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ORIGINAL ARTICLE

Exposure to bisphenol A and breast cancer risk in northern Mexican women

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Abstract

Objective To evaluate the association between BC and urinary concentrations of free-bisphenol A (BPA-F), the biological form of BPA, among women residing in Northern Mexico.

Methods The population under study comprised 394 histologically confirmed BC cases and 404 age-matched controls. Women were interviewed face to face about their sociodemographic and reproductive characteristics. BPA-F was determined by high-pressure liquid chromatography equipped with a fluorescence detector (HPLC/FLD). Logistic regression models were used to estimate the adjusted BC risk in relation to BPA-F.

Results BPA-F geometric mean was significantly higher among cases compared to controls (3.16 µg/L in cases and 2.47 µg/L in controls). A significant adjusted BC odds ratio of 2.31 (95% CI: 1.43–3.74) was estimated for the highest category of BPA-F compared to the lowest category.

Conclusion BPA-F may be an environmental cofactor of BC. Since this is the first report on BPA-F association with BC, our results need to be replicated.

Keywords Breast cancer · Bisphenol A · Case · Control study · Mexico

Introduction

Breast cancer (BC) is by far the most common cancer among women worldwide, with a relative proportion of 25% of all female malignancies. Likewise, BC is the leading cause of cancer among Mexican women with an incidence rate of 39.5 per 100,000 (Bray et al. 2018). There is strong evidence that the use of exogenous hormones, alcohol consumption, greater birthweight and adult-attained height increase BC risk. In contrast, parity, young age at first birth, physical activity, lactation and body fatness in pre-menopause decrease BC risk (Institute of Medicine 2012; World Cancer Research Fund/American Institute for Cancer Research 2018). Additionally, it has been initially proposed that genetic and environmental factors may play a role in BC development, but more information is needed (Rudolph et al. 2016).

In recent years, there has been great interest in identifying environmental chemical pollutants such as bisphenol A (BPA), that may be associated with BC (Institute of Medicine 2012). BPA is a synthetic monomer used in the production of polycarbonate plastics and epoxy resins and is present in food containers, baby bottles, dental materials, medical devices and personal care products, among others (Wang et al. 2017). Heat and storage time increase BPA migration from the epoxy resins that line cans into foods (Munguia-Lopez and Soto-Valdez 2001; Munguía-López et al. 2005). Human environmental BPA exposure pathways include the ingestion of contaminated food and beverages, as well as inhalation and dermal absorption (Wang et al. 2017). BPA is metabolized in the liver and further eliminated in urine. The highest BPA proportion (57%) is excreted in its inactive conjugated form (BPA-G), 32% as unconjugated or free

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BPA (BPA-F), and in lesser amounts as disulfate and chloride (11%) (Liao and Kannan 2012). BPA has been found in serum, adipose tissue, breast milk and placenta, which suggests that it is able to accumulate in the human body (Wang et al. 2017).

BPA body burden has been associated with endometrium disorders, premature birth, and lower weight at birth (Rochester 2013). In vitro studies have shown that BPA is an estrogen receptor α agonist that promotes cell proliferation, and is also an antagonist of the estrogen receptor β that inhibits proliferation in mammary glands. Moreover, BPA affects the functional differentiation of progenitor mammary cells and their microenvironment. Additionally, BPA forms adducts with DNA and induces epigenetic alterations, such as DNA methylation, histone modifications and non-coding microRNA expression (Acconcia et al. 2015; Wang et al. 2017). These findings provide potential mechanisms underlying the alterations observed in mammary architecture and functionality (Moral et al. 2008).

In human populations, there is scarce and inconclusive information on the relationship between BPA exposure and BC. A study performed in Korea, found no significant differences in conjugated BPA blood levels between BC cases and controls (Yang et al. 2009). Likewise, in Polish women, conjugated BPA was not associated with post-menopausal BC (Trabert et al. 2014). The biologically active form of BPA (BPA-F) has not been evaluated in relation to BC, but it has been positively correlated with mammographic density, an important risk factor for BC (Sprague et al. 2013).

In this report, we evaluated the association between urinary BPA-F concentrations and BC in northern Mexican women.

Materials and methods

A population-based, case–control study was conducted in five states of northern Mexico from 2007 to 2011 to evaluate the exposure to various environmental pollutants and the risk of BC (López-Carrillo et al. 2010, 2014). The original study comprised 1045 patients with histologically confirmed BC, matched by age (±5 years) with 1030 women without cancer and residing in the same study area (controls). Cases were identified in the public tertiary hospitals in the study region ($n=17$ hospitals). The inclusion criteria were: minimum age of 18 years with no history of any other type of cancer and a residency period of > 1 year in the study area. The controls were identified through the master sampling framework of the national surveys of the Ministry of Health, which provided a representative list of houses and their respective geographical locations. The inclusion criteria were: minimum age of 18 years, without cancer and a residency period of > 1 year in the study area. The detailed procedures for the selection of cases and controls have been published elsewhere (López-Carrillo et al. 2014). The response rates were 93.7% for cases and 99.7% for controls. The project was approved by the Institutional Review Board at Mexico's National Institute of Public Health.

In the present report, a subsample of 394 cases and 404 controls which had available information on BPA-F was included.

Interviews

Women were directly interviewed after giving their informed consent. Information was obtained on their sociodemographic, reproductive and clinical characteristics. They were measured and weighed to calculate their body mass index (BMI). Interviews among controls were carried out at their homes, whereas cases were interviewed at the hospital, after BC diagnosis (the average time from diagnosis to interview was 2 months).

Urine samples

. A first-morning void urine sample was collected from each participant in disposable sterile polypropylene containers, not necessarily the same day of the interview. Cases provided urine samples before they received any treatment (including surgery and radiation therapy). Samples were maintained at or below − 20 °C and stored at − 70 °C until analysis.

Bisphenol a determination

BPA-F was extracted from urine by solid-phase extraction (SPE columns Agilent Bond Elut – C18, 200 mg 3 mL) and blindly determined by high-pressure liquid chromatography equipped with a fluorescence detector (HPLC/FLD), according to a previous methodology with minor adaptations (Kato et al. 2005; Chen et al. 2012). Chemical analysis was carried out in batches that included approximately 20 study samples, one standard, one blank and one fortified sample. The procedure included three injections of one study sample that was evaluated in duplicate in each batch, with a coefficient of variation of 6.19%. A sample with a 99% BPA standard (Supelco, Darmstadt, Germany), at a known concentration and contained within the calibration curve, was also injected in triplicate, yielding a coefficient of variation of 2.1%. Likewise, three injections of a sample fortified with 97% BPA (Sigma-Aldrich, Darmstadt, Germany) were measured, with a coefficient of variation of 2.5%. A recovery up to 91% (maximum 148.22%) was obtained in 75% of samples. Except in one batch where the coefficient of variation was 5.20%, three injections of blanks showed

non-detectable BPA-F values. The limit of detection (LOD) was 2.78 µg/L and 14.8% of samples were above it.

BPA-F concentrations were corrected by recovery percentage. Samples that were below the LOD were imputed with 1.97 µg/L (LOD/$\sqrt{2}$), as it has been suggested elsewhere (Barr et al. 2006).

Creatinine determination

Urinary creatinine was determined by spectrophotometry using a commercial kit (Randox, Antrim County, UK), according to previously described methodology (Blanco-Muñoz et al. 2010).

Statistical analysis

Using Mann–Whitney's *U* test, the reproductive characteristics, BMI and creatinine concentrations were compared between included and non-included women, as well as between cases and controls in the study population. Likewise, urinary concentrations of BPA-F were compared between cases and controls. The relationship between BPA-F and known reproductive BC risk factors and creatinine was assessed by simple linear regression models among controls. Only creatinine was significantly associated with BPA-F and was further included in multivariate models along with age, which was a matching variable by design. Logistic regression models were used to estimate the association between BPA-F and BC. Because our detection limit was relatively high, we used three categories of exposure according to BPA-F distribution among controls: ≤ LOD/2, under and above the median of BPA-F values > LOD/2. The natural logarithm of BPA-F on a continuous scale was used to estimate a linear trend in the models. As a sensitivity analysis, we estimated the adjusted odds ratios between BPA-F and BC among women with BPA-F ≥ LOD, with two categories of exposure that were set on BPA-F median value according to the distribution among controls. In addition, we further stratified the models including all women by recovery percentages (< 80% and ≥ 80%). An α of 0.05 was set as the level of significance. All analyses were performed in Stata 14 statistical software (StataCorp, College Station, TX, USA).

Results

Due to the study design, included cases and controls had similar age (median: 52 years) (data not shown in Table 1). Compared to controls, cases had significantly earlier age at menarche, lower parity and breastfeeding, and late age at first pregnancy. Compared with women not included in this report, our study sample comprised thinner women with lower concentration of creatinine and fewer post-menopausal participants (Table 1).

The creatinine-adjusted and unadjusted medians of BPA-F were significantly higher in cases than controls among participants who had BPA-F concentrations > LOD and among the total sample when they were not adjusted by creatinine (Table 2).

BPA-F did not vary significantly through the categories of BC associated factors among controls. A statistically significant positive association ($\beta = 0.002$; 95% CI: 0.001–0.003; $p < 0.05$) was found only between creatinine and the natural logarithm of BPA-F (Table 3).

BC was significantly associated (OR = 2.31; 95% CI: 1.43–3.74) with BPA-F among women in the highest exposure category compared to women in the lowest category. This result remained significant among women whose urinary BPA-F had a recovery ≥ 80% (OR = 1.66, 95% CI: 1.28–2.14) and after excluding women with undetectable BPA-F (OR = 4.43, 95% CI: 1.89–10.42) (Table 4).

Discussion

Our results showed that urinary BPA-F is significantly positively associated with BC. Currently, there are no epidemiological studies to which our results could be compared. The only two previous reports examining the relationship of BPA and BC did not measure BPA-F. Previous studies have, instead, assessed the non-biologically active form of BPA in relation to BC, which yielded no associations (Yang et al. 2009; Trabert et al. 2014).

Our findings concur with several studies in mice, rats, and monkeys which indicate that prenatal or pre-pubertal exposure to BPA causes multiple alterations in the offspring mammary gland morphology and increases the risk of mammary cancer later in life (Wang et al. 2017). Moreover, a recent study suggested that chronic BPA exposure during adulthood might increase mammary carcinogenesis and metastasis in a transgenic mouse model (Jenkins et al. 2011).

It is important to mention that there is a debate in the literature surrounding the discrepancies that have been found in BPA-F levels in different studies. Based on a BPA-F intake of no more than 0.5 mg/kg bw/day, it has been estimated that there could be no value greater than 2 ng/ml in blood, serum, or plasma. Under this consideration, some authors attribute the differences in BPA-F in various studies to contamination in the handling and storage of the samples and/or to the different analytical methods used. Other authors, however, believe that there could be real discrepancies, since ingestion is not the only route of exposure and possibly, the dermal, sublingual, and inhalation routes contribute significantly to its exposure (Thayer et al. 2015).

Table 1 Reproductive characteristics, body mass index, and creatinine among women included and not included in this report, by case–control status

Characteristics	Included		Non-included	
	Cases	Controls	Cases	Controls
Age at menarche (years)				
Median (p5, p95)	13 (11, 15)	13 (11, 16)[b]	13 (11, 15)	13.0 (11, 15)
(*n*)	(393)	(404)	(651)	(626)
Age at first pregnancy (years)[a]				
Median (p5, p95)	21 (16, 35)	19 (15, 29)[b]	21 (16, 33)	19 (15, 29)
(*n*)	(361)	(393)	(589)	(605)
Parity (number of children)				
Median (p5, p95)	4 (0, 10)	4 (1, 13)[b]	3 (0, 9)	4 (1, 12)
(*n*)	(393)	(404)	(651)	(626)
Breastfeeding in first pregnancy (months)[a]				
Median (p5, p95)	6 (0, 24)	12 (0, 24)[b]	6 (0, 24)	12 (0, 35)
(*n*)	(327)	(381)	(523)	(582)
Menopausal status				
Premenopause				
%	40.6	38.9	37.0	30.2
(*n*)	(160)	(157)	(241)	(189)
Postmenopause				
%	59.4	61.1	63.0	69.8[c]
(*n*)	(234)	(247)	(410)	(437)
Body mass index (kg/m^2)				
Premenopause				
Median (p5, p95)	27.5 (20.4, 36.8)	28.2 (19.9, 40.1)	28.1 (20.3, 38.7)	31.2 (21.9, 43.4)[c]
(*n*)	(157)	(157)	(236)	(189)
Postmenopause				
Median (p5, p95)	29.5 (22.8, 39.8)	29.0 (21.3, 38.9)	30.3 (22.6, 40.4)	30.6 (23.7, 42.8)[c]
(*n*)	(234)	(247)	(404)	(436)
Creatinine (mg/dL)				
Median (p5, p95)	60.0 (16.5, 154.9)	51.7 (9.0, 169.9)	68.2 (14.0, 200.5)[d]	71.2 (13.0, 196.5)[c]
(*n*)	(394)	(404)	(622)	(624)

[a]Among parous women

[b]Mann–Whitney's U $p < 0.05$, included cases vs. included controls

[c]Mann–Whitney's U $p < 0.05$, included controls vs. non-included controls

[d]Mann–Whitney's U $p < 0.05$, included cases vs. non-included cases

Because we used HPLC/FLD, our LOD was higher than if we had used HPLC/MS/MS (Milićević et al. 2010). Limits of detection in other studies where HPLC/MS/MS was used were 0.003 ng/ml (Liao and Kannan 2012) and 0.05 ng/ml (Gerona et al. 2016) vs. 2.78 µg/L in ours. Therefore, we had to impute BPA-F in many cases (82.2%) and controls (88.1%), which in turn may have produced an overestimation of our BPA-F average concentration and may limit our ability to compare it with studies with lower LODs. Furthermore, it was not possible to evaluate whether BPA-F at lower concentrations is associated with BC, but this situation does not invalidate our conclusions. In our population, the levels of BPA-F are higher than in European countries and in the USA, since the existing BPA regulation in those countries reduces, to some extent, the exposure to this compound in the population, while in Mexico, BPA is not regulated (Mandel et al. 2019). However, we cannot rule out some degree of contamination in the processing and/or analysis of urine samples from this study.

Hormonal activity of BPA is 1000–10,000 times lower than that reported for natural hormones, thus, high concentrations of BPA may be required to observe an effect (Takayanagi et al. 2006). In this context, we performed a sensitivity analysis in women who had urinary BPA-F concentrations above the LOD, and we observed that the increase in BC odds remained statistically significant.

When we stratified the results by the recovery percentage, the association between BPA-F and BC remained positive but not significant in the samples with the lower recovery percentage (< 80%). This result can be explained by the

Table 2 Urinary concentrations of free bisphenol A among the study population

Free bisphenol A	(*n*)	Geometric mean	Percentiles		
			10th	50th	90th
µg/L	All (798)	2.79	1.97	1.97	12.96
	Cases (394)	3.16	1.97	1.97[a]	22.65
	Controls (404)	2.47	1.97	1.97	4.46
	>LOD (118)	20.81	4.86	21.57	70.08
	Cases (70)	28.11	6.78	25.44[a]	82.20
	Controls (48)	13.42	3.72	12.84	48.69
µg/g creatinine	All (798)	5.43	1.54	4.15	32.45
	Cases (394)	5.83	1.49	3.98	55.80
	Controls (404)	5.07	1.63	4.43	24.16
	>LOD (118)	37.07	5.66	41.64	192.01
	Cases (70)	57.23	15.17	60.85[a]	219.53
	Controls (48)	19.67	3.74	23.85	88.66

Percentage of samples above the limit of detection (*LOD*): 14.8% among all women; 11.9% among controls; and 17.8% among cases

[a]Mann–Whitney's U $p < 0.05$, cases vs. controls

attenuation caused by the non-differential measurement error due to the lack of total recovery of the BPA-F. In addition, in the case that there had been contamination by BPA-F in the handling and/or analysis of the samples, it is likely that it would have been random. Random measurement error produces attenuation in association measures (Kelsey et al. 1996). Thus, it is possible that the magnitude of the association measures that we report in this article are conservative estimators of the real ones.

It also should be considered that, due to the retrospective design of this study, some women with breast cancer could have changed their cooking methods/diet because of their cancer diagnosis. However, since the interview and sample collection were made within an average of two months after BC diagnosis and before cases received any treatment, the probability that BPA-F concentrations would have been the result of important changes in BPA sources after cancer diagnosis or metabolic alterations due to cancer treatment is low.

In addition, the measurement of contaminants in a single urine sample may not necessarily reflect chronic exposure (Townsend et al. 2013), unless a constant exposure is assumed, which might be the case with BPA. Sources of exposure for BPA include devices and products that are used on a daily basis such as food containers, bottles and toilet paper (Liao and Kannan 2011; Konieczna et al. 2015). In Mexico, as it was mentioned before, the use of BPA is not regulated, and there is a high prevalence of storing, heating, and consuming food in plastic containers (Viñas and Watson 2013). It is very likely, therefore, that there is a permanent exposure to BPA through the use of plastics. Also, other BPA sources may contribute to exposure such as, dental products, electronic devices, thermal paper used in register receipts, books, labels, tickets, mailing envelopes, newspapers, kitchen rolls, and food cartons (Liao and Kannan 2011; Huang et al. 2012; Konieczna et al. 2015). Creatinine-adjusted analytical concentrations may serve as a good surrogate for blood dose if a body size adjustment is performed. However, in many population studies, the body size adjustment is not performed. As a result, it has been suggested that unadjusted concentrations of analytes should be included in the analysis with urinary creatinine added as a separate independent variable (Barr et al. 2005), as was performed in this study.

It is important to mention that our research group previously evaluated the association between BC and the urinary concentrations of nine phthalates and three arsenic metabolites. We found BC to be associated with certain metabolites (López-Carrillo et al. 2010, 2014). We assessed if those compounds were potential confounders of the BPA-F/BC relationship. First, in the control group of this report we calculated their correlation with BPA-F which was low and non-significant; second, we added each compound to the multivariate models, and the significant BPA-F/BC relationship remained. All these results suggest that our BPA-F/BC estimators are not likely confounded by the presence of phthalates nor arsenic (data not shown).

In conclusion, BPA-F may be an environmental cofactor for BC, which deserves special attention due to its widespread use in daily products. Since this is the first report on the association between BPA-F and BC, our results need to be replicated.

Table 3 Geometric means of free bisphenol A levels in control women according to factors associated with breast cancer

Factors	Free bisphenol A (µg/L)	
	GM (95% CI)	
Age at menarche (years)		
≥ 15	2.89	(2.34–3.57)
13–14	2.32	(2.12–2.54)
≤ 12	2.49	(2.22–2.81)
β (95% CI)[b]	0.002 (− 0.041–0.044)	
Age at first pregnancy (years)[a]		
< 19	2.41	(2.19–2.66)
19–21	2.52	(2.18–2.92)
> 21	2.54	(2.22–2.92)
β (95% CI)[b]	0.005 (− 0.011–0.022)	
Parity (number of children)		
0	2.15	(1.77–2.62)
1–3	2.53	(2.25–2.85)
4–6	2.48	(2.18–2.81)
> 6	2.43	(2.14–2.75)
β (95% CI)[b]	0.001 (− 0.017–0.020)	
Breastfeeding in first pregnancy (months)[a]		
0	2.25	(1.88–2.69)
1–6	2.46	(2.15–2.82)
7–12	2.39	(2.18–2.62)
≥ 13	2.88	(2.32–3.57)
β (95% CI)[b]	0.005 (− 0.003–0.014)	
Menopausal status		
Premenopause	2.54	(2.27–2.86)
Postmenopause	2.43	(2.23–2.65)
β (95% CI)[b]	− 0.046 (− 0.189–0.095)	
Body mass index (kg/m^2)		
Premenopause		
< 24.9	2.69	(2.10–3.45)
25.0–29.9	2.89	(2.22–3.76)
≥ 30.0	2.21	(2.00–2.44)
β (95% CI)[b]	− 0.012 (− 0.031–0.006)	
Postmenopause		
< 24.9	2.19	(1.98–2.42)
25.0–29.9	2.41	(2.08–2.80)
≥ 30.0	2.59	(2.21–3.04)
β (95% CI)[b]	0.010 (−0.005–0.026)	
Creatinine (mg/dL)		
1–38	2.27	(2.07–2.49)
38.1–78.5	2.42	(2.15–2.72)
78.6–327.00	2.76	(2.38–3.19)
β (95% CI)[b]	0.002 (0.001–0.003)	

GM Geometric mean

[a]Among parous women

[b]Simple linear regression model with ln-transformed BPA-F

Table 4 Association between urinary free bisphenol A and breast cancer

Free bisphenol A (µg/L)	Ca/Co	OR (95% CI)[a]	OR (95% CI)[b]
All women			
≤1.39	319/350	1.00	1.00
1.40–12.05	18/27	0.73 (0.40–1.36)	0.73 (0.39–1.35)
>12.05	57/27	2.32 (1.43–3.75)	2.31 (1.43–3.74)
Women with BPA-F < 80% of recovery			
≤1.39	185/138	1.00	1.00
1.40–12.05	11/6	1.37 (0.49–3.83)	1.42 (0.50–4.00)
>12.05	28/17	1.23 (0.65–2.33)	1.18 (0.62–2.27)
Women with BPA-F ≥ 80% of recovery			
≤1.39	134/212	1.00	1.00
1.40–12.05	7/21	0.53 (0.22–1.28)	0.54 (0.22–1.32)
>12.05	29/10	4.59 (2.17–9.73)	4.59 (2.17–9.74)
Women with BPA-F ≥ LOD			
≤12.83	13/24	1.00	1.00
>12.83	57/24	4.32 (1.89–9.90)	4.43 (1.89–10.42)

[a]Adjusted for age (years)

[b]Adjusted for age (years) and creatinine (mg/dL)

Limit of Detection (LOD) = 2.78 µg/L

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Compliance with ethical standards

Conflicts of interest The authors declare they have no conflict of interest.

Ethical approval All procedures performed in the study participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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