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Urinary bisphenol A-glucuronide and postmenopausal breast cancer in Poland

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Abstract

Purpose—Concerns regarding a possible link between bisphenol A (BPA) and breast cancer have been mounting but studies in human populations are lacking. We evaluated the association between the major urinary BPA metabolite (BPA-glucuronide (BPA-G)) and postmenopausal breast cancer risk in a large population-based case-control study conducted in two cities in Poland (2000–2003); we further explored the association of BPA-G levels with known postmenopausal breast cancer risk factors in our control population.

Methods—We analyzed creatinine-adjusted urinary BPA-G levels among 575 postmenopausal cases matched on age and study site to 575 controls without breast cancer using a recently developed assay. Odds ratios (OR) and 95% confidence intervals were used to estimate the association between urinary BPA-G level and breast cancer using conditional logistic regression. Among controls, geometric mean BPA-G levels were compared across categories of breast cancer risk factors using linear regression models.

Results—There was no indication that increased BPA-G was associated with post-menopausal breast cancer (p-trend = 0.59). Among controls, mean BPA-G was higher among women reporting extended use of menopausal hormones, a prior screening mammogram, and residence in Warsaw. Other comparisons across strata of postmenopausal breast cancer risk factors were not related to differences in BPA-G.

Conclusions—Urinary BPA-G, measured at the time of diagnosis, is not linked to postmenopausal breast cancer.

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Keywords

breast cancer; bisphenol A-glucuronide; postmenopausal; case-control

Introduction

Bisphenol A (BPA) is a man-made compound that is suspected to act as an endocrine disruptor, most notably as a weak estrogen agonist [1]. Widespread and continuous human exposure to BPA is believed to be mainly through diet, drinking water, dental sealants, dermal exposure, and inhalation of household dusts [2]. Concerns about health effects from BPA have been mounting. In animal models, exposure to BPA in the neonatal period or in early life may lead to reproductive system changes, including alterations to mammary gland development that may increase cancer susceptibility [3–5]. In laboratory settings, BPA stimulates growth in estrogen-dependent breast cancer tissues [6] and cell lines [7;8].

However, evidence from human studies for a role in breast cancer, including the relevant window/timing of exposure, is lacking. Measurable levels of total urinary BPA have been detected in greater than 90% of samples from populations worldwide [9–11] and in a cross-section of US adults, urinary BPA has been associated with known breast cancer risk factors such as obesity and markers of metabolic syndrome [12;13]. In the only published breast cancer study to date, a small case-control study of Korean women (70 cases/82 controls), the median level of total serum BPA was higher, albeit not statistically significant, in breast cancer cases than controls [14]. However BPA was detected in only 51% of serum samples and interpretation of these findings is hampered by analytical limitations [14]. Being metabolized and cleared very rapidly, levels of circulating BPA are frequently below assay detection limits, as evidence in the case-control study above, and regardless of the specimen used, levels of total BPA may be inflated due to contamination from materials used to store and analyze the samples. To circumvent these concerns, we used a recently developed assay to measure BPA-glucuronide (BPA-G), the primary excreted BPA metabolic conjugate [15] in urines collected over a 12 hour period, to explore the relationship between current BPA exposure and postmenopausal breast cancer in a large population-based case-control study conducted in Poland. We further explored the association of BPA-G levels with known postmenopausal breast cancer risk factors in our control population.

Materials and Methods

Study Population

Data for this study were collected as part of a previously described Polish Breast Cancer Study [16]. Briefly, eligible cases included women ages 20 to 74 living in Warsaw or Lodz, Poland that were diagnosed with cytologically or histologically confirmed *in situ* or invasive breast cancer between January 2000 and January 2003. Cases were identified through a rapid identification system organized at participating hospitals that were responsible for diagnosing and treating approximately 90% of breast cancer patients in the two study areas. Periodic checks were made against cancer registries in both Warsaw and Lodz to ensure complete case identification. Population-based controls were randomly selected from the

Polish Electronic System (PESEL), a database with demographic information from all residents of Poland. Controls were frequency matched to cases based on study site and 5-year age category and were breast cancer-free at the time of enrollment. All study participants were Caucasian. Study participants provided written informed consent and the study protocol was approved by ethics boards in Poland and the United States.

Study participants provided information on demographic characteristics, reproductive and medical history, and other potential breast cancer risk factors during an in-person interview. Height, weight, and waist and hip circumference were measured by a trained nurse. As part of the original study protocol overnight 12-hour urine samples were collected from 1,962 breast cancer cases (1,338 postmenopausal) and 2,241 controls (1,529 postmenopausal), which represent 82% and 89%, respectively, of the interviewed study population. The urine samples were collected in propylene tubes and stored at -80°C . Of the 1,338 postmenopausal breast cancer cases with urine samples we selected a subset of 575 invasive breast cancer cases including 384 estrogen receptor positive (ER+) cases with available tumor tissue microarray and genetic data and an additional 191 estrogen receptor negative (ER-) cases. Cases were selected to obtain sufficient power to evaluate the overall association with BPA while maintaining a representative distribution of ER+ and ER- postmenopausal breast cancers. These cases were matched to an equal number of controls on age (5-year category) and study site.

Laboratory measurements

Unconjugated BPA and BPA-G were measured in urine samples by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) [17;18]. Unconjugated BPA and BPA-G were derivatized with dansyl chloride and measured directly with $\text{d}_6\text{-BPA}$ and $\text{d}_6\text{-BPA-G}$ as internal standards, eliminating the need for enzymatic hydrolysis and extraction steps prior to analysis. All assays were performed in the same lab, by the same technician, using the same instrument. BPA-G concentrations within the range of 0.1 ng/mL–10,000 ng/mL were calculated using an eight-parameter standard curve. BPA-G was detected in 1,118 of the 1150 samples (97.2%). Unconjugated BPA was detected in 3% of the urine samples ($n=37$) measured, thus it was not evaluated in subsequent analyses. Total urinary creatinine was measured in each sample by an enzymatic assay (Pharmaceutical Product Development, LLC, Wilmington, NC). Cases and matched controls were included in the same analytic batch, each of which included 38 unique samples. To evaluate assay performance we included blinded duplicate samples from three study participants within each batch. The overall coefficient of variation (CV) for the BPA-G assay was 12.6% and the intraclass correlation coefficient (ICC) was 67.3%. For creatinine, the corresponding CV and ICC were 1.2% and 98.5%, respectively. We accounted for differences in urine concentration by calculating creatinine-adjusted BPA-G levels (ng BPA-G/mg creatinine). For this report, all BPA-G measurements are creatinine-adjusted.

Given that we preferentially selected cases and controls with tumor tissue microarray and/or genetic data, the urine samples for cases were selected at various time points before or after treatment and/or surgery. BPA-G, however, did not vary by time of collection, the geometric mean of samples collected before treatment ($n=328$, 57.0%) or surgery ($n=145$, 25.2%) were

comparable to geometric mean of samples collected after treatment or surgery (p-value = 0.49 and 0.52, respectively Supplemental Figure 1).

Statistical analysis

For analyses using the continuous BPA-G measurement, values below the limit of detection were set to 0.1 ng BPA-G divided by the creatinine (mg) concentration of the sample. Creatinine-adjusted BPA-G levels were categorized according to the quartile distribution in controls and values below the limit of detection (n=32) were included in the first quartile, which served as the reference category. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between creatinine-adjusted urinary BPA-G level and breast cancer were estimated using conditional logistic regression, conditioned on strata of 5-year age category and study site. To assess a linear trend in the association between breast cancer and BPA-G, we fit models using the log-transformed continuous variable.

All analyses were adjusted for the following *a priori* defined postmenopausal breast cancer risk factors: education (less than high school, high school education, some post high school education, college graduate), body mass index (< 25, 25–29.9, 30+ kg/m²), age at menarche (< 12, 13–14, 15+ years), parity (nulliparous, parous), years since menopause (<1, 1–5, 6–10, 11–15, 16+ years), duration of menopausal hormone therapy (MHT) use (never, < 5, 5+ years), family history of breast cancer, history of benign breast disease, and ever had a screening mammogram.

Given the difference in geometric mean BPA-G level by study site, we further explored the associations with postmenopausal breast cancer risk separately by study site. For these analyses, we re-classified study subjects based on the site-specific quartile distribution of BPA-G in controls. In addition, we compared geometric mean BPA-G across postmenopausal breast cancer risk factors among controls using linear regression models adjusted for age and study site. Statistical significance was defined as p-value < 0.05; all statistical tests were two-sided. Data analyses were performed using SAS software (version 9.3 for Windows; SAS Institute Inc, Cary, NC).

Results

Characteristics of the study population

The distribution of selected demographic and health characteristics for the case and control women with BPA-G measurements are provided in Table 1. The mean age of study participants was 59 years. Cases and controls were similar with respect to body mass index, age at menarche and parity. Cases tended to be better educated than controls, and were more likely to have had a family history of breast cancer, a personal history of benign breast disease, and a screening mammogram and more likely to use menopausal hormones.

The distribution of demographic and health characteristics were similar for study subjects who were and were not selected for analysis (Supplemental Table 1). In general cases and controls were representative of the entire study population with regard to common breast cancer risk factors. There were two notable exceptions. Compared to those not selected: 1) cases in the current study were more frequently from Warsaw (73.0% vs. 64.5%,

respectively); and 2) the controls selected for the current study were slightly younger (mean age 59.7 vs. 61.3, respectively).

BPA-G associations with postmenopausal breast cancer

Overall, BPA-G levels were slightly higher in breast cancer cases than controls (geometric mean=4.11 and 3.92, respectively p-value=0.48, Table 2) but there was no indication of a trend with increased BPA-G and breast cancer (p-trend = 0.59; Table 2). We did observe an increased odds of breast cancer (Quartile 2 (Q2) vs. Q1: OR 1.70, 95% CI 1.15–2.52) comparing the second to first quartile of BPA-G; however, the OR was not significantly increased for the third or fourth quartile of exposure. In analyses stratified by ER+ and ER– breast cancer subtypes, BPA-G was higher in ER+ women than controls (geometric mean ER+=4.30, p-value=0.25), but again, the association was null (p-trend = 0.84). For ER– cancer, BPA levels were non-significantly lower than levels in controls (geometric mean ER–=3.83, p-value=0.94) and no trend across categories was seen (p-trend = 0.34). Similar to the overall finding, the OR for ER– breast cancer was elevated for the second quartile of BPA-G exposure compared to the first quartile (OR=2.89, 95% CI 1.41–5.93), however, the OR was not significantly elevated for the third or fourth quartile. OR estimates were not substantially different in unadjusted analyses or in analyses restricted to cases with urine collected prior to surgery and/or treatment (results not shown).

BPA-G levels in control women from Warsaw were almost twice as high as levels in women from Lodz. In order to rule out the possibility that this obscured a BPA-G breast cancer association we explored the associations separately by study site in post hoc analyses (p-value interaction = 0.009; Supplemental Table 2). Postmenopausal breast cancer risk was not associated with BPA-G in Warsaw, however, there was evidence of a positive association between BPA-G and breast cancer risk (p-trend = 0.05) among women from Lodz. In that group, the risk of breast cancer was more than doubled for the third and fourth quartiles, with a similar OR pattern observed across ER+ and ER–. Of note women from Lodz were predominantly in the lower two quartiles of BPA-G exposure in the overall analysis, which likely accounts for the anomalous increased OR observed for the second quartile.

BPA-G associations with breast cancer risk factors among postmenopausal controls

As discussed, women from Warsaw had significantly higher levels of BPA-G than did women from Lodz (geometric mean 4.88 ng/mg and 2.29 ng/mg, respectively, $p < 0.001$). Levels of BPA-G also varied across strata of duration of menopausal hormone therapy use, with women reporting never using menopausal hormone therapy having the lowest BPA-G levels (geometric mean = 3.04 ng/mg) and women reporting 5 or more years use having the highest (geometric mean = 4.78 ng/mg, $p = 0.06$). Women who ever had a screening mammogram had significantly higher levels of BPA-G compared to women reporting never having had a mammogram (3.68 vs. 2.75 ng/mg, $p = 0.002$). Other comparisons across strata of education, body mass index, menstrual and reproductive factors, family history of breast cancer, and personal history of benign breast disease were not related to differences in BPA-G levels among controls. Given the difference in BPA-G concentration by study site, we evaluated the distributions of the demographic and health characteristics across study site

(results not shown). With the exception of women from Lodz more frequently reporting never using menopausal hormone therapy than women from Warsaw, other comparisons across strata of variables listed in Table 1 were not different by study site. We have accounted for both study site and duration of menopausal hormone therapy use in the study design and analysis, thus it is not likely that this accounts for the unexpected association between BPA-G and breast cancer among women from Lodz.

Discussion

To our knowledge this is the first population-based case-control study of the association between urinary BPA-G levels and postmenopausal breast cancer. Overall BPA-G was not associated with postmenopausal breast cancer, although we did observe an unexpected increased odds of postmenopausal breast cancer for women in the second quartile of exposure. However, in additional post hoc analyses by study site, the association did not exhibit an exposure-response relationship that would strengthen the evidence for causation and is likely due to chance. In the only published breast cancer study to date, a small hospital-based case-control study of Korean women (70 cases/82 controls), the median value of total BPA was higher, albeit not statistically significant, in breast cancer cases than controls [14]. However, this study measured total BPA in serum, and it has since been suggested that a more relevant exposure measurement is the measure of the excreted urinary conjugate, BPA-G [19].

The present study had several strengths including its population-based design, the recruitment of newly diagnosed incident breast cancer cases, and an extensive collection of risk factor, pathologic and immunohistochemistry data. Measurement of the conjugated form of BPA, which reflects BPA metabolism, reduces potential BPA contamination of samples that may arise during processing or laboratory analyses [19]. Further, the BPA-G concentration in our Polish controls (geometric mean = 2.76 ng/mL) was comparable to the BPA-G concentrations of a sample of hospital patients (n=163) in Lyon, France (geometric mean = 4.64 ng/mL) [20]. The analyses presented, however, have some limitations. The post-diagnostic assessment of BPA-G in breast cancer cases suffers from limitations characteristic of all retrospective case-control studies of blood biomarkers and chronic disease; first, that the underlying disease process may influence biomarker levels and second, such studies cannot provide insight into the temporality of exposure on disease risk. While it is unlikely that BPA-G levels are affected by the disease itself, some cases had urine collected after breast cancer treatment or surgery which may have introduced additional BPA exposure. To address this concern, we conducted sensitivity analyses excluding samples collected after treatment and/or surgery. The OR estimates were not substantially changed in these analyses, suggesting that the potential increases in BPA-G in these samples had little impact on our results. Further, we did not observe any differences in BPA-G levels before or after treatment or surgery. Levels of BPA-G were notably higher in women from Warsaw than Lodz, and despite having matched controls to cases by recruitment site, differences in absolute levels of BPA-G may have confounded the risk estimates. In stratified analyses, BPA-G was associated with increased breast cancer risk among women from Lodz; however, the absolute BPA-G values associated with these estimates were much lower than corresponding values in Warsaw, where no risk was

observed. Given the small numbers and the fact that it is not biologically plausible that lower BPA-G levels would be associated with breast cancer risk in Lodz when similar or higher exposures in Warsaw were not associated with increased risk, this finding is likely due to chance.

One concern of all epidemiologic studies is whether the biomarker is measured during the appropriate window of exposure. In animal models, a wide range of adverse effects associated with BPA exposure have been seen at low doses in early life, including alterations to reproductive systems and mammary gland development. Later life exposure to BPA may also be relevant to breast cancer development, since in adults, high total urinary BPA has been linked to conditions that share some similar etiologic features with breast cancer, such as cardiovascular disease and diabetes [12;21;22]. Additionally, high BPA has been positively associated with known breast cancer risk factors such as abdominal obesity [13;23], insulin resistance [23] and breast density in postmenopausal women [24]. However, for breast cancer etiology, the relevant window of BPA exposure is not clear. Finally, BPA has a relatively short elimination half-life, and recent studies report poor reproducibility in single spot urine samples collected over time [25,26]. Although it has been suggested that timed urine samples, like those used in the current study, may be less variable over-time than spot-urines measurements [27], it is unlikely that our one-time measurement of urinary BPA-G adequately reflects long-term exposure.

Our findings suggest that urinary BPA-G measured at the time of diagnosis and within the range of exposure observed in Poland was not associated with postmenopausal breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and health characteristics of breast cancer cases and matched controls, Polish Breast Cancer Case-Control Study, 2000–2003.

	Cases n = 575		Controls n = 575	
	mean	stdev	mean	stdev
Age (years)	59.5	8.0	59.7	8.4
Study Site	n *	%	n *	%
Warsaw	420	73.0	420	73.0
Lodz	155	27.0	155	27.0
Education				
Less than high school	176	30.6	235	40.9
High school	206	35.8	211	36.7
Some post-high school	57	9.9	46	8.0
College graduate	134	23.3	81	14.1
Body Mass Index (kg/m ²)				
< 25	216	37.6	211	36.7
25–29.9	217	37.7	217	37.7
30	136	23.7	132	23.0
Age at menarche (years)				
12	145	25.2	130	22.6
13–14	288	50.1	282	49.0
> 14	141	24.5	154	26.8
Parity				
Nulliparous	56	9.7	48	8.4
Parous	519	90.3	527	91.6
Years since menopause				
< 1	97	16.9	33	5.7
1–5	117	20.4	166	28.9
6–10	113	19.7	118	20.5
11–15	100	17.4	98	17.0
> 15	148	25.7	160	27.8
Duration of menopausal hormone use				
Did not use MHT	400	69.6	435	75.7
< 5 years	113	19.7	100	17.4
5 years	50	8.7	30	5.2
Family history of breast cancer **	55	9.6	42	7.3
History of benign breast disease	108	18.8	45	7.8
Ever had a screening mammogram	374	65.0	329	57.2

* Columns may not sum to total because of missing values.

** Mother, sister, daughter, excludes half-sisters.

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for the association between creatinine-adjusted bisphenol A-glucuronide (BPA-G) and breast cancer risk, Polish Breast Cancer Study, 2000–2003.

	Controls* n=575			Cases* n=575			ER+ n=384			ER- n=191		
	Geometric mean	n	%	Geometric mean	OR**	(95% CI)	Geometric mean	OR**	(95% CI)	Geometric mean	OR**	(95% CI)
Creatinine adjusted BPA-G (ng/mg)												
log-transformed continuous	3.92			4.11	1.04	(0.91–1.17)	4.30	0.99	(0.85–1.14)	3.83	1.12	(0.89–1.43)
<i>p-trend</i>					0.59			0.84			0.34	
Quartiles												
< 2.06	144	25.0	123	21.4	1.00	reference	76	19.8	reference	47	24.6	reference
2.06–4.16	143	24.9	176	30.6	1.70	(1.15–2.52)	113	29.4	(0.83–2.17)	63	33.0	(1.41–5.93)
4.17–7.80	142	24.7	130	22.6	1.02	(0.67–1.55)	91	23.7	(0.51–1.43)	39	20.4	(0.69–3.39)
> 7.80	145	25.2	143	25.9	1.09	(0.73–1.63)	102	26.6	(0.51–1.36)	41	21.5	(0.94–4.74)

* Columns may not sum to total because urinary creatinine measures were missing for 1 control and 3 cases.

** Conditional logistic regression models, conditioned on age and study site and adjusted for education, body mass index, age at menarche, parity, years since menopause, duration of menopausal hormone therapy use, family history of breast cancer, history of benign breast disease, and ever had a screening mammogram.

Table 3

Creatinine-adjusted BPA-G levels by demographic and health characteristics among 575 postmenopausal control women, Polish Breast Cancer Study.

	Creatine adjusted BPA-G (ng/mg)			
	n *	Geometric Mean	(95% CI)	p-value **
All controls	575	3.92	(3.19–4.81)	
Age categories (years)				
40–49	62	2.96	(2.24–3.90)	0.64
50–59	228	3.46	(2.98–4.02)	
60–69	197	3.46	(2.95–4.07)	
70+	87	3.09	(2.45–3.89)	
Study Site				
Warsaw	419	4.88	(4.41–5.41)	< 0.001
Lodz	155	2.29	(1.91–2.75)	
Education				
Less than high school	235	3.37	(2.90–3.92)	0.42
High school education	211	2.92	(2.47–3.45)	
Some post high school education	46	3.59	(2.59–4.98)	
College graduate	81	3.43	(2.65–4.44)	
Body Mass Index (kg/m ²)				
< 25	211	3.26	(2.76–3.84)	0.53
25 – 29.9	217	3.42	(2.90–4.02)	
30	131	2.98	(2.44–3.64)	
Age at menarche (years)				
12	130	3.23	(2.65–3.94)	0.71
13–14	281	3.33	(2.88–3.86)	
> 15	154	3.04	(2.50–3.69)	
Parity				
Nulliparous	48	2.51	(1.83–3.44)	0.09
Parous	526	3.31	(2.95–3.72)	
Duration of menopausal hormone use				
Did not use MHT	434	3.04	(2.69–3.44)	0.06
< 5 years	100	3.89	(3.07–4.93)	
5 years	30	4.78	(3.22–7.10)	
Family history of breast cancer				
No	533	3.27	(2.91–3.67)	0.39
Yes	41	2.81	(1.99–3.96)	
History of benign breast disease				
No	526	3.22	(2.87–3.61)	0.72
Yes	44	3.42	(2.45–4.79)	
Ever had screening mammogram				

	Creatine adjusted BPA-G (ng/mg)			
	n *	Geometric Mean	(95% CI)	p-value **
No	242	2.75	(2.36–3.20)	0.002
Yes	328	3.68	(3.20–4.23)	

* Columns may not sum to total because of missing values.

** Adjusted for age and study site.