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Breast cancer and urinary metal mixtures in Mexican women

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ABSTRACT

Humans are environmentally exposed to many metals throughout their lives. Simultaneous exposure to several metals could result in synergistic or antagonistic toxicological effects among them; however, the information on exposure to mixtures of metals and breast cancer (BC) is scarce. The objective of this report was to compare metals considered human carcinogens, individually and as mixtures, in women with and without BC.

This is a secondary analysis of a population-based case-control study that was carried out from 2007 to 2011 in Northern Mexico. A total of 499 histologically confirmed BC cases and 499 controls were included. Information about sociodemographic, lifestyle and reproductive characteristics was obtained by in-person interviews. Urinary concentrations of aluminum (Al), cadmium (Cd), chromium (Cr), nickel (Ni), lead (Pb), antimony (Sb), cobalt (Co), molybdenum (Mo), tin (Sn), and vanadium (V) were determined by inductively coupled plasma triple quadrupole. Metal mixtures were identified by principal component analysis with creatinine-corrected metals.

Over 90% of subjects had metal measurements above the detection limit except tin (86%) and antimony (78.4%). After adjusting by selected covariables, we observed that the individual urinary concentrations of V, Co, and Mo were lower among cases compared to controls; in contrast to Sn that had higher concentrations. We identified two principal component mixtures with opposite relationships with BC: Cr, Ni, Sb, Al, Pb and Sn (OR = 1.15; CI95% 1.06,1.25) and Mo and Co (OR = 0.56; CI95% 0.49,0.64).

This is the first study that identified urinary metal mixtures that differed between women with and without BC. Our results warrant confirmation in further prospective epidemiological studies. In addition, the elucidation of underlying mechanisms of metal interactions on BC risk deserves further research.

1. Introduction

Breast cancer (BC) is the most common cancer in women worldwide. It is estimated that at least three million BC new cases will be diagnosed in 2040 (International Agency for Research on Cancer(IARC), 2020a). The study of BC and environmental exposure to metals and metalloids (herein referred as metals) has focused mainly on cadmium (Cd) (Filippini et al., 2020) and arsenic (As) (Pullella and Kotsopoulos, 2020), with inconclusive evidence. Likewise, a few studies have reported no conclusive results regarding exposure to aluminum (Al) (Allam, 2016; Linhart et al., 2017), chromium (Cr) (O'Brien et al., 2019; Pasha et al., 2008; White et al., 2019), lead (Pb) (Gaudet et al., 2019; McElroy et al., 2008), cobalt (Co) (O'Brien et al., 2019; Pasha et al., 2008; White et al., 2019), vanadium (V) (O'Brien et al., 2019; L.-Y. Tang et al., 2012), nickel (Ni) (Yu and Zhang, 2017), antimony (Sb) (Niehoff et al., 2021; White et al., 2019), molybdenum (Mo) (Niehoff et al., 2021; O'Brien et al., 2019) and tin (Sn) (Niehoff et al., 2021; O'Brien et al., 2019). Human beings are environmentally exposed to many metals through contaminated food, water, and air; as well as by using products that contain them, such as: cosmetics, pesticides, medical equipment, and batteries (Braun et al., 2016; Institute of Medicine, 2012; Klaassen, 2001a, 2001b).

The International Agency for Research on Cancer (IARC) has classified Al production, as well as inorganic As, Cd, Cr VI, and Ni compounds as human carcinogens (Group I). Similarly, the IARC has identified inorganic Pb and compounds as probable carcinogens (Group 2A) based on sufficient evidence in animal studies, but with insufficient evidence in humans. Meanwhile, Co and compounds; and some Sb, Sn, Mo and V oxides are considered possible human carcinogens (Group 2B) since more evidence is required in both humans and animals (International Agency for Research on Cancer(IARC), 2020b).

Metals have been reported to accumulate in breast tissue, alter DNA

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integrity, suppress antioxidant protection, and cause epigenetic damage (Romaniuk et al., 2017). There are several metals called metalloestrogens, due to their ability to activate estrogen receptors (ER), which promote cell proliferation (Byrne et al., 2014; White et al., 2019). In contrast, some other metals participate in the maintenance of DNA, have antioxidant potential, and protect cells from genomic instability (L.-Y. Tang et al., 2012; Zoroddu et al., 2019). Simultaneous exposure to several metals could cause toxicological interactions between them (Bauer et al., 2020); however, the information on exposure to mixtures of metals and BC development is practically nil (Niehoff et al., 2021; White et al., 2019). In addition, because BC status might modify metal metabolism (Lossow et al., 2021; Olaiya et al., 2019), and there is few information in this regard, the comparison of metal concentrations between groups of individuals with and without this tumor is a potential limitation in retrospective studies.

Previously, our research group reported a positive association between BC and the capacity to methylate inorganic As (López-Carrillo et al., 2014), as well as a small and uncertain negative relationship with Cd ($OR_{>\text{median vs. }\leq\text{median}} = 0.97$ (95% CI 0.72, 1.30)) (Rojas-Lima et al., 2021), in women living in Northern Mexico. In that region, the incidence of BC is higher than in most of the country (Global Burden of Disease (GBD), 2020) and is characterized by the natural contamination of metals in the water (Fisher et al., 2017) and the presence of the fourth largest non-ferrous metal processing site worldwide (Quandt et al., 2011). This scenario offers the opportunity to assess the joint exposure to metals.

The objective of this report was to compare metals considered human carcinogens, individually and as mixtures, in women with and without BC.

2. Material and methods

2.1. Study design

We carried out a population-based case-control study from 2007 to 2011 in some states of Northern Mexico to evaluate environmental and genetic factors associated with BC; detailed information regarding its methodology has been reported elsewhere (López-Carrillo et al., 2014). Briefly, 1045 histopathologically confirmed BC cases were identified in the main public and academic hospitals from the included states. The inclusion criteria included a minimum age of 18 years, no personal history of other type of cancer, and at least one year of residency in the study area. Cases were classified by the Tumor, Node, Metastasis (TNM) system as: 0.22% in situ, 10.47% stage I, 56.41% stage II, 25.00% stage III, 2.65% stage IV, and 5.31% had no information. In addition, 56.00%, 22.89% and 21.11% cases were diagnosed as: luminal (ER + and/or progesterone receptor [PR] +/human epidermal growth factor receptor 2 – [HER2]), HER2+ (ER+/– and/or PR+/–/HER2+), or triple negative (ER– and PR–/HER2–), respectively.

A total of 1030 controls with no personal history of cancer and at least one year of residence in the study area, were matched by age to cases (±5 years). Controls were identified through the Master Sample Framework used for the National Health Surveys, which provides a probabilistic list of households in urban and rural areas. In households where there was more than one eligible woman, only one participant was chosen at random, while if there were no eligible woman or she declined participation, another house was systematically located according to standardized procedures. The participation rates were above 90% for cases and controls.

We developed and performed the study according to the Declaration of Helsinki guidelines; and obtained a written informed consent from each participant. The Ethics, Biosafety and Research Committees of the National Institute of Public Health approved the protocol.

In this report, we included 499 cases and 499 controls (age-matched 1:1) with available information of urinary metal concentrations.

2.2. Interviews

We directly interviewed participants about their sociodemographic, clinical, and reproductive characteristics, as well as their alcohol consumption. Controls interviews were carried out at home, whereas cases were interviewed at the hospital after BC diagnosis and before receiving any type of treatment (average time from diagnosis to interview was 2 months). At the time of the interview, we measured and weighed women to calculate their body mass index (BMI).

2.3. Estrogens exposure index

To control for reproductive factors associated with BC, we previously calculated a cumulative endogenous estrogen exposure index (Rojas-Lima et al., 2020). For postmenopausal women, the difference in years of age at menopause minus age at menarche was calculated; the difference of age at the time of the study minus age at menarche was obtained for premenopausal women. The corresponding years of pregnancy and breastfeeding were subtracted from both results. In our study sample, this index ranged from 0 years (multiparous women, with long breastfeeding periods and hysterectomized at an early age) to 45 years (women with early menarche, nulliparous, who did not breastfeed and with late menopause).

2.4. Urine samples

Participants donated a first morning void urine sample, near the day of interview. Urine from cases were collected before any treatment. We collected samples in a sterile disposable polypropylene urine collection cup, and an aliquot of 4 mL of urine was prepared in a Cryovial and stored frozen at or below −20 °C. Creatinine was determined at the Center for Research and Advanced Studies (CINVESTAV-Zacatenco, Mexico City) by spectrophotometry using a commercial kit (Randox Creatinine Kit) with 1 mg/dL as detection limit (Randox, Antrim County, UK). Participants with creatinine concentration <20 mg/dL (Holden and Guice, 2014; Lin et al., 2018) or > 300 mg/dL (Barr et al., 2005) were excluded, reaching a final sample size of 452 cases and 439 controls.

2.5. Metal determination

Metal analyses was done at Icahn School of Medicine in Mount Sinai. Urinary samples (200 μl) were diluted with 8.8 mL of diluent solution that contained 0.5% nitric acid, 0.005% Triton X-100 and mixed internal standard, in a polypropylene trace metal free Falcon tubes (VWR® Metal-Free Centrifuge Tubes). They were analyzed using matrix matched calibration standards with Agilent 8800 inductively coupled plasma triple quadrupole (ICP-QQQ) (Agilent technologies, Inc., Delaware, USA) in tandem mass spectrometry mode (MS/MS). Each sample was analyzed five times; the final concentration reported was the mean of those five times. Internal standards (yttrium, indium, tellurium and lutetium) were used to correct for different sample introduction, ionization and reaction rates in the reaction cell.

Quality assurance and quality control included analysis of initial and ongoing calibration verification standards. The recovery percentage ranged from 89% for nickel and molybdenum, to 119% for vanadium, respectively. Detection limits (DL) (ng/ml) for each metal were as follows: Al = 9.73; As = 0.25; Cd = 0.12; Cr = 0.65; Ni = 1.56; Pb = 0.03; Sb = 0.16, Co = 0.08; Mo = 0.28, Sn = 0.35 and V = 0.04. Most metals had sample percentages above the DL of at least 90%, except Sn (86%) and Sb (78.4%). Samples with metal concentrations below the DL were imputed with their corresponding DL divided by two according to methodology previously described (Barr et al., 2006). The inter-day coefficient of variation was less than 10% for most metals except for Al (14.9%), Ni (13.1%) and Sb (21.1%). The intra-day coefficient did not exceed 20% for all metals, but Al (66.6%), Ni (36.4%), and Sb (52.2%). Likewise, the coefficients of variation for nine internal duplicate samples

ranged from 3.8% to 19.1% for Cr and Ni, respectively. Additionally, a blind duplicate analysis of two samples was performed, obtaining a coefficient of variation that ranged from 3.0% to 13.0% for V and Sb, respectively.

2.6. Statistical analysis

Selected characteristics were compared between cases and controls through chi2, Mann-Whitney U, *t*-test or Fisher's exact test, both within the study sample and versus not included. We evaluated Spearman correlations between metals. To account for urine dilution we divided metal concentrations by creatinine levels (Barr et al., 2005). Urinary concentrations of each metal were compared between cases and controls, using the U-Mann-Whitney test.

We selected principal component analysis since it is used to find patterns of exposure without reference to the outcome of interest and allows to evaluate contrasting effects, for this analysis we log-transformed metal concentrations (Jolliffe, 2002; Lever et al., 2017). We obtained orthogonal varimax rotated metal mixtures from the inclusion of all log-transformed creatinine-corrected urinary metal concentrations, and two with an eigenvalue equal or greater than 1 were retained in further analysis. The first two principal components representing metal mixtures and retained for further analysis represented 57% of the total variance among the metals.

Based on the quartile distribution of metal concentrations among controls, we compared metals between the study groups, using unconditional logistic regression models. We evaluated as potential confounders: schooling, BMI, tobacco consumption, alcohol intake, estrogenic index, family history of BC and menopausal status; and those that were statistically different between cases and controls were considered in multivariable models, along with age that was a-priori included. Only one control had a family history of BC, so this variable could not be included in the final models. In addition, we adjusted by those metals which resulted statistically significant related to BC and were not correlated to each other (Co, Sn and V). Molybdenum was highly correlated with Co (Coefficient = 0.41), thus it was not included. We further evaluated pair interactions between all metals of interest, adding a continuous multiplicative term to the previous models.

Likewise, we evaluated metal mixtures with BC, which were further stratified by menopausal status. In a sensitivity analysis, the final models of metal mixtures were rerun excluding diabetic women, stratifying by As methylation capacity (Low = % methylarsonic acid $\geq$9.76; high = % methylarsonic acid <9.76), including total arsenic in metal mixtures and re-estimating the metal mixtures from the distribution among controls. An alpha of 0.05 was set as the level of significance. All analyses were performed in Stata 14 (StataCorp, College Station, TX, E.U.A).

Data Availability: Data sharing is not possible for ethical considerations.

3. Results

Cases had higher education, alcohol consumption, estrogenic index, and family history than controls. In contrast, among premenopausal women, cases had lower BMI. Even though the medians of education between cases and controls were the same, there was higher proportion of women with more years of education among cases compare to controls (13 years vs 12 years at p90, respectively) (Table 1). There was lower proportion of history of BC in our study sample compared to the non-included cases and controls. In addition, study controls were slightly younger and with more premenopausal women than non-included controls (Supplementary table 1).

Median urinary concentrations of Co, Mo and V were lower among cases compared to controls, in contrast to Sn that had higher concentrations among cases (Table 2). The correlation coefficients between all metals included in this report, ranged from 0.05 between Sb and Mo, to 0.72 between Cr and Sb, and Cr and Ni (Supplementary table 2).

Table 1
Selected characteristics in the study sample.

Characteristics	(n)	Cases	(n)	Controls
Age, years [mean ± SD]	(452)	53.1 ± 12.5	(439)	52.2 ± 12.3
Schooling, years [p50 (p10, p90)]	(452)	**6.0 (2.0, 13.0)**	(439)	**6.0 (1.0, 12.0)**
Body mass index, kg/m^2 [mean ± SD]				
Premenopausal	(179)	**28.6 ± 5.7**	(165)	**30.1 ± 6.4**
Postmenopausal	(268)	30.2 ± 5.7	(274)	31.2 ± 6.1
Tobacco, cigarettes/day [p50 (p10, p90)][a]	(117)	5(1, 20)	(126)	4(1, 20)
Alcohol, g/day [p50 (p10, p90)][b]	(84)	**0.9 (0.2, 2.9)**	(50)	**0.2 (0.2, 0.9)**
Estrogenic Index, years [mean ± SD]	(449)	**26.0 ± 7.9**	(436)	**21.5 ± 8.6**
Family history of breast cancer, yes [% (95% CI)]	(58)	**12.8 (10.0,16.3)**	(1)	**0.2 (0.0,1.6)**
Menopausal status, premenopausal [% (95% CI)]	(182)	40.3 (35.8,44.9)	(165)	37.6 (33.2,42.2)
Urinary creatinine, mg/dL [p50 (p10, p90)]	(452)	66.6 (29.0,156.5)	(439)	70.5 (30.0, 158.8)

[a] among smokers.
[b] among drinkers. P50 = 50 percentile, p10 = percentile 10, p90 = percentile 90. Bold and shadow numbers correspond to case-control differences with *P*-value<0.05.

Table 2
- Metal urinary concentrations between cases and controls.

Metals (μg/g-creatinine)	Cases (n = 452)	Controls (n = 439)
	p50 (p10, p90)	
Aluminum [Al]	41.28 (18.07, 116.10)	42.42 (18.66, 111.79)
Antimony [Sb]	0.46 (0.10,2.50)	0.55 (0.12,1.57)
Cadmium [Cd]	0.53 (0.19, 1.48)	0.56 (0.22, 1.51)
Chromium [Cr]	3.16 (1.27, 8.93)	3.00 (1.35, 7.97)
Cobalt [Co]	**0.43 (0.18, 1.30)**	**0.56 (0.23, 2.04)**
Lead [Pb]	2.71 (1.03, 7.33)	2.99 (0.93, 8.16)
Molybdenum [Mo]	**37.87 (9.47, 95.47)**	**61.13 (22.62, 136.61)**
Nickel [Ni]	10.76 (4.86, 24.94)	10.72 (4.78, 26.65)
Tin [Sn]	**1.27 (0.40, 8.21)**	**0.85 (0.36, 2.84)**
Vanadium [V]	**0.50 (0.23, 1.39)**	**0.66 (0.28, 1.80)**

P50 = 50 percentile, p10 = percentile 10, p90 = percentile 90. Bold and shadow numbers correspond to case-control differences with *P*-value<0.05.

After adjusting for age, education, estrogenic index, alcohol consumption and BMI, and comparing the higher quartiles vs. quartile 1, we observed lower concentrations of Co, Mo and V among cases compared to controls, with odd ratios that ranged from 0.20 for Mo to 0.45 for Co and V, with *p*-values for trend <0.05. In contrast, Sn concentrations were 2.23 times frequent among cases (Table 3). These results remained after further adjustment by Co, Sn and V. In addition, we observed a negative interaction between Sn and V (*p*-value = 0.014); as well as positive interaction between Sb and Cr (*p*-value = 0.002) and Co and Mo (*p*-value = 0.004) (Data not shown).

The two metal mixture components that we obtained explained 57% of the total variance, with the first mixture strongly determined (high loadings) by Cr, Ni, Sb, Al, Pb and Sn; while the second by Mo and Co (Fig. 1). We observed, after adjustment for covariables, that mixture 1, in the total sample, was 1.15 times frequent among cases compared to controls (OR = 1.15; CI95% 1.06, 1.25), as well as 1.20 times among postmenopausal (OR = 1.20; CI 95%1.08, 1.33) and 1.13 times among premenopausal women (OR = 1.13; CI95% 0.98, 1.29). In contrast, we found that mixture 2 was 0.56 times frequent in cases compared to controls (OR = 0.56; CI95% 0.49,0.64), which did not change by menopausal status (Table 4). All these results remained after excluding diabetics women, including total As in the mixtures, stratifying by As methylation capacity, and including metal mixtures based on metal distribution among controls (Supplementary table 3).

Table 3
- Associations between each metal and breast cancer.

Metals	(Ca, Co)	Metal quartiles (μg/g creatinine)				*P* for trend
		Q1	Q2	Q3	Q4	
		OR (95% CI) [a]				
Aluminum [Al]	(444, 436)	1.00	0.84 (0.56,1.26)	0.78 (0.52,1.18)	0.85 (0.52,1.27)	0.389
Antimony [Sb]	(444, 436)	1.00	0.70 (0.47,1.05)	**0.37 (0.24,0.57)**	0.92 (0.63,1.35)	0.269
Cadmium [Cd]	(444, 436)	1.00	1.08 (0.72,1.60)	1.03 (0.69,1.54)	0.94 (0.62,1.41)	0.735
Chromium [Cr]	(444, 436)	1.00	0.68 (0.45,1.03)	0.90 (0.60,1.34)	1.00 (0.68,1.49)	0.709
Cobalt [Co]	(444, 436)	1.00	1.20 (0.82,1.75)	0.79 (0.54,1.18)	**0.45 (0.28,0.70)**	0.000
Lead [Pb]	(444, 436)	1.00	0.90 (0.61,1.34)	0.79 (0.53,1.18)	0.79 (0.53,1.19)	0.201
Molybdenum [Mo]	(444, 436)	1.00	**0.45 (0.31,0.66)**	**0.39 (0.26,0.57)**	**0.20 (0.12,0.31)**	0.000
Nickel [Ni]	(444, 436)	1.00	0.95 (0.63,1.43)	1.02 (0.68,1.52)	0.90 (0.60,1.36)	0.724
Tin [Sn]	(444, 436)	1.00	0.66 (0.42,1.05)	1.29 (0.84,1.96)	**2.23 (1.50,3.32)**	0.000
Vanadium [V]	(444, 436)	1.00	0.84 (0.57,1.22)	**0.47 (0.31,0.71)**	**0.45 (0.29,0.68)**	0.000

[a] adjusted by age, schooling, estrogenic index, alcohol consumption and BMI. Bold and shadow numbers correspond to case-control OR differences > or <1.00 with P-value<0.05.

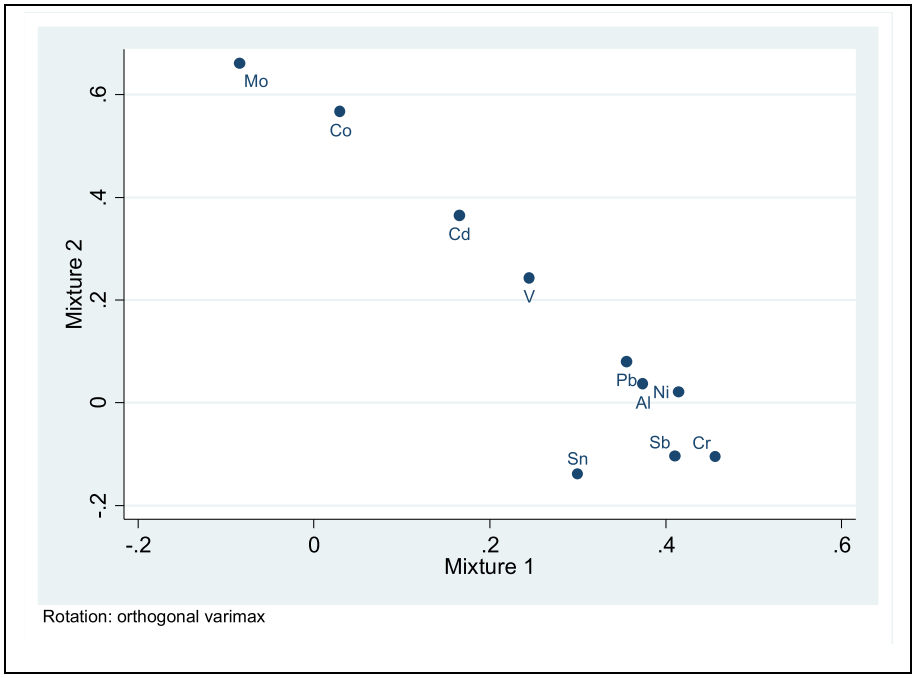

Fig. 1. Metal loadings in each mixture.

Table 4
- Association between breast cancer and each metal mixture, by menopause status.

Models	(Ca, Co)	Mixture 1	Mixture 2
		OR (95% CI)	
Model 1			
All	(452, 439)	**1.16 (1.08, 1.25)**	**0.54 (0.48, 0.62)**
Premenopause	(182, 165)	**1.14 (1.01, 1.29)**	**0.52 (0.42, 0.65)**
Postmenopause	(270, 274)	**1.20 (1.09, 1.33)**	**0.54 (0.46, 0.63)**
Model 2			
All	(444, 436)	**1.15 (1.06, 1.25)**	**0.56 (0.49, 0.64)**
Premenopause	(178, 165)	1.13 (0.98, 1.29)	**0.59 (0.47, 0.74)**
Postmenopause	(266, 271)	**1.20 (1.08, 1.33)**	**0.54 (0.45, 0.65)**

Model 1: adjusted by age.
Model 2: adjusted by age, schooling, estrogenic index, alcohol consumption and BMI.
Metals were included as ln-μg/g-creatinine.
Bold and shadow numbers correspond to OR > or < 1.00 with *P*-value<0.05.
Mixture 1: high loadings of Cr, Ni, Sb, Al, Pb and Sn; mixture 2: high loadings of Mo and Co.

4. Discussion

Our results showed that a metal mixture characterized by Sn, Cr, Ni, Sb, Al and Pb was more frequent among women with BC compared to women without this tumor. Likewise, they showed that another mixture determined by Mo and Co was less common in cases. Additionally, when compared to controls, we observed that cases had higher individual Sn; and lower V, Co and Mo concentrations. Because this is the first report worldwide regarding joint urinary metal exposure and BC, our results will have to be confirmed in future studies.

To our knowledge, there are only two recent reports on the relationship of mixtures of metals and BC that come from the cohort named the Sister Study, yielding inconsistent results. In one of them (Niehoff et al., 2021) no association was found between this tumor and the mixture of Al, Sb, As, Cd, Cr, Co, Pb, Mo, Ni, Sn, copper (Cu), iron (Fe), manganese (Mn), zinc (Zn) and selenium (Se), measured in nails. In contrast, in postmenopausal women a positive association (OR = 1.1, 95% CI 1.0,1.1) was reported with air exposure to the mixture of Sb, As, Cd, Cr, Co, Pb, Ni, Mn, Se and mercury (Hg) (White et al., 2019). These discrepancies could be explained by the presence of different metals in

the mixtures and/or the use of different exposure matrices; however, our results of mixture 1 measured in urine confirm an association with BC in postmenopausal women (OR = 1.20, 95% CI 1.08,1.33).

In this report we found that mixture 1, characterized by Sn, Sb, Ni, Pb, Cr and Al, was positively related to BC. These metals, except Sn, did not show an individual association with this cancer. This suggests that the association of the mixture 1 with BC could be the result not only of the presence of Sn, which did show an individual association with BC, but also of the positive interaction that we identified between Sb and Cr, as well as the negative interaction between Sn and V, without ruling out the existence of other underlying interactions between these metals. On the other hand, the Co and Mo that were in mixture 2, were jointly and individually associated with BC, and since a positive interaction was identified between them, it would be reasonable to think they share biological mechanisms that explain their relationship with this tumor. In any case, little information exists regarding mechanisms of metal mixtures and BC (Niehoff et al., 2021; White et al., 2019); however, some important efforts are being developed to better understand potential biological relationships within metal mixtures, as the Toxicological profile for Pb, Cd, and Cr (Agency for Toxic Substances and Disease Registry, 2004).

Previous studies on exposure to Sn, V, Co and Mo in relation to the development of BC are scarce and inconclusive. Tin has been recognized as a metalloestrogen for its ability to induce estrogen target gene expression and cell proliferation (Byrne et al., 2014; Choe et al., 2003; Lappano et al., 2017). Similarly, stannous chloride, used in tin coatings, has been observed to induce the growth of the MCF-7 cell line (ATSDR, 2005). Our results agree with those carcinogenic mechanisms by identifying higher Sn concentrations in BC cases compared to controls. Likewise, they support the results of the "Sister Study" that was performed in American women where a positive association ($OR_{Q4\ vs\ Q1}$ = 1.22; CI 95% 0.78, 1.90) was identified between this tumor and exposure to Sn (O'Brien et al., 2019). It is possible that the lack of statistical significance in that report was due to the inclusion of sisters of the case women as controls, which could attenuate the differences in Sn concentrations between relatives who may share similar exposure environments (Linton et al., 2013). Considering the above, the results to date are suggestive that tin may increase the risk of BC.

Regarding V, our results confirm those of another case-control study in Chinese women, where it was found that participants in the second and third tertile of urinary V concentrations showed a negative association with BC ($OR_{T2\ vs\ T1}$ = 0.36; CI 95% 0.21,0.60; $OR_{T3\ vs\ T1}$ = 0.60; CI 95% 0.37,0.97) (L.-Y. Tang et al., 2012). These findings seem to differ from those of the Sister Study ($OR_{Q4\ vs\ Q1}$ = 1.36; CI 95% 0.84, 2.21) (O'Brien et al., 2019). Vanadium has been suggested to suppress cell proliferation, induce apoptosis, and arrest the cell cycle in mammary carcinogenesis in rats and human BC cell lines (Roy et al., 2018; L.-Y. Tang et al., 2012). Furthermore, V has been shown to produce substantial protection against breast carcinogenesis induced by 7,12-dimethylbenz[a]anthracene, an immunosuppressant and potent carcinogen (Bishayee et al., 2000).

Cobalt and Mo, considered essential for humans, are antioxidants (Simonsen et al., 2012; Zoroddu et al., 2019) possibly associated with the reduction of testosterone (Galbraith and Krey, 1989; Lewis and Meeker, 2015) that is a precursor of estrogen synthesis in postmenopausal women (Simpson, 2002), therefore they may reduce BC risk. In addition, Co and Mo have been recognized as weak metalloestrogens (Byrne et al., 2014; Choe et al., 2003) that might also contribute to their role in the development of breast tumors. Our results agree with a negative relationship found between Mo and BC in a report from the Sister Study where this metal was evaluated in toenails prior to diagnosis ($HR_{T3\ vs.\ T1}$ = 0.82, 95% CI 0.67, 1.00, *p*-trend 0.03) (Niehoff et al., 2021); and contrast with a positive relationship found in a case-control study ($OR_{Q4\ vs\ Q1}$ = 1.33; CI 95% 0.84, 2.12) (O'Brien et al., 2019).

Regarding Co, our results do not confirm those suggesting a positive relationship between BC and Co in toenails ($OR_{Q4\ vs\ Q1}$ = 1.31; CI 95% 0.82, 2.08) (O'Brien et al., 2019), as well as those from a small report of 53 cases and 61 controls carried out in Pakistan, in which it was found that Co concentrations in malignant tissue were statistically higher than in benign tissue (Pasha et al., 2008). Additionally, in a report where exposure was evaluated in air, no association was found between BC and exposure to Co ($OR_{Q5\ vs\ Q1}$ = 1.0; CI 95% 0.91, 1.2) (White et al., 2019). It is possible that the discrepancies in these studies are due to various methodological limitations such as: small sample size (Pasha et al., 2008), possible overmatching (O'Brien et al., 2019), null or poor control for confounders (O'Brien et al., 2019; Pasha et al., 2008), as well as the use of various matrices to measure exposure to these metals (O'Brien et al., 2019; White et al., 2019), since they may represent different timing or types of exposures (Klaassen, 2001a, 2001b). Therefore, it is important that our findings are confirmed in future studies.

Exposure to Cd has been widely studied in relation to BC development (Gaudet et al., 2019; Lin et al., 2016). According to the evidence from prospective studies included in a recent meta-analysis, little association was found between BC and Cd (RR = 1.12; CI 0.44, 2.87) (Filippini et al., 2020), which is consistent with our results.

Important sources of Sn, Cr, Ni, Sb, Al and Pb include tobacco, canned food containers, toothpaste, perfumes, and some foods like nuts and fruits (Curtis D. Klaassen, 2001a, 2001b; International Agency for Research on Cancer (IARC), 2012; Jaishankar et al., 2014; Klotz et al., 2017; Poddalgoda et al., 2016). In addition, some sources of Mo and Co, are dietary supplements, as well as certain legumes, grain cereals and fish (Finley et al., 2012; Hays et al., 2016). However, metal sources may vary among regions (Jaishankar et al., 2014), thus research is needed to identify metal sources within a specific area of interest.

Our findings should be interpreted considering some methodological features. The metals selected in this report were those considered by IARC to be carcinogens. However, this classification was based on salts that contain them (ie. Indium stannous oxide, V pentoxide, Mo trioxide), specific chemical forms (ie. Cr VI, inorganic Pb) and in the case of Al, occupational exposure during its production (International Agency for Research on Cancer(IARC), 2020b). In contrast, our results are based on the total urinary concentrations of each metal, which are a summary measure of their different chemical forms or processes, which do not necessarily reflect their individual carcinogenicity. In addition, we did not include total As in the metal mixtures because we decided not to combine exposure and metabolism markers since our group previously showed that BC was associated with capacity to methylate it and not its exposure *per se* (López-Carrillo et al., 2014). However, we performed a sensitivity analysis including total As in the mixtures and the results did not change (Supplementary table 1).

In this report, the exposure to metals was estimated from a single urine sample, which might not represent the accumulated exposure to each of them except for Cd, which has a half-life of 10–30 years in humans (Klaassen, 2001a, 2001b). Also, the use of a single matrix may not be the best choice across a large panel of metals, for example the recommended matrix to evaluate Pb chronic exposure is bone (Barbosa et al., 2005). Many metals analyzed in this study have short half-lives so they are rapidly excreted from the body; in such a way that their urinary concentrations and correlations could vary over time (Wang et al., 2016, 2017). However, control for creatinine concentrations was carried out, to correct for urinary dilution (Barr et al., 2006). In this context, it should be assumed that the errors in the estimates of chronic exposures to these metals in the same matrix were randomly distributed in the study sample and our results are a conservative approximation of the relationship between BC and metals.

Because of the study design, it is not possible to rule out that urinary metal concentrations are due to the BC (reverse causality). There is few information in patients with BC to show that due to the disease, a modification in the excretion of metals exists. For example, it has been seen that Cr can be concentrated in tumor cells (Lossow et al., 2021; Olaiya et al., 2019) and possibly its concentrations in urine decrease,

which could produce reverse causation in our results. In contrast, there is no obvious evidence suggesting that BC status would change the metabolism of V (L. Y. Tang et al., 2012). Nevertheless, we cannot rule out the possibility that other BC co-morbidities (e.g., osteoporosis or poor nutritional status) might affect metal metabolism (Klaassen, 2001a, 2001b). In addition, both, the loss of bone mass during treatment and changes in lifestyle (ie. diet, smoking) have been associated with changes in metal body burden concentrations (Bell et al., 2012; Filippini et al., 2020; Lei et al., 2018; McElroy et al., 2008; Zaman et al., 2012). Although we think that this situation would not be an important factor in our report because we included women recently diagnosed and before they received any treatment.

Our cases were identified in several hospital units that covered 90% of the study area, and along with the controls, had high participation rates. In addition, there were no important differences between the women included and not included in this report, except that the studied cases had a lower family history of BC than those not included; however, there is no information to suggest that family history of this tumor is related to the metals of interest. Furthermore, compared to the rest of the controls included in the original study, the controls in this report were younger and therefore with more premenopausal women. For some metals (Chang et al., 2018) age determines their accumulation in the body, for others the menopausal state is related to their elimination. For example, due to low iron stores in premenopausal women, increased absorption of some metals, like Cd, has been documented. In contrast, it has been observed in postmenopausal women greater removal of some metals from bone (Vahter et al., 2004). Notwithstanding the above, we consider that the possibility of having studied a biased sample is low. In addition, the age matching criteria used in this study increased the comparability between cases and controls. However, although we controlled for potential confounders within the metal exposure and BC relationship, we did not consider other factors such as diet (Byrne et al., 2014).

5. Conclusions

It has been shown that some metals can exert synergistic or antagonistic effects between them (Bauer et al., 2020), so the evaluation of mixtures should overcome the approach of a single metal at a time (Di Ciaula et al., 2020). The identification of the two metal mixtures in this report (the first characterized by Sn, Cr, Ni, Sb, Al and Pb; and the second determined by Mo and Co), that were different in women with and without BC, requires future confirmation in prospective epidemiological studies. In addition, the possible underlying mechanisms of interaction among metals warrants further experimental research.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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