1.23, 1.30)[a]	0.42 (0.41, 0.44)[a]	0.91 (0.87, 0.95)
Female hormone use				
Yes	1993	1.40 (1.36, 1.44)[a]	0.42 (0.40, 0.44)[a]	1.07 (1.01, 1.12)[a]
No	7267	1.01 (1.00, 1.03)	0.38 (0.37, 0.39)	0.90 (0.88, 0.93)
Smoking status				
Never smoker	5726	1.00 (0.98, 1.02)	0.29 (0.28, 0.29)	0.98 (0.95, 1.01)
Past smoker	1807	1.21 (1.17, 1.25)[a]	0.38 (0.36, 0.39)[a]	1.05 (1.00, 1.11)
Current smoker	1727	1.29 (1.25, 1.33)[a]	1.01 (0.97, 1.05)[a]	0.74 (0.70, 0.78)[a]
Alcohol consumption				
Yes	5620	1.08 (1.06, 1.10)	0.40 (0.39, 0.41)	1.00 (0.97, 1.04)[a]
No	3640	1.12 (1.10, 1.15)	0.37 (0.36, 0.39)	0.82 (0.79, 0.85)

Weighted geometric means (95% CI)

[a]Statistically significant difference compared to the reference group

respectively (these data are not shown in Table 2). Blood levels of Pb and Cd were significantly increased with increasing ages, but blood Hg levels were only significantly increased in the age group of 60–74 years as compared with the age group of 20–59 years. Non-Hispanic black and other racial group had significantly elevated blood levels of metals than non-Hispanic white, but Hispanic has significantly decreased levels of these metals than White women. Women with lower family income showed significantly increased Cd but decreased Hg levels as compared to women with higher family income. There were no significant differences in Pb levels between the family income groups. Women with lower education level (< high school) had significantly higher levels of Pb and Cd, but lower levels of Hg than women with high school diploma or above. In addition, women who were not physically active had a significantly increased level of Pb and Cd, but decreased level of Hg compared to physically active ones. Among the reproductive health variables selected in the study, women with pregnant history, but without oral contraceptive use, had significantly elevated levels of Pb and Cd. Women with female hormone use had significantly elevated levels of all the three metals. Further, both past and current smokers showed significantly higher levels of Pb and Cd, compared to women who had never smoked; especially current smokers had 3.5-fold higher levels of Cd than non-smokers. Women who drank alcohol showed significantly higher levels of Hg than non-alcohol users.

We further determined blood levels of the three metals in women with and without breast cancer (Table 3). The geometric mean of blood levels of Pb and Cd in breast cancer women was significantly higher than women without breast cancer ($p < 0.0001$ and $p = 0.0013$, respectively). However, there was no statistically significant difference in blood Hg levels between women with and without breast cancer ($p = 0.1715$).

We then examined the association between blood metal levels and prevalent breast cancer using multivariate logistic regression models (Table 4). BLLs was shown to have a statistically significant and strong association with breast cancer in a dose-dependent manner in the unadjusted model with an odds ratio (OR) of 3.78 in Q2, 4.32 in Q3, and 7.24 in Q4. After adjusting for age, race/ethnicity, poverty status, education, BMI, physical activity, age at menarche, pregnancy history, oral contraceptive use, female hormone use, cigarette smoking, and alcohol consumption, significant associations between BLLs and breast cancer still remained, although the OR values became smaller compared with the unadjusted model. In reference to Q1, the OR of the association was 2.52 (95% CI 1.35, 4.73) for Q2, 2.01 (1.05, 3.84) for Q3, and 2.63 (1.36, 5.09) for Q4. A significant association was observed between blood levels of Cd and prevalent breast cancer in the unadjusted model; however, the association did not exist after adjusting for potential confounders. No significant associations were seen between blood Hg levels and breast cancer in both unadjusted and adjusted models (Table 4).

Table 3 Blood levels of lead, cadmium, and total mercury among women with and without breast cancer

Metal	With breast cancer	Without breast cancer	*p* Value
	$n = 284$	$n = 8976$	
Lead (μg/dL)	1.52 (1.42, 1.62)[a]	1.08 (1.07, 1.10)	< 0.0001
Cadmium (μg/L)	0.44 (0.41, 0.49)[a]	0.39 (0.38, 0.40)	0.0013
Mercury (μg/L)	1.02 (0.91, 1.14)	0.94 (0.91, 0.96)	0.1715

Weighted geometric means (95% CI)

[a]Statistically significant increase compared to participants without breast cancer

Table 4 Odds ratios (OR, 95% CI) of the association between blood lead, cadmium, and mercury levels and breast cancer ($n = 9260$)

Metal	*n*	Unadjusted model	Adjusted model[a]
Lead (μg/dL)			
Q1 (< 0.8)	2315	1.00	1.00
Q2 (0.8 to < 1.2)	2309	3.78 (2.09, 6.86)[b]	2.52 (1.35, 4.73)[b]
Q3 (1.2 to < 1.8)	2314	4.32 (2.44, 7.63)[b]	2.01 (1.05, 3.84)[b]
Q4 (≥ 1.8)	2322	7.24 (4.19, 12.49)[b]	2.63 (1.36, 5.09)[b]
Cadmium (μg/L)			
Q1 (< 0.3)	2309	1.00	1.00
Q2 (0.3 to < 0.4)	2246	1.79 (1.12, 2.86)[b]	1.29 (0.78, 2.12)
Q3 (0.4 to < 0.6)	2364	2.10 (1.34, 3.28)[b]	1.20 (0.74, 1.97)
Q4 (≥ 0.6)	2341	1.94 (1.22, 3.08)[b]	1.29 (0.73, 2.28)
Mercury (μg/L)			
Q1 (< 0.5)	2223	1.00	1.00
Q2 (0.5 to < 0.9)	2308	1.22 (0.79, 1.89)	1.20 (0.77, 1.88)
Q3 (0.9 to < 1.7)	2342	1.09 (0.70, 1.68)	1.07 (0.69, 1.66)
Q4 (≥ 1.7)	2387	1.30 (0.85, 1.99)	1.27 (0.82, 1.97)

[a]Adjusted for age, race/ethnicity, poverty status, education, body mass index, physical activity, age at menarche, pregnancy history, oral contraceptive use, female hormone use, cigarette smoking, and alcohol consumption

[b]Statistically significant compared to the reference group (Q1)

Discussion

Breast cancer is a multifactorial disease resulting from an interaction between genetic and environmental factors. Accumulating evidence has suggested a role of chemical exposures in the environment in breast cancer etiology [3–7]. In this study, we observed a significant association between Pb exposure, measured as BLLs, and prevalent breast cancer among US women who participated in the 2003–2012 NHANES, after adjusting for potential confounders. Breast

cancer women showed significantly elevated BLLs compared with women without breast cancer. To our knowledge, this is among the first few studies investigating the potential relationship between Pb exposure and breast cancer. Our results support the findings of the previous reports [6, 25] and the two recent studies by White et al. [24, 31], and provide further evidence on the potential role of exposure to the ubiquitous environmental pollutant Pb in breast cancer etiology. In particular, White et al. [31] evaluated several airborne metals (including Pb, Cd, and Hg) as well as polycyclic aromatic hydrocarbons in relation to mammographic breast density and found that women living in areas with higher concentrations of airborne Pb were more likely to have dense breast, a risk factor for breast cancer.

In this study, we did not observe a significant association between blood Cd and Hg levels and prevalent breast cancer after adjusting for potential confounders although blood Cd levels were higher in breast cancer women. Cadmium has been extensively studied for the association of dietary intake and urinary levels with risk of breast cancer; however, there are discrepancies with the findings [16–22]. Instead, blood levels of Cd were found to be inversely associated with risk of breast cancer in a very recent meta-analysis of three prospective cohorts by Gaudet et al. [23]. In line with this finding, a significant inverse association between blood and urinary Cd and serum estradiol levels was observed [32, 33]. Therefore, further epidemiologic evidence is needed for the relationship between Cd exposure and breast cancer risk. Different from our results, higher levels of airborne Hg was found to be associated with postmenopausal breast cancer in a recent cohort study [24]. The variations of findings between the studies might be due to the difference in study design, assessment of exposure, and the adjustment of confounding variables. Among the three metals analyzed in our study, we only observed a significant association of blood Pb levels with breast cancer. This is an intriguing result that warrants further investigations to unpick the effect of environmental lead exposure on breast cancer and any possible biological mechanisms that might be related to the association.

Lead could be associated with breast cancer via direct and indirect mechanisms. Lead is a metalloestrogen that could mimic the actions of endogenous estrogens involving in breast cancer development. Lead was found to exert estrogen-like activity by binding to estrogen receptors and activate transcription of estrogen receptor-dependent genes in human breast cancer MCF-7 cells [13, 14]. In line with the in vitro studies, BLLs was reported to be positively associated with serum levels of estradiol in animals and humans [34, 35]. Further, increases in mean serum levels of progesterone were observed with increasing BLLs in premenopausal women [36] and the concentrations of other reproductive hormones, serum follicle-stimulating hormone and luteinizing hormone, increased as BLLs increased in postmenopausal and premenopausal women [37]. Relating to this, a high level of Pb has been detected in breast tumor tissues as well as in the endometrium [38–40]. However, the significance and mechanisms of Pb-associated increases in reproductive hormones in breast cancer etiology are yet to be determined.

According to the International Agency for Research on Cancer, Cd and inorganic Pb have been classified as human carcinogen (Group 1) and probable human carcinogen (Group 2A), respectively, but Hg is not classifiable as to its carcinogenicity to humans, although methylmercury compounds has been classified as possible human carcinogen. Considerable epidemiologic evidence is needed to elucidate the relationship between exposure to these metals and breast cancer. Some studies also pointed out the indirect mechanisms of genotoxicity of lead such as inhibition of DNA repair or production of free radicals [41]. In addition, Pb was found to abolish the anticarcinogenic effect of selenium (Se) at 0.5 and 5 ppm in drinking water in C3H mice infected with the murine mammary tumor virus (MMTV) [42]. The Se deficiency in Pb-exposed individuals could result in depressed immune functions and increased cancer susceptibility. However, the involvement of Se deficiency is speculative and lacks human data. It seems unlikely that the levels of BLL in this study would result in Se deficiency.

Metal exposure is common, due to its wide use in industry and its persistence in the environment. Among the general population, the exposure is widespread but generally at substantially lower levels than have been found in the workplace [43]. In our study, low blood levels (geometric mean) of metals were detected from the NHANES participants; however, there was a wide range. Consistent with an earlier report [38], significantly higher blood levels of Pb were found among breast cancer women indicating the possible involvement of Pb in breast cancer development. We also observed elevated levels of Pb and Cd in non-Hispanic black and other racial group (including Asian and multiracial), and in women with lower education, which indicates a possible higher exposure occurring among these women who may live in old buildings or in close proximity to industrial and traffic sources [44]. Biological mechanisms could also occur as we observed increased blood Pb and Cd levels in older women, and in women with pregnant history and female hormone use but without oral contraceptive use. Cigarette smoking is another major route of exposure to metals, especially for Cd, as seen in our study that both Pb and Cd levels were significantly higher in past and current smokers and Cd in current smokers was 3.5-fold higher than that in non-smokers. However, cigarette smoking is not a major source of exposure to Hg. It is noted that although blood metal levels indicate recent exposure, it may reflect long-term exposure on a daily basis due to its widespread

and persistent nature. Moreover, lead accumulates in bone and increased endogenous lead exposure can occur during periods of increased bone turnover, particularly in women in pregnancy and menopause [45].

Due to the nature of a cross-sectional design of the NHANES, our study by analyzing the NHANES data cannot reveal a causal relationship between Pb exposure and breast cancer. Also, misclassification of exposure could occur as variations in the length of time between breast cancer diagnosis and blood sample collection exist among the cases of breast cancer, which could affect our findings. Further prospective epidemiological studies are needed to clarify the relationship between exposure of metals during etiologically relevant periods and the development of breast cancer. As we analyzed the other two toxic metals, Cd and Hg, in the same population, and did not find associations between blood levels of either Cd or Hg and prevalent breast cancer, the observed association with breast cancer was specific to Pb, which suggests an important role of environmental exposure to Pb in breast cancer etiology. Furthermore, self-reported breast cancer diagnosis may be subjected to report bias, which might be related to participants' education and socioeconomic status, and other factors. A single time point of measurement of exposure in the NHANES is another limitation for this study; the mean of serial blood levels of metals should be a more accurate index of long-term exposure [46]. Finally, several risk factors for breast cancer, such as family history, parity, age at first live birth, lactation history, and age of menopause, were not included as covariates in the analysis because these variables are either not available in the NHANES or having too many missing data.

Despite the limitations of this study, there are a number of strengths. First, we explored the association between metal exposure and breast cancer in a large and nationally representative sample of US women who participated in the NHANES. Second, we were able to adjust for a number of potential confounders while assessing the association, including demographic, behavioral, and reproductive health factors. Third, we examined the prevalence of breast cancer and blood levels of metals in US women for a 10-year period of time, and determined metal concentrations in women with and without breast cancer as well as by different subgroups of the population. Lastly, this is among a few studies assessing the association between exposure to the endocrine-disrupting metal Pb and female breast cancer.

In summary, our findings suggest a potential association between exposure to Pb, measured as BLLs, and breast cancer in US women. This finding provides insights on the endocrine-disrupting property of Pb and its potential role in the involvement of endocrine-related cancer etiology. No associations were observed between blood levels of Cd and Hg and prevalent breast cancer. Additional epidemiologic and mechanistic studies would further explore these interactions. Further, significant variations in the levels of metal exposure among women indicate that social and behavioral factors play an important role in the exposure, suggesting the need for policies and actions to reduce the disparities in exposures and the related health outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Parkin DM, Muir CS. Cancer incidence in five continents. Comparability and quality of data. IARC Sci Publ. 1992;120:45–173.
2. Boulos DN, Ghali RR, Ibrahim EM, Boulos MN, AbdelMalik P. An eight-year snapshot of geospatial cancer research (2002-2009): clinico-epidemiological and methodological findings and trends. Med Oncol. 2011;28:1145–62.
3. Johnson-Thompson MC, Guthrie J. Ongoing research to identify environmental risk factors in breast carcinoma. Cancer. 2000;88:1224–9.
4. Brody JG, Rudel RA. Environmental pollutants and breast cancer. Environ Health Perspect. 2003;111:1007–19.
5. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer: epidemiologic studies. Cancer. 2007;109:2667–711.
6. Ekenga CC, Parks CG, Sandler DP. Chemical exposures in the workplace and breast cancer risk: a prospective cohort study. Int J Cancer. 2015;137:1765–74.
7. Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ Res. 2018;160:152–82.
8. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Anton-Cuver H. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. Environ Health Perspect. 1993;101:372–7.
9. Knower KC, To SQ, Leung YK, Ho SM, Clyne CD. Endocrine disruption of the epigenome: a breast cancer link. Endocr Relat Cancer. 2014;21:T33–55.
10. Lecomte S, Habauzit D, Charlier TD, Pakdel F. Emerging estrogenic pollutants in the aquatic environment and breast cancer. Genes (Basel). 2017;8:229.
11. Garcia-Esquinas E, Perez-Gomez B, Fernandez MA, Perez-Meixeira AM, Gil E, de Paz C, et al. Mercury, lead and cadmium in human milk in relation to diet, lifestyle habits and sociodemographic variables in Madrid (Spain). Chemosphere. 2011;85:268–76.
12. Darbre PD. Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J Appl Toxicol. 2006;26:191–7.
13. 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.
14. Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, et al. Estrogen-like activity of metals in MCF-7 breast cancer cells. Endocrinology. 2003;144:2425–36.
15. Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. Metals and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18:63–73.

16. Gallagher CM, Chen JJ, Kovach JS. Environmental cadmium and breast cancer risk. Aging. 2010;2:804–14.
17. Adams SV, Newcomb PA, White E. Dietary cadmium and risk of invasive postmenopausal breast cancer in the VITAL cohort. Cancer Causes Control. 2012;23:845–54.
18. Itoh H, Iwasaki M, Sawada N, Takachi R, Kasuga Y, Yokoyama S, et al. Dietary cadmium intake and breast cancer risk in Japanese women: a case-control study. Int J Hyg Environ Health. 2014;217:70–7.
19. Strumylaite L, Kregzdyte R, Bogusevicius A, Poskiene L, Baranauskiene D, Pranys D. Association between cadmium and breast cancer risk according to estrogen receptor and human epidermal growth factor receptor 2: epidemiological evidence. Breast Cancer Res Treat. 2014;145:225–32.
20. Adams SV, Shafer MM, Bonner MR, LaCroix AZ, Manson JE, Meliker JR, et al. Urinary cadmium and risk of invasive breast cancer in the women's health initiative. Am J Epidemiol. 2016;183:815–23.
21. Lin J, Zhang F, Lei Y. Dietary intake and urinary levels of cadmium and breast cancer risk: a meta-analysis. Cancer Epidemiol. 2016;42:101–7.
22. Eriksen KT, McElroy JA, Harrington JM, Levine KE, Pedersen C, Sorensen M, et al. Urinary cadmium and breast cancer: a prospective Danish cohort study. J Natl Cancer Inst. 2017;109:djw204.
23. Gaudet MM, Deubler EL, Kelly RS, Ryan Diver W, Teras LR, Hodge JM, et al. Blood levels of cadmium and lead in relation to breast cancer risk in three prospective cohorts. Int J Cancer. 2019;144:1010–6.
24. White AJ, O'Brien KM, Niehoff NM, Carroll R, Sandler DP. Metallic air pollutants and breast cancer risk in a nationwide cohort study. Epidemiology. 2019;30:20–8.
25. McElroy JA, Shafer MM, Gangnon RE, Crouch LA, Newcomb PA. Urinary lead exposure and breast cancer risk in a population-based case-control study. Cancer Epidemiol Biomark Prev. 2008;17:2311–7.
26. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed 19 October 2017.
27. Sugita M. The biological half-time of heavy metals. Int Arch Occup Environ Health. 1978;41:25–40.
28. Gulson BL, Mizon KJ, Korsch MJ, Howarth D, Phillips A, Hall J. Impact on blood lead in children and adults following relocation from their source of exposure and contribution of skeletal tissue to blood lead. Bull Environ Contam Toxicol. 1996;56:543–50.
29. Centers for Disease Control and Prevention (CDC). Laboratory procedure manual (Method No: ITB001A). https://wwwn.cdc.gov/nchs/data/nhanes/2003-2004/labmethods/l06_c_met_pb_cd_hg.pdf. Accessed 19 October 2017.
30. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey: specifying weighting parameters. http://www.cdc.gov/nchs/tutorials/nhanes/surveydesign/Weighting/intro.htm. Accessed 7 November 2017.
31. White AJ, Weinberg CR, O'Meara ES, Sandler DP, Sprague BL. Airborne metals and polycyclic aromatic hydrocarbons in relation to mammographic breast density. Breast Cancer Res. 2019;21:24.
32. Ali I, Engstrom A, Vahter M, Skerfving S, Lundh T, Lidfeldt J, et al. Associations between cadmium exposure and circulating levels of sex hormones in postmenopausal women. Environ Res. 2014;134:265–9.
33. Nagata C, Konishi K, Goto Y, Tamura T, Wada K, Hayashi M, et al. Associations of urinary cadmium with circulating sex hormone levels in pre- and postmenopausal Japanese women. Environ Res. 2016;150:82–7.
34. Swarup D, Naresh R, Varshney VP, Balagangatharathilagar M, Kumar P, Nandi D, et al. Changes in plasma hormones profile and liver function in cows naturally exposed to lead and cadmium around different industrial areas. Res Vet Sci. 2007;82:16–21.
35. Chang SH, Cheng BH, Lee SL, Chuang HY, Yang CY, Sung FC, et al. Low blood lead concentration in association with infertility in women. Environ Res. 2006;101:380–6.
36. Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Albert PS, Jones RL, et al. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women. Environ Health Perspect. 2011;119:1156–61.
37. Krieg EF, Feng HA. The relationship between blood lead levels and serum follicle stimulating hormone and luteinizing hormone in the National Health and Nutrition Examination Survey 1999-2002. Reprod Toxicol. 2011;32:277–85.
38. Alatise OI, Schrauzer GN. Lead exposure: a contributing cause of the current breast cancer epidemic in Nigerian women. Biol Trace Elem Res. 2010;136:127–39.
39. Mohammadi M, Riyahi Bakhtiari A, Khodabandeh S. Concentration of Cd, Pb, Hg, and Se in different parts of human breast cancer tissues. J Toxicol. 2014;2014:413870.
40. Rzymski P, Rzymski P, Tomczyk K, Niedzielski P, Jakubowski K, Poniedzialek B, et al. Metal status in human endometrium: relation to cigarette smoking and histological lesions. Environ Res. 2014;132:328–33.
41. Garcia-Leston J, Mendez J, Pasaro E, Laffon B. Genotoxic effects of lead: an updated review. Environ Int. 2010;36:623–36.
42. Schrauzer GN. Effects of selenium and low levels of lead on mammary tumor development and growth in MMTV-infected female mice. Biol Trace Elem Res. 2008;125:268–75.
43. Hayes RB. The carcinogenicity of metals in humans. Cancer Causes Control. 1997;8:371–85.
44. Bushnik T, Haines D, Levallois P, Levesque J, Van Oostdam J, Viau C. Lead and bisphenol A concentrations in the Canadian population. Health Rep. 2010;21:7–18.
45. Vahter M, Akesson A, Liden C, Ceccatelli S, Berglund M. Gender differences in the disposition and toxicity of metals. Environ Res. 2007;104:85–95.
46. Barbosa F, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect. 2005;113:1669–74.