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BPA, Parabens, and Phthalates in Relation to Endometrial Cancer Risk: A Case–Control Study Nested in the Multiethnic Cohort

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Introduction

Bisphenol A (BPA), phthalates, parabens, and triclosan are endocrine disrupting chemicals (EDCs); that is, they are exogenous substances that alter functions of the endocrine system and may cause adverse health effects. BPA and phthalates are plasticizers, whereas parabens and triclosan are antimicrobial chemicals or preservatives (Giulivo et al. 2016). Nuclear estrogen and progesterone receptors are EDC targets and BPA, selected phthalates, and parabens can bind to the estrogen receptor (ER) (Mallozzi et al. 2017; Nowak et al. 2018; Zacharewski et al. 1998). Because exposure to estrogen unopposed by progesterone is key to endometrial cancer development (Key and Pike 1988), we investigated whether BPA, triclosan, parabens, and phthalate metabolites were associated with endometrial cancer risk among participants in the prospective Multiethnic Cohort (MEC).

Methods

The MEC has been described previously (Kolonel et al. 2000). A baseline questionnaire was completed by participants in Hawaii and California in 1993–1996. In 2001–2006, biospecimens and a short questionnaire were collected. The study was approved by institutional review boards at the participating institutions, and participants provided written informed consent at biospecimen collection. This study included postmenopausal women from five main racial/ethnic groups included in the MEC, each of whom provided an overnight or first morning urine sample and had no previous hysterectomy or diagnosis of endometrial or breast cancer. Incident invasive endometrial cancers (International Classification of Diseases for Oncology 3rd revision codes C54.0-C54.9) diagnosed after urine collection, and through 2017, were identified by linkage to Hawaii and California Surveillance, Epidemiology, and End Results cancer registries. Controls were selected from participants who were alive and endometrial/breast cancer–free at the time of diagnosis of their index case. Controls were matched 1:1 on race/ethnicity and birth year, as well as on urine type, time of day, year, fasting hours, and current postmenopausal hormone use at biospecimen collection.

Urinary concentrations (in nanograms per milliliter) of BPA, triclosan, parabens, and phthalate metabolites were measured using liquid chromatography high-resolution accurate-mass mass spectrometry (Model Q-Exactive; Thermo Scientific) (Li and Franke 2015; Townsend et al. 2013); creatinine (in milligrams per milliliter) was measured using a clinical autoanalyzer (Cobas MiraPlus; Roche), all in the Analytical Biochemistry Shared Resource, University of Hawaii Cancer Center. Personnel were blinded to sample status. Case–control sets were analyzed in the same batch. Intrabatch coefficients of variation (CVs) were $<14\%$ except for butyl paraben (24%) and BPA (22%); interbatch CVs were $<16\%$ except for methyl paraben (30%) and monoethyl phthalate (MEP) (23%).

Observations with urinary EDC concentrations below the limit of detection (LOD) for butyl paraben (35%) and BPA, triclosan, methyl paraben, ethyl paraben, MEP, monoisobutyl phthalate (MiBP), and monomethyl phthalate (MMP) ($\leq 8\%$ each) were set to half of their respective LOD values. Urinary concentrations of benzyl paraben and monocyclohexyl phthalate were below the LOD for $\geq 95\%$ of participants, and these markers were excluded from analysis. We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between EDC metabolite excretion (in nanograms per milligram creatinine; tertiles based on the distribution in controls) and endometrial cancer risk, adjusted for body mass index (BMI), diabetes, and Mediterranean Diet Score. A two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed using SAS (version 9.4; SAS Institute Inc.).

Results

In 139 case–control sets, comparisons of the crude creatinine-adjusted EDC excretion showed similar median values and overlapping interquartile ranges (Table 1). BMI at urine collection was higher in cases than controls (42% vs. $22\% \geq 30\,kg/m^2$ BMI), whereas diabetes prevalence was lower (12% vs. 22%). Endometrial cancer cases were diagnosed a median of 6.6 y after urine collection. Most cases were diagnosed with endometrioid histology (75%) and localized disease (71%).

All estimates had wide 95% CIs, reflecting the modest sample size, with no significant trends (Table 2). However, mono-*n*-butyl phthalate (MnBP) excretion was positively associated with endometrial cancer risk (second vs. first tertile: OR = 2.35 (95% CI: 1.19, 4.65), and a nonsignificant association was observed for the third vs. first tertile: OR = 1.82 (95% CI: 0.81, 4.10). Associations were similar for dibutyl phthalate [DBP (sum of MiBP and MnBP excretion)], with corresponding ORs = 2.09 (95% CI: 1.05, 4.16) and 1.77 (95% CI: 0.75, 4.17). No other associations were statistically significant.

Discussion

In this case–control study nested in the MEC, prediagnostic urinary DBP metabolite excretion was positively associated with endometrial cancer risk. Trend tests showed no clear indication of linearly increasing endometrial cancer risk for any of the EDCs in our study; associations for MnBP were limited to the second (vs. the first) tertile, whereas ORs were similar but nonsignificant when comparing extreme tertiles.

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Table 1. Population characteristics in postmenopausal endometrial cancer cases and matched controls nested within the Multiethnic Cohort.

Characteristic	Controls $n = 139$	Cases $n = 139$
Creatinine-adjusted EDC excretion [median (IQR)]		
BPA[a]	1.54 (0.81–2.95)	1.62 (1.01–2.93)
Triclosan[a]	9.70 (2.94–32.67)	9.29 (2.52–37.99)
Methyl paraben[a]	98.73 (28.37–246.26)	78.64 (21.30–229.18)
Ethyl paraben[a]	3.23 (0.48–12.19)	1.47 (0.33–11.75)
Propyl paraben	20.16 (4.18–82.67)	11.30 (2.54–41.62)
Butyl paraben[a]	0.36 (0.00–2.83)	0.15 (0.00–1.29)
Total parabens[b]	137.13 (36.93–358.83)	111.55 (29.01–323.44)
MBzP	13.65 (8.77–23.41)	14.17 (9.03–19.76)
MECPP	33.03 (21.23–63.80)	34.40 (22.79–59.59)
MEHHP	33.57 (23.30–55.40)	34.74 (21.76–57.97)
MEHP	8.02 (5.46–12.18)	7.97 (4.42–13.65)
MEOHP	19.47 (13.45–32.35)	20.97 (13.14–39.63)
MEP[a]	64.53 (28.36–133.23)	51.51 (31.70–116.34)
MiBP[a]	4.22 (3.05–7.23)	5.38 (3.44–7.89)
MMP[a]	7.17 (5.21–11.50)	7.09 (4.69–10.06)
MnBP	22.01 (15.10–42.21)	22.44 (17.36–41.78)
PA	58.94 (40.28–91.89)	54.24 (39.05–98.34)
DBP[c]	27.90 (19.46–50.11)	30.00 (22.04–55.58)
DEHP[d]	90.81 (67.34–161.01)	95.33 (66.25–157.6)
Total phthalates[e]	259.37 (181.45–387.84)	253.07 (176.75–450.75)
Creatinine	0.53 (0.33–0.76)	0.54 (0.32–0.80)
Population characteristics [*n* (%) or median (IQR)]		
Age at urine collection (y)[f]	62 (59–69)	62 (59–69)
Race/ethnicity[f]		
White	35 (25)	35 (25)
African American	9 (6)	9 (6)
Native Hawaiian	26 (19)	26 (19)
Japanese American	52 (37)	52 (37)
Latina	17 (12)	17 (12)
Parity at baseline		
Nulliparous	28 (20)	26 (19)
Parous	111 (80)	113 (81)
Oral contraceptive use at baseline		
Never	55 (40)	64 (46)
Former	84 (60)	75 (54)
Postmenopausal hormone use at urine collection[a]		
Not current	114 (82)	114 (82)
Current	25 (18)	25 (18)
BMI at urine collection (kg/m^2)[g]		
<25	56 (40)	43 (31)
25–29	52 (37)	37 (27)
≥30	31 (22)	59 (42)
Diabetes prevalence[h]		
No	108 (78)	122 (88)
Yes	31 (22)	17 (12)
Case characteristics [*n* (%) or median (IQR)]		
Age at diagnosis (y)	—	69 (65–75)
Years from urine collection to diagnosis	—	6.6 (3.4–9.4)
Tumor histology		
Endometrioid[i]	—	104 (75)
Serous	—	15 (11)
Other	—	20 (14)
Disease stage[j]		
Localized	—	99 (71)
Regional and distant	—	36 (26)
Tumor grade		
1	—	46 (33)
2	—	27 (19)
3	—	42 (30)
4	—	24 (17)

Note: —, not applicable; BMI, body mass index; BPA, bisphenol A; DBP, dibutyl phthalate; DEHP, di (2-ethylhexyl) phthalate; EDC, endocrine disrupting chemical; IQR, interquartile range; LOD, limit of detection; MBzP, mono-benzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; MMP, monomethyl phthalate; MnBP, mono-*n*-butyl phthalate; PA, phthalic acid.

[a]Including observations with concentrations below the LOD of the assay, set to half the LOD: butyl paraben (35%) and BPA, triclosan, methyl paraben, ethyl paraben, MEP, MiBP, and MMP (≤8% each).

[d]Sum of butyl, ethyl, methyl, and propyl paraben excretion.

[c]Sum of MiBP and MnBP excretion.

[d]Sum of MECPP, MEHHP, MEHP, and MEOHP excretion.

[e]Sum of MBzP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MMP, and MnBP excretion.

[f]Matching factor.

[g]BMI at baseline used for three cases missing BMI at urine collection.

[h]Self-reported diabetes at baseline and/or diabetes medication use at biospecimen collection.

[i]Including adenocarcinoma with squamous cell differentiation and adenocarcinoma not otherwise specified.

[j]$n = 4$ (3%) cases missing stage.

Table 2. Number (cases/controls) and odds ratios with 95% confidence intervals for associations between creatinine-adjusted urinary EDC metabolite excretion (ng/mg) and endometrial cancer risk in 139 matched case–control sets nested within the Multiethnic Cohort.

EDC metabolite	Tertile 1	Tertile 2	Tertile 3	p_{Trend}[a]
BPA	44/47	45/46	50/46	0.50
	Ref	0.86 (0.44, 1.67)	1.21 (0.60, 2.44)	
Triclosan	49/47	45/46	45/46	0.80
	Ref	1.09 (0.53, 2.25)	0.97 (0.47, 2.01)	
Methyl paraben	50/47	46/46	43/46	0.83
	Ref	1.36 (0.68, 2.73)	1.17 (0.60, 2.28)	
Ethyl paraben	62/47	36/46	41/46	0.85
	Ref	0.65 (0.33, 1.28)	0.95 (0.48, 1.89)	
Propyl paraben	54/47	55/46	30/46	0.25
	Ref	1.35 (0.70, 2.61)	0.80 (0.39, 1.65)	
Butyl paraben	55/47	43/46	41/46	0.67
	Ref	0.80 (0.40, 1.61)	0.78 (0.38, 1.63)	
Total parabens[b]	51/47	48/46	40/46	0.81
	Ref	1.36 (0.71, 2.60)	1.03 (0.52, 2.02)	
MBzP	43/47	51/46	45/46	0.97
	Ref	1.20 (0.62, 2.33)	1.07 (0.55, 2.11)	
MECPP	45/47	46/46	48/46	0.28
	Ref	1.24 (0.64, 2.41)	1.52 (0.74, 3.13)	
MEHHP	50/47	42/46	47/46	0.78
	Ref	1.14 (0.62, 2.10)	0.95 (0.48, 1.87)	
MEHP	46/47	44/46	49/46	0.30
	Ref	1.27 (0.64, 2.52)	1.43 (0.75, 2.75)	
MEOHP	55/47	33/46	51/46	0.42
	Ref	0.68 (0.35, 1.35)	1.17 (0.57, 2.42)	
MEP	47/47	49/46	43/46	0.92
	Ref	0.85 (0.43, 1.68)	0.93 (0.43, 2.00)	
MiBP	36/47	49/46	54/46	0.13
	Ref	1.51 (0.75, 3.01)	1.85 (0.90, 3.82)	
MMP	54/47	46/46	39/46	0.21
	Ref	0.77 (0.38, 1.55)	0.59 (0.27, 1.31)	
MnBP	32/47	63/46	44/46	0.44
	Ref	2.35 (1.19, 4.65)	1.82 (0.81, 4.10)	
PA	47/47	50/46	42/46	0.84
	Ref	1.39 (0.72, 2.67)	1.00 (0.45, 2.22)	
DBP[c]	33/47	63/46	43/46	0.54
	Ref	2.09 (1.05, 4.16)	1.77 (0.75, 4.17)	
DEHP[d]	52/47	39/46	48/46	0.65
	Ref	0.99 (0.51, 1.89)	1.15 (0.56, 2.36)	
Total phthalates[e]	47/47	46/46	46/46	0.58
	Ref	1.09 (0.59, 1.99)	1.22 (0.61, 2.43)	

Note: Tertiles are based on EDC distributions in controls. Conditional logistic regression models adjusted for BMI at specimen collection (kg/m^2; rounded to whole units), diabetes (no, yes; defined as participants reporting diabetes on the baseline questionnaire and/or diabetes medication use at biospecimen collection), and the energy-adjusted alternate Mediterranean Diet Score from the baseline questionnaire (continuous). BMI, body mass index; BPA, bisphenol A; DBP, dibutyl phthalate; DEHP, di (2-ethylhexyl) phthalate; EDC, endocrine disrupting chemical; IQR, interquartile range; MBzP, mono-benzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; MMP, monomethyl phthalate; MnBP, mono-*n*-butyl phthalate; PA, phthalic acid; Ref, reference.
[a]p_{Trend} calculated using tertile medians.
[b]Sum of butyl, ethyl, methyl, and propyl paraben excretion.
[c]Sum of MiBP and MnBP excretion.
[d]Sum of MECPP, MEHHP, MEHP, and MEOHP excretion.
[e]Sum of MBzP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MMP, and MnBP excretion.

MiBP and MnBP are metabolites of low-molecular-weight DBP, and have been found to be weakly estrogenic *in vitro* (Zacharewski et al. 1998). A previous cross-sectional study observed no significant association between urinary excretion of MiBP, MnBP, or other phthalate metabolites (above vs. below the median) with a self-reported history of uterine cancer ($n = 3{,}003$ National Health and Nutrition Examination Survey participants; 27 cases) (Morgan et al. 2016). High exposure to DBP, estimated using redeemed prescriptions for phthalate-containing drug products, has been associated with increased ER-receptor–positive breast cancer risk in a Danish nationwide cohort (Ahern et al. 2019).

A limitation of the current study is the use of a single urine specimen. In the Nurses' Health Study (NHS)/NHSII there was a fair within-person reproducibility over 1–3 y for urinary phthalate excretion (Townsend et al. 2013). Reproducibility of urinary methyl and propyl paraben (median = 6.7 y) was poor in the Shanghai Women's Health Study (Engel et al. 2014). Both studies reported poor reproducibility over time for BPA, indicating that a single measurement may not reflect usual exposure. Although we included all postmenopausal incident endometrial cancer cases with an available prediagnosis urine sample in our study, estimates were imprecise owing to the small number of observations and were not adjusted for coexposure to related metabolites. In addition, 35% of observations for butyl paraben were below the LOD.

EDC exposures differ between racial/ethnic groups (Nguyen et al. 2020), and it is important to study health outcomes in diverse populations. As far as we are aware, this study is the first to investigate prediagnosis EDC excretion in relation to endometrial cancer risk using prospectively collected urine samples. This work highlights new avenues for collaborative research that aim to explain observed racial/ethnic disparities in endometrial cancer risk.

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