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Risk of Breast Cancer and pre-diagnostic urinary excretion of bisphenol A, triclosan, and parabens: the Multiethnic Cohort Study

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Abstract

Exposure to bisphenol A (BPA), triclosan and parabens is widespread but their impact on breast cancer risk remains unclear. This nested case-control study investigated endocrine-disrupting chemicals (EDCs) and breast cancer risk within the Multiethnic Cohort (MEC). We measured

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pre-diagnostic urinary BPA, triclosan, and parabens in 1,032 mostly postmenopausal women with breast cancer (48 African American, 77 Latinos, 155 Native Hawaiian, 478 Japanese American, and 274 White) and 1,030 individually matched controls, using a sensitive and validated liquid chromatography mass spectrometry assay. Conditional logistic regression was used to examine risk with these EDCs with adjustment for creatinine and potential confounders. In all women, breast cancer risk was not associated with BPA (P_{trend}=0.53) and was inversely associated with triclosan ($OR_{T3\ vsT1}$= 0.83, 95% CI 0.66–1.04, P_{trend}=0.045) and total parabens ($OR_{T3\ vsT1}$= 0.77, 95% CI 0.62–0.97, P_{trend}=0.03). While risk of hormone receptor (HR+) cancer was 20–23% lower among women in the upper two tertiles of paraben exposure (P_{trend}=0.02), risk of HR− was reduced 27% but only among those in the upper tertile of exposure. Although risk associations did not differ significantly by race/ethnicity or by body mass index (BMI), the inverse association with triclosan was observed mainly among overweight/obese women ($OR_{T3\ vsT1}$= 0.76, 95% CI 0.56–1.02, P_{trend}=0.02). In summary, breast cancer risk in a multiethnic population was unrelated to BPA and was weakly inversely associated with triclosan and paraben exposures. Studies with multiple urine samples collected before breast cancer diagnosis are needed to further investigate these EDCs and breast cancer risk.

Keywords

breast cancer; urinary bisphenol A; triclosan; parabens; multiethnic; hormone receptor status

Introduction

Non-persistent endocrine disrupting chemicals (EDCs), including bisphenol A (BPA), triclosan and parabens continue to be of intense public health concern because of their widespread exposure via multiple routes (dermal, inhalation, ingestion) and putative adverse effects on numerous health endpoints including obesity, and breast cancer[1–3]. BPA is an industrial chemical that is used to make plastics, particularly polycarbonates and epoxy resins; exposure occurs mainly through diet or dermal contact as they are used in linings of food and beverage cans, medical equipment, and thermal papers[4]. Triclosan with its antimicrobial properties is found as preservatives in toothpastes, underarm deodorants, and other products[5]. Parabens, a group of alkyl esters of p-hydroxy-benzoic acid, are used as preservatives in topical products especially cosmetics[6]. Although some studies have characterized these EDCs in blood specimens[7, 8], urine is considered the optimal matrix to measure these nonpersistent chemicals with short half-lifes[9]. In the US National Health and Nutrition Examination Survey studies, over 75% of those tested showed detectable urinary triclosan[5] while BPA and paraben concentrations were found in over 90% of the participants[4, 10].

Despite the ubiquity of exposures to these EDCs and their purported deleterious effects on breast cancer[1, 2], epidemiologic studies on breast cancer risk in relation to urinary exposure of BPA, triclosan, and parabens are sparse. The Long Island Breast Cancer Study Project (LIBCSP)’s investigation of exposure to BPA, parabens, and triclosan was based on urine specimens collected after breast cancer diagnosis. In LIBCSP, breast cancer risk increased with increasing exposure to total parabens (1.09, 95% CI 1.00–1.18) but risk was unrelated

to BPA and triclosan exposures[11]. The LIBCSP findings on BPA are consistent with results from case-control studies conducted in Korea[8] and Poland[12]. Although there are no other studies on urinary parabens and triclosan and breast cancer risk, case-control studies have suggested associations between breast cancer risk and self-reported use of antiperspirant/deodorant, as a marker of paraben/triclosan exposure[13–15]. However, recent results from two prospective studies on breast cancer risk and self-reported use of personal care products differed[16 17] (see discussion).

To provide much needed information, we investigated the role of pre-diagnostic urinary BPA, triclosan, and parabens in relation to breast cancer risk in a case-control study nested in the prospective Multiethnic Cohort (MEC), including 1,032 postmenopausal women diagnosed with incident breast cancer (48 African American, 77 Latinos, 155 Native Hawaiian, 478 Japanese American, and 274 White women), and 1,030 matched postmenopausal controls[18].

Methods

Study population

The MEC is a prospective cohort of 96,810 men and 118,441 women aged 45 – 75 years from five racial/ethnic groups (African American, Latinos, Native Hawaiian, Japanese American and White) living in Hawai'i (HI) and California (CA) (primarily Los Angeles County (LAC)) at enrollment between 1993–1996. Participants completed a baseline questionnaire which assessed demographics, lifestyle, diet, and anthropometrics, and for women, menstrual and reproductive histories and hormone therapy (HT) use. Participants were followed prospectively for diagnosis of incident breast cancer through linkage with the CA and HI statewide cancer registries, and for vital status through linkages to the National Death Index and state death certificate files.

In 2001–2006, a prospective biorepository was established by collecting urine and blood specimens from 67,594 MEC participants[19]. Weight, HT use, and medications were assessed at biospecimen collection. For this nested case-control study, 1,032 incident breast cancer (22% in-situ, 78% invasive) were diagnosed from 2001 through 2014 after urine collection (mean ± standard deviation (SD): 5.5 ± 3.3 years). For each case, we selected one control, who was alive and free of breast cancer at the age of the case's breast cancer diagnosis, and individually matched each control to a case on area (HI or CA), birth year (± 1 year), race and ethnicity, urine type (first morning from CA, overnight and first morning from HI), urine collection date (±1 year), fasting hours (8–10, >10 hours), and blood draw time (±2 hours). Controls were sampled from the representative pool of subjects with existing data on genotype, obesity-related and inflammation biomarkers. The urine specimens for one White and one Native Hawaiian control were not usable and their cases were rematched to existing controls, resulting in 1,030 controls matched to 1,032 cases.

Laboratory measurement of urinary BPA, triclosan and parabens

These EDC measurements were conducted at the University of Hawai'i Cancer Center Analytical Biochemistry Shared Resource using liquid chromatography (LC) with sensitive

isotope-dilution orbitrap based high-resolution accurate-mass mass spectrometry (HRAM-MS) under the supervision of Dr. Adrian Franke. All analytes were measured by a method we originally developed for steroidal estrogens[20,21], then extended to BPA[22] and now to parabens and triclosan by applying LC/HRAM-MS after derivatization to increase measurement sensitivity. This is possible because all these analytes possess a phenolic moiety within their molecular structure which is needed to add the tag that improves mass spectrometric sensitivity 50–100 fold. Laboratory personnel were blinded to case-control status and matched pairs of cases and controls were assayed in the same batch. Replicate samples of pooled urines (5%) were included in each of 37 batches for quality control measures and coefficients of variations (CV) were calculated. The CV% (SD/mean concentration × 100) within-batch was 21.9% for BPA, 20.6% for triclosan, and 21.5% averaged for the parabens. The larger CVs likely reflect several samples close to the lower limit of quantification (LLOQ). The mean CV of the non-blinded pooled samples was 8.3 (SD=3.4). About 0.5 ml of urine was used for all assays and creatinine levels were measured using a Roche-Cobas MiraPlus clinical chemistry auto analyzer (Roche Diagnostics) with a kit from Randox Laboratories (Crumlin, UK) based on the Jaffe reaction. We accounted for differences in urine volume by calculating analytes adjusted to creatinine levels by dividing the analyte concentration by the creatinine concentration yielding ng/g units for analyte excretion. The LLOQ was 1 pg/mL for the 7 analytes; analytes below the LLOQ were assigned a value half of the LLOQ for data evaluations. The percent of samples with values below the LLOQ was low for BPA (2%), triclosan (3%) and the two high concentration parabens (methyparaben (2%), propylparaben (1%)), intermediate for ethylparabens (12%) but were high for the very low concentration parabens (butylparaben (29%), and benzylparabens (82%)).

Statistical analyses

We conducted conditional logistic regression, with the matched sets as strata (1028 pairs and 2 triplets), and modeled BPA, triclosan, total and individual paraben variables as tertiles using selected cutoff points based on the distribution among all controls. Odds ratios ($OR_{tertiles}$) and 95% confidence intervals (Cis) were the primary statistics of interest, and inference was based on the Wald test. We found no evidence of a nonlinear relationship (on the log odds scale) between each EDC and risk using restricted cubic splines (data not shown). Therefore, log-transformed BPA (triclosan, paraben) variables were used as trend variables to test for dose-response relationships. Models included adjustment for potential confounders that were not matching factors (e.g. established breast cancer risk factors) using propensity scores for exposure to these EDCs in order to maximize power. In particular, an ordinal logistic regression models for tertiles of BPA, triclosan, parabens (total and individual) were performed using the following independent variables collected at baseline (education, number of children, age at menarche, alcohol intake, and Mediterranean diet energy adjusted total score[24]) and at urine collection (age, menopausal status, body mass index (BMI), smoking, neighborhood socioeconomic status[23]). The propensity for each exposure was determined for each individual as the weighted average = $1 \times \rho_1 + 2 \times \rho_2 + 2 \times \rho_3$, where ρ_i is the model-based probability of exposure to tertile *i*. Indicators variables for tertiles of the propensity score were entered in the models of that specific exposure. Heterogeneity of the associations by race/ethnicity was assessed by a global test of the

interaction terms between race and the BPA (triclosan, paraben) trend variable. All the variables were modeled as categorical variables in the interaction models and heterogeneity testing. We repeated subgroup analyses for hormone receptor (HR) status (HR positive (ER+ or PR+) and HR negative (ER- and PR-)), BMI (<25, 25-<30, 30+ kg/m^2), and use HT at urine collection. We explored risk associations by waist-hip ratio (WHR), which was obtained in a follow-up questionnaire and was available for 333 cases prior to diagnosis and 946 control women. We also conducted sensitivity analysis by restricting to invasive cases (n=798) and by lag time between time of urine collection and breast cancer diagnosis (≤5 years versus > 5 years), as well as excluding 187 cases that were diagnosed within two years of urine collection to minimize the potential effect of pre-diagnostic breast cancer on EDC levels. Associations with $P < 0.05$ were considered statistically significant. The correlations among these EDCs were examined using Spearman's Rho among control women and cases.

Results

In this nested case-control study, Japanese Americans represented the largest racial/ethnic group of participants (46.3%), followed by Whites (26.6%), Native Hawaiians (15.0%), Latinos (7.5%) and African Americans (4.7%). Eighty-six percent of the participants (883 cases, 881 controls) were from Hawai'i, who donated overnight (875 cases, 873 controls) or first morning urines (8 cases, 8 controls), whereas 14% of the participants were from Los Angeles County (149 cases, 149 controls) who donated first morning samples. All cases and controls were postmenopausal at the time of urine collection; their respective ages at urine collection were 66.7 (SD 7.7) and 66.8 (SD 7.7). Cases compared to control women were more likely to be nulliparous (15.8% vs 10.8%) and had higher BMI (27.05 ±5.59 vs 26.00 ±5.61 kg/m^2) and waist to hip ratio (0.862 ± 0.076 vs 0.856 ± 0.082) at urine collection but were otherwise comparable in other characteristics that have been described previously[18].

Table 1 shows geometric mean (95% CI) and correlations between these analytes among 1030 control women. Mean concentrations/mg creatinine were highest for methylparabens (49.4 μg/mg), intermediate for propylparabens (18.5 μg/mg), and lower for ethylparabens (1.15 μg/mg), butylparabens (0.15 μg/mg), and benzylparabens (0.004 μg/mg) among control women. Four parabens (methyl-, ethyl-, propyl-, butyl-) were strongly correlated with each other (Rho's were 0.37 to 0.77; P<0.001) while benzylparaben was modestly correlated with propyl- and butylparabens (0.17–0.19, P<0.001) but not correlated with methyl- and ethylparabens (0.06 and 0.08, P>0.05). Triclosan was correlated with methyl- and benzylparabens and BPA (Rho's were 0.11–0.13) but not with the other parabens. BPA was correlated with all the parabens except for ethylparabens (Rhos were 0.10–0.19). (Table 1). Similar geometric mean distribution patterns and correlations between these analytes were observed among 1032 women with breast cancer (Supplemental Table 1).

Breast cancer risk was not associated with BPA exposure ($OR_{T2\ vs\ T1}$=0.84 (95% CI:0.67–1.06); $OR_{T3\ vs\ T1}$=0.95 (95% CI:0.75–1.21), P_{trend} =0.53; Table 2). In contrast, risk was inversely associated with triclosan exposure; risk was lower among women in the upper two tertiles of exposure compared to those in the lowest tertile ($OR_{T2\ vs\ T1}$=0.75 (95% CI:0.60–0.93), $OR_{T3\ vs\ T1}$=0.83 (95% CI:0.66–1.04), P_{trend}= 0.045). Although none of the individual parabens were significantly associated with breast cancer risk, exposure to total

parabens was inversely associated with risk; women in the highest tertile compared to those in the lowest tertile showed a 23% lower risk ($OR_{T3\ vs\ T1}$=0.77 (95% CI:0.62–0.97), P_{trend}=0.03). When we examined risk associations mutually adjusted for these exposures as categorical variables, the null association with BPA (P_{trend} =0.85) and the 23% risk reduction among women in the upper tertile of total parabens remained (P_{trend} =0.03), while the inverse association with triclosan was slightly weakened ($OR_{T3\ vs\ T1}$=0.84, 95% CI:0.67–1.06 P_{trend}=0.06).

The inverse association with triclosan was observed mainly for HR+ (n=859) breast cancer where risk was 25% and 16% lower, respectively, among women in the second and third tertile compared to women in the first tertile (P_{trend}=0.07) but this was not observed for HR− breast cancer (n=124) (P_{trend}=0.93) ($P_{heterogeneity}$=0.39). Similarly, the inverse association with total parabens was observed for HR+ breast cancer; risk was 20% and 23% lower among women in the upper two tertiles compared to women in the lowest tertile (P_{trend} =0.02). Although risk of HR− breast cancer was 27% lower among women in the third tertile of paraben exposure, risk was 42% higher among women in the second tertile of exposure (P_{trend}= 0.48) ($P_{heterogeneity}$ =0.75) (Table 2).

Breast cancer associations in relation to exposures to BPA, triclosan and total parabens did not differ by years of follow-up after urine collection, or between all (invasive and in situ combined) versus invasive breast cancers only (Supplementary Table 2). There were also no suggestive differences in these risk associations by use of hormone therapy at urine collection (Supplementary Table 3). The association between triclosan and breast cancer risk did not differ significantly by body size at urine collection. However, the inverse association was more prominent among those who were overweight/obese (>25 kg/m^2) ($OR_{T3\ vs\ T1}$=0.76, 95% CI:0.56–1.02 P_{trend}=0.02) or had higher (≥0.854) WHR ($OR_{T3\ vs\ T1}$=0.56, 95% CI:0.33–0.95 P_{trend}=0.04) and was not observed among women with normal BMI ($OR_{T3\ vs\ T1}$=0.98, 95% CI:0.72–1.35 P_{trend}=0.85) or lower (<0.854) WHR ($OR_{T3\ vs\ T1}$=1.03, 95% CI:0.63–1.69 P_{trend}=0.91). Results for BPA and total parabens did not differ by BMI or WHR at urine collection (Table 3).

Geometric mean distributions of these chemicals differed by race/ethnicity (Supplementary Table 4). However, we found no evidence of differences in breast cancer associations by race/ethnicity (Supplementary Table 5). The null risk pattern with BPA exposure was observed across race/ethnicity groups ($OR_{T3\ vs\ T1}$ ranged from 0.86 in Japanese Americans to 1.05 in Native Hawaiians). The inverse association between triclosan and risk was suggested among Whites ($OR_{T3\ vs\ T1}$=0.71, 95% CI:0.46–1.10 P_{trend}=0.10) and Japanese Americans ($OR_{T3\ vs\ T1}$=0.73, 95% CI:0.52–1.03 P_{trend}=0.06) but not among Native Hawaiians ($OR_{T3\ vs\ T1}$=1.17, 95% CI:0.61–2.22 P_{trend}=0.93) or African Americans and Latinos combined ($OR_{T3\ vs\ T1}$=1.20, 95% CI:0.65–2.23 P_{trend}=0.85). The inverse association with total parabens was observed in Japanese Americans, Whites, and African Americans and Latinos combined (respective $OR_{T3\ vs\ T1}$ was 0.65 (95% CI:0.47–0.90), 0.72 (95% CI:0.46–1.14), and 0.75 (95% CI:0.38–1.46)) but not among Native Hawaiians ($OR_{T3\ vs\ T1}$=1.03, 95% CI:0.54–1.97).

Discussion

To our knowledge, this is the first study to examine the association between breast cancer risk and pre-diagnostic exposures of urinary BPA, triclosan and parabens. Our nested case-control results on BPA agree with the generally null findings from previous case-control studies[8, 11, 12]. However, our findings of a weak inverse risk association with triclosan and parabens differ from previous studies that found weak positive associations, including one study of urinary parabens and triclosan exposures determined after breast cancer diagnosis[11] and other studies which were based on self-reported use of various products as surrogates of triclosan and paraben exposures[17, 25–27].

Although there is extensive evidence on the estrogenic properties and carcinogenic potential of BPA[28, 29], epidemiological findings on BPA and breast cancer have largely been null. Our results, based on 1,032 breast cancer cases and 1,030 control women whose urine was collected before diagnosis, are based on a larger sample size than previous studies including the LIBCSP (711 cases, 598 controls), the Polish case-control study (575 cases, 575 controls), and the Korean case-control study (70 cases, 82 controls), all using post-diagnosis biospecimens. The null BPA findings in the MEC were consistently observed in Whites, Japanese Americans, Native Hawaiians, and African Americans/Latinos combined, for HR+ and HR− breast cancers, and among normal BMI and overweight/obese women. A challenge that we and others face in epidemiologic studies of BPA and breast cancer is that we are using a single measure of BPA to capture long-term exposures. Given the intra-individual variability of urinary BPA measures[30], misclassification on exposure, biasing results towards the null, is very likely.

Results from our nested case-control study suggest a weak inverse association between urinary triclosan and breast cancer risk that was slightly diluted after adjustment for total parabens and BPA. No association with triclosan was found in LIBCSP[11]. While there were no significant racial/ethnic differences in our finding, triclosan exposure was inversely associated with risk in Whites and Japanese American women but not in the other groups. The inverse risk association with triclosan in the MEC was also more prominent among overweight/obese women or those with higher WHR. Results on EDCs and breast risk for the subgroup with WHR information were very similar to the overall results. Interestingly, MEC women in the highest tertile of triclosan had lower BMI than those in the lowest tertile of triclosan (BMI of 27.7 vs 29.0 for cases, P=0.001; BMI of 26.9 vs 27.6 for controls, P=0.008), similar to results from a large NHANES cross-sectional study of urinary triclosans where higher concentrations were associated with a lower BMI and a smaller waist circumference in women and men, in adults and children[31]. Reasons underlying an inverse association between triclosan levels and obesity traits is not well understood but triclosan has been found to inhibit adipocyte differentiation of human mesenchymal stem cells[32, 33] and to alter thyroid hormone levels[34].

Our findings on total parabens and breast cancer risk differed from the LIBCSP results[11]. It is difficult to directly compare our results as the LIBCSP results were based on post-diagnostic samples while our results are based on pre-diagnostic samples; reverse causation may be a factor. In LIBCSP, the multivariable-adjusted results on parabens were also

stronger than the age adjusted results (e.g., OR for highest total parabens category increased from 1.09 (0.77–1.55) to 1.35 (0.93–1.97)) whereas the multivariable and age-adjusted odds ratios for BPA and triclosan were essentially identical. While we found no evidence of effect measure modification by BMI in our findings on parabens, the paraben-breast cancer association in the LIBCSP was more prominent in normal BMI (<25 kg/m^2) and not among higher BMI women.

Our results on triclosan and parabens and breast cancer risk suggest no evidence of a deleterious effect and thus qualitatively consistent with the null results on skincare products and breast cancer risk in the Norwegian Women and Cancer Cohort[16]. Compared to postmenopausal Norwegian women who were light users of skincare products, the respective HRs for moderate/frequent users and heavy users were 0.97 and 0.87 (P_{trend}=0.27) while the corresponding HRs among premenopausal women were 1.05 and 1.10 (P_{trend}=0.56)[16]. In the Sister study, relative to ethnic-specific infrequent users of beauty products, elevated risks for female breast cancer were observed among White frequent users (HR 1.15, 95% CI 1.02–1.30) but not among Black frequent users (HR 0.86, 95% CI 0.53–1.39)[17]. However, in both prospective studies, the products that were investigated only represent some of the sources of parabens and the findings may reflect exposure to non-paraben chemicals or other correlated behaviors.

Strengths of this study include being the first prospective study to investigate urinary BPA, triclosan and parabens among five racial/ethnic groups in the same study, providing the first such data in Native Hawaiian and Japanese American women. In addition, we carefully considered potential confounders, potential effect modification by two measures of body size (BMI and WHR) and use of HT, as well as potential differences by HR status, tumor stage (invasive versus in situ), and by length of follow-up time. We used a highly sensitive assay for analyte quantitation and carefully examined risk associations with both individual parabens and all parabens combined as they may represent different sources and routes of exposure. However, there are several limitations. We relied on a single urine sample measurement; the modest within-person variability for BPA, triclosan and parabens in this study as in other studies[11, 30] may have reduced our statistical power. Although the contribution of benzylparabens and butylparabens to total parabens was negligible, a large number of assays for these very low concentration parabens were also below the lower limit of quantification. The urine samples were collected from postmenopausal women who were in their 60's while it has been suggested that it is important to examine the role of these chemicals and breast cancer risk during specific windows of susceptibility[2, 35]. We also examined results in African American and Latinos women combined because of their modest sample sizes. Information on pre-diagnostic WHR was available on only a subset of breast cancer cases. All the urine samples from LAC were first morning compared to mostly overnight specimens from Hawaii; urine volume was adjusted by creatinine which should eliminate most of the differences between these collection protocols. Since misclassification of exposure is unavoidable, non-differential misclassification of exposure would tend to attenuate the overall results and underestimate the true association. We did not correct for multiple comparisons and due to the number of tests performed, some of the findings may have been due to chance.

Results from this large nested case-control study suggest a weak inverse association between breast cancer risk and exposure to triclosan and parabens and no association with exposure to BPA. Additional studies with repeated pre-diagnostic samples are needed to improve assessment of exposures and to better understand the effects of these ubiquitous chemicals during possible susceptibility windows of exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

Data requests can be submitted to Multiethnic Cohort Online Request System. https://www.uhcancercenter.org/for-researchers/mec-data-sharing

Abbreviations

BMI	body mass index kg/m^2
BPA	bisphenol A
CA	California
CI	confidence interval
CV	coefficient of variation
EDC	endocrine disrupting chemical
ER/PR	estrogen/progesterone receptor
HI	Hawaii
HR+	hormone receptor positive status
HR−	hormone receptor negative status
HT	hormone therapy
LAC	Los Angeles County
LLOQ	lower limit of quantitation
LCMS	liquid chromatography mass spectrometry

LIBCSP	Long Island Breast Cancer Study Project
MEC	Multiethnic Cohort
NHANES III	Third National Health and Nutrition Examination Survey
nSES	neighborhood socioeconomic status
SEER	Surveillance, Epidemiology, and End Results Program
SD	standard deviation
WHR	waist to hip ratio

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Novelty and Impact:

In the first study to examine the association between breast cancer risk and pre-diagnostic exposures of urinary BPA, triclosan and parabens, we found a weak inverse association between exposure to triclosans and parabens and no association with BPA exposure in whites and nonwhites after careful adjustment of potential confounders. Studies with repeated pre-diagnostic samples are needed to improve assessment of exposures and to better understand the effects of these ubiquitous chemicals during possible susceptibility windows of exposure.

Table 1.

Geometric means and summary spearman correlation for adjusted creatinine of paraben, triclosan and bisphenol A among 1030 women in the Multiethnic Cohort.

Variable	Methy paraben	Ethyl paraben	Propyl paraben	Butyl paraben	Benzl paraben	Total Paraben	Triclosan	BPA
Geometric mean (95% CI)	49.40 (43.49–56.12)	1.15 (0.95–1.39)	18.54 (16.78–20.49)	0.15 (0.13–0.19)	0.004 (0.004–0.005)	93.69 (85.45–102.73)	8.76 (7.59–10.11)	1.15 (1.06–1.25)
Methyl paraben	1.00							
Ethyl paraben	**0.41** [a]	1.00						
Propy lparaben	**0.77** [a]	**0.37** [a]	1.00					
Butyl paraben	**0.42** [a]	**0.49** [a]	**0.41** [a]	1.00				
Benz lparaben	0.06	0.08[b]	**0.17** [a]	**0.19** [a]	1.00			
Total Paraben	**0.97** [a]	**0.49** [a]	**0.85** [a]	**0.48** [a]	0.10[b]	1.00		
Triclosan	**0.11** [a]	0.05	0.10[b]	0.08[b]	**0.12** [a]	**0.11** [a]	1.00	
BPA	**0.15** [a]	0.04	**0.19** [a]	**0.10** [a]	**0.19** [a]	**0.17** [a]	**0.13** [a]	1.00

[a] P value <0.001

[b] P value 0.001≤P≤0.05

Table 2.

Association between breast cancer risk and urinary bisphenol A (BPA), triclosan, and parabens, in all women and by hormone receptor (HR) status, using nested case-control data from the Multiethnic Cohort Study (1993–2014)

Analyte (ng/g creatinine)	All (1032 ca/1030 co)			HR positive[b] (859 ca/981 co)			HR negative[b] (124 ca/ 981co)		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
BPA									
≤ 0.84	372	350	1.00	305	333	1.00	47	333	1.00
0.84– ≤1.76	313	344	0.84 (0.67–1.06)	265	331	0.87 (0.69–1.09)	35	331	0.78 (0.49–1.24)
>1.76	347	336	0.95 (0.75–1.21)	289	317	0.98 (0.78–1.24)	42	317	1.00 (0.64–1.59)
P trend[c]			0.53			0.73			0.84
P Het[d]									0.97
Triclosan									
≤ 5.27	397	339	1.00	331	320	1.00	44	320	1.00
5.27– ≤20.57	297	341	0.75 (0.60–0.93)	249	327	0.75 (0.60–0.94)	34	327	0.79 (0.49–1.27)
>20.57	338	350	0.83 (0.66–1.04)	279	334	0.84 (0.67–1.05)	46	334	1.06 (0.67–1.68)
P trend[c]			0.05			0.07			0.93
P Het[d]									0.39
Methylparaben									
≤ 28.28	379	340	1.00	320	324	1.00	42	324	1.00
28.28-≤121.63	350	339	0.98 (0.79–1.22)	282	323	0.93 (0.74–1.17)	50	323	1.14 (0.73–1.79)
>121.83	303	351	0.83 (0.66–1.04)	257	334	0.85 (0.67–1.07)	32	334	0.69 (0.41–1.14)
P trend[c]			0.15			0.18			0.25
P Het[d]									0.65
Propylparaben									
≤ 9.27	373	339	1.00	313	325	1.00	42	325	1.00
9.27– ≤38.89	350	341	0.98 (0.79–1.21)	285	321	0.94 (0.75–1.18)	45	321	1.07 (0.68–1.68)
>38.89	309	350	0.84 (0.67–1.06)	261	335	0.84 (0.67–1.06)	37	335	0.83 (0.51–1.35)
P trend[c]			0.19			0.16			0.55
P Het[d]									0.94

Analyte (ng/g creatinine)	All (1032 ca/1030 co)			HR positive[b] (859 ca/981 co)			HR negative[b] (124 ca/ 981co)		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
Ethylparaben									
≤ 0.65	383	340	1.00	311	323	1.00	46	323	1.00
0.65– ≤4.85	324	340	0.87 (0.70–1.08)	271	329	0.88 (0.70–1.10)	43	329	0.92 (0.59–1.44)
>4.85	325	350	0.87 (0.69–1.09)	277	329	0.92 (0.73–1.17)	35	329	0.75 (0.46–1.23)
P trend[c]			0.19			0.41			0.29
P Het[d]									0.56
Butylparaben									
≤ 0.03	378	341	1.00	314	323	1.00	42	323	1.00
0.03– ≤0.974	328	337	0.89 (0.71–1.11)	271	322	0.88 (0.70–1.11)	41	322	0.99 (0.63–1.58)
>0.974	326	352	0.87 (0.69–1.10)	274	336	0.87 (0.69–1.10)	41	336	0.97 (0.60–1.55)
P trend[c]			0.22			0.22			0.89
P Het[d]									0.68
Benzlparaben									
≤ 0.001	135	151	1.00	110	140	1.00	12	140	1.00
0.001– ≤0.003	581	540	1.26 (0.96–1.66)	482	512	1.21 (0.91–1.61)	70	512	1.74 (0.90–3.34)
>0.003	316	339	1.09 (0.79–1.49)	267	329	1.05 (0.77–1.43)	42	329	1.68 (0.83–3.38)
P trend[c]			0.64			0.92			0.19
P Het[d]									0.26
Total Parabens									
≤ 49.26	395	339	1.00	339	322	1.00	38	322	1.00
49.26–201.53	338	340	0.90 (0.73–1.12)	265	325	0.80 (0.64–1.00)	56	325	1.42 (0.91–2.23)
>201.53	299	351	0.77 (0.62–0.97)	255	334	**0.77 (0.61–0.97)**	30	334	0.73 (0.43–1.24)
P trend[c]			**0.03**			**0.02**			0.48
P Het[d]									0.75

[a]Conditional logistic regression with the matched sets as strata and adjusted for education, number of children, age at menarche, menopausal status at urine collection, BMI at urine collection, neighborhood socioeconomic status at urine collection, smoking at urine collection, alcohol intake, and Mediterranean energy adjusted total score. Missing categories of covariates were included in the analyses

[b]Unconditional logistic regression analyses were conducted. There were 49 missing HR status (35 in situ, 6 stage I, 1 stage II, 1 stage III, 6 missing stage); their corresponding subjects were excluded.

[c] P trend (log analyte) df=1

[d] P heterogeneity (HR+ vs HR-)

Table 3.

Breast cancer risk[a] and exposure to urinary BPA, triclosan, and total parabens by body mass index (BMI) and waist hip ratio (WHR), using nested case-control data from the Multiethnic Cohort Study (1993–2014)

	BMI at urine collection						All cases/controls with WHR OR[a] (95% CI	WHR at urine collection[b]					
	≤25 kg/m^2			>25 kg/m^2				≤0.854			>0.854		
	Case	Control	OR[a] (95% CI)	Case	Control	OR (95% CI)		Case	Control	OR[a] (95% CI)	Case	Control	OR (95% CI)
BPA													
≤ 0.84	141	172	1.00	231	178	1.00	1.00	40	158	1.00	43	165	1.00
0.84– ≤1.76	119	184	0.77 (0.56–1.06)	194	160	0.94 (0.70–1.25)	0.86 (0.60–1.23)	32	157	0.80 (0.48–1.34)	37	154	0.92 (0.56–1.51)
>1.76	146	173	0.99 (0.72–1.36)	201	163	0.96 (0.72–1.28)	1.01 (0.71–1.44)	44	160	1.08 (0.66–1.76)	37	152	0.94 (0.57–1.57)
P trend[c]			0.73			0.73	0.92			0.89			0.78
P het[d]						0.98							0.77
Triclosan													
≤ 5.27	136	173	1.00	261	166	1.00	1.00	41	150	1.00	52	157	1.00
5.27– ≤20.57	115	162	0.89 (0.64–1.23)	182	179	**0.65 (0.49–0.87)**	0.71 (0.50–1.02)	29	169	0.61 (0.36–1.03)	38	148	0.82 (0.51–1.33)
>20.57	155	194	0.98 (0.72–1.35)	183	156	0.76 (0.56–1.02)	0.78 (0.54–1.11)	46	156	1.03 (0.63–1.69)	27	166	**0.56 (0.33–0.95)**
P trend[c]			0.85			**0.02**	0.11			0.91			**0.04**
P het[d]						0.16							0.17
Total Parabens													
≤ 49.26	118	136	1.00	277	203	1.00	1.00	35	145	1.00	46	163	1.00
49.26 ≤201.53	133	182	0.80 (0.57–1.12)	205	158	0.95 (0.72–1.26)	1.06 (0.74–1.50)	39	158	1.06 (0.63–1.78)	43	153	1.07 0.66–1.72)
>201.53	155	211	0.78 (0.56–1.09)	144	140	0.75 (0.55–1.02)	0.89 (0.61–1.30)	42	172	1.07 (0.63–1.84)	28	155	0.72 (0.42–1.23)
P trend[c]			0.14			0.10	0.65			0.80			0.34
P het[d]						0.96							0.40

[a]Unconditional logistic regression stratified by BMI or WHR and adjusted for education, number of children, age at menarche, menopausal status at urine collection, neighborhood socioeconomic status at urine collection, smoking at urine collection, alcohol intake, and Mediterranean energy adjusted total score. Missing categories of covariates were included in the analyses

[b]Waist hip ratio(WHR) information was collected at the third follow-up questionnaire (2003–2006); we included subjects with WHR information before breast cancer diagnosis and for all control women.

[c]P trend (log analyte) df=1

$d_{\text{P heterogeneity for BMI (≤25 vs >25 kg/m2) or for WHR (≤0.854 vs >0.854)}}$