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Original Article

Association between Urinary Phenols and Parabens as Well as Breast Cancer

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Abstract

Background: Phenols and parabens have been associated with various adverse health outcomes. However, their relationship with breast cancer remains inconsistent, and the combined effect is still unknown. This study aimed to examine the association between mixed phenols and parabens and breast cancer among female adults.

Method: Participants for this study were obtained from six cycles of the National Health and Nutrition Examination Survey (NHANES). The weighted logistic regression model was employed to investigate the relationship between individual chemicals and breast cancer. Furthermore, the weighted quantile sum (WQS) regression was used to assess the joint effects of phenols and parabens on breast cancer.

Results: The study included 4993 participants, with 154 women diagnosed with breast cancer. After adjusting for all potential covariates, triclosan (TCS) showed a positive association with breast cancer (OR for Q3 = 2.12, 95% CI: 1.23-3.65), while propylparaben (PrPB) exhibited a negative association with breast cancer (OR for Q4 = 0.48, 95% CI: 0.23-0.98). The WQS regression mode found no significant difference between mixed chemicals and breast cancer (OR for positive model = 1.09, 95% CI: 0.65-1.84 and OR for negative model = 0.95, 95% CI: 0.57-1.58).

Conclusion: Exposure to phenols and parabens has distinct effects on breast cancer risk. High-quality research is essential to obtain conclusions that are more reliable and uncover potential underlying mechanisms.

Keywords: Breast neoplasms; Parabens, Phenols; Endocrine disruptors

Introduction

Breast cancer is a malignant tumor that originates from the breast tissue and ranks as one of the most common cancers affecting women worldwide (1). In 2020, approximately 2.3 million cases were reported worldwide (2), with increasing prevalence observed across both developed and emerging economies (3, 4). This escalating prevalence underscores the importance of addressing breast cancer as a critical public health challenge for women.

Genetics, lifestyle, and environmental factors play complex roles in breast cancer pathogenesis (5-10). Among adverse environmental factors, environmental endocrine-disrupting chemicals (EDCs) represent a category of exogenous substances that can disrupt hormone synthesis, me-

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tabolism, or regulation (11). Phenols and parabens are two major groups of EDCs commonly found in personal care products, pharmaceuticals, and food. Bisphenol A (BPA) is frequently used as a component in the production of plastics, resins, food packaging, and various everyday items (12). Benzophenone-3 (BP3), also known as oxybenzone or hydroxyl-4 methoxy-benzophenone, is used as a UV filter and sunscreen (13). Triclosan (TCS) is often incorporated into toothpaste, hand sanitisers, soaps, cosmetics, and other daily-use products as an antibacterial preservative (14). BPA, BP3, and TCS are all common phenolic compounds found in personal care products. Parabens are a group of substances widely used as preservatives in cosmetics, pharmaceuticals, and personal care products. Common parabens include propylparaben (PrPB), methylparaben (MePB), butylparaben (BePB), and ethyl paraben (EtPB) (15, 16). These chemicals have been widely detected in human biological specimens, with detection rates exceeding 90% (17, 18).

Exposure to common EDCs like BPA, BP3, TCS, and parabens may disrupt sex hormone levels and affect sex steroid hormone receptors, contributing to breast cancer pathogenesis (19-24). Some epidemiological studies have found positive associations between urinary concentrations of these chemicals and breast cancer risk. For example, a case-control study among Chinese women linked higher urinary BPA levels with increased breast cancer risk (25), and similar associations were found for urinary paraben (26, 27). However, other studies have reported conflicting results, such as a non-significant association between BPA and breast cancer (28), and an inverse association was reported in a cohort study for the risk of breast cancer with TCS and parabens (29). Additionally, the joint effects of these chemicals remain unclear, as most research has focused on individual exposures. Considering the high prevalence of breast cancer, the widespread exposure to phenols and parabens, and the limitations and inconsistencies in existing research, exploring their potential association is of critical public health importance.

Given the knowledge gaps identified above, this study aimed to evaluate the association between urinary phenols and parabens and breast cancer using participants from the National Health and Nutrition Examination Survey (NHANES) database. The weighted logistic regression model was employed to examine the relationship between individual chemicals and the incidence of breast cancer. Furthermore, weighted quantile sum (WQS) regression model was applied to assess the relationship between breast cancer and co-exposure to phenols (BPA, BP3, and TCS) and parabens (MePB, PrPB, BtPB, and EtPB).

Methods

Ethics considerations

The National Health and Nutrition Examination Survey (NHANES) is a publicly available database and approved by the National Center for Health Statistics institutional review board. All participants provided written informed consent when they did the national survey in the United States. Ethical review and approval were waived for this study since secondary analysis did not require additional institutional review board approval.

Study participants

The NHANES program is a comprehensive and nationally representative initiative conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) in the United States. The survey collects data on a wide range of health-related factors, including demographics, dietary surveys, physical activity, and various health indicators such as blood pressure, cholesterol levels, and biomarkers of exposure to environmental contaminants (30). Participants were extracted from six cycles spanning from 2005 to 2016 of the NHANES database (In the NHANES database, the relevant research data has only been updated through 2016), with 60,936 participants. Only female participants were included, and those with missing data on phenols, parabens, or cancer sta-

tus, as well as those with other cancer types, were excluded. The final analysis included 4,993 participants, with 154 self-reporting breast cancer. The participants' screening process is shown in Fig. 1.

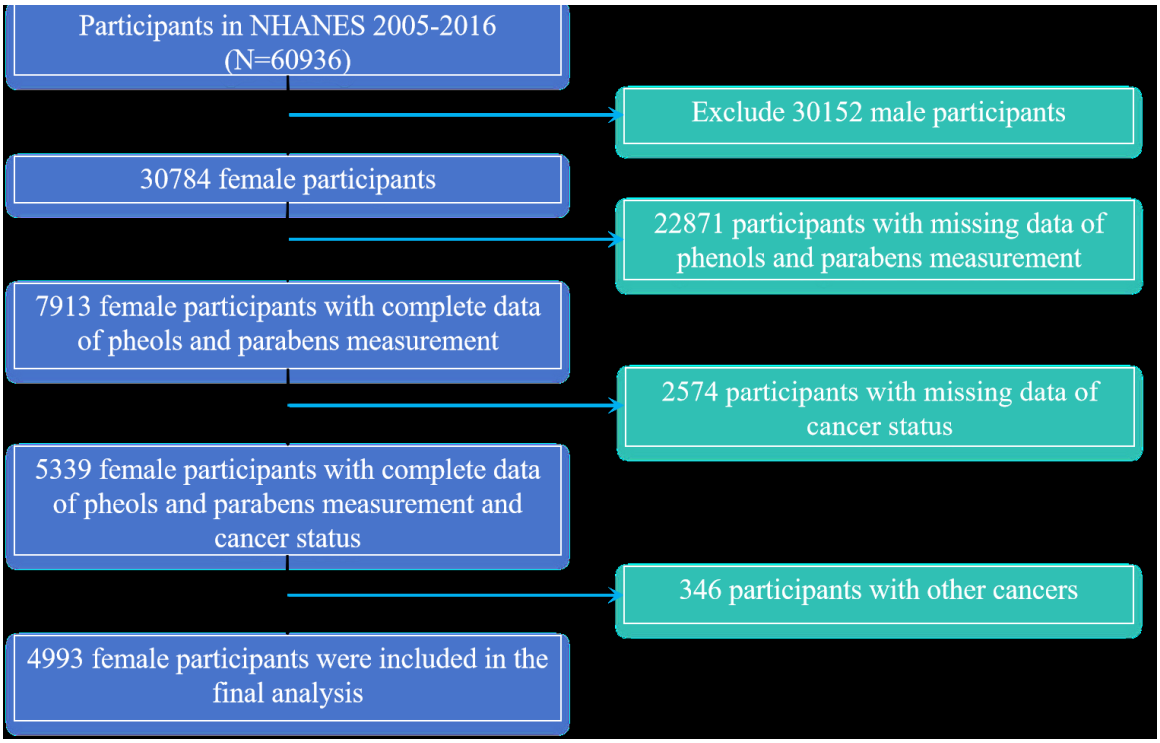

Fig. 1: Flowchart of participants included in the final analysis (N=4993)

Breast cancer status measurement

Breast cancer status was determined through the Medical Condition Questionnaire in the NHANES survey. Participants were asked if a doctor or health professional had ever diagnosed them with cancer. If they answered yes, they provided details about the type of cancer. Those who reported a breast cancer diagnosis were included in the breast cancer group.

Urinary phenols and parabens measurement

Urinary concentrations of BPA, BP3, TCS, and four parabens were measured using solid phase extraction (SPE) coupled online with high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS). Further details of laboratory procedures can be found in the NHANES laboratory methods guideline and previous studies (31). The lower limit of detection (LLOD) for BPA, BP3, TCS, PrPB, BePB, EtPB, and MePB were 0.2-0.4 ng/ml, 0.4 ng/ml, 1.7-2.3 ng/ml, 0.1-0.2 ng/ml, 0.1-0.2 ng/ml, 1.0 ng/ml, and 1.0 ng/ml, respectively. For concentrations below the LLOD, the value was imputed using the LLOD divided by the square root of 2. Additionally, chemicals with a detection frequency below 75% were excluded to address potential bias.

Covariates

Demographic factors and health-related factors were included as covariates in this study. Demographic factors encompassed age, race/ethnicity (Non-Hispanic white, Non-Hispanic black, other Hispanic, Mexican American, and other races), educational level (below high school, completed high school, some college or AA degree, and college degree or above), marital status (married or

living with a partner, widowed, divorced, separated, and never married), and the poverty-to-income ratio (PIR) (≤1.30 and >1.30) (32). Health-related factors included body mass index (BMI) (<25 kg/m^2, 25-30 kg/m^2, and ≥30 kg/m^2), alcohol consumption status (yes or no), and smoking status (yes or no). Given the influence of urine volume and the association between urinary creatinine and breast cancer, urinary creatinine concentration (mg/dl) was also included as a covariate, as suggested by a previous study (33).

Statistical analysis

Categorical variables were described using frequency and percentage, with differences assessed via chi-square tests. Continuous variables were summarized using mean and standard deviation (SD) for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. Differences were assessed using t-tests and nonparametric rank sum tests, respectively. Chemical concentrations were described using mean, geometric medians (GM), and percentiles (25th, 50th, 75th, 95th). Spearman rank correlation analysis was used for the correlation between chemicals.

A weighted logistic regression model assessed the association between individual chemical exposure and breast cancer risk. Chemical concentrations were categorized into four quantiles (Q1, Q2, Q3, Q4), with Q1 as the reference. Model 1 adjusted for age and race, while Model 2 additionally adjusted for education, marital status, PIR, BMI, alcohol consumption, smoking status, and urinary creatinine (log-transformed). The natural log-transformed concentration of each chemical was included as a continuous variable.

The WQS regression model explored the joint effect of chemicals on breast cancer risk. The WQS index was calculated from the quantiles of these chemicals, with weights derived from 1000 bootstrap iterations on a training dataset and evaluated in a validation dataset. Both negative and positive models were tested due to uncertainty about the association direction.

Considering NHANES's complex sampling, the combined weight for phenol and paraben exposure, denoted as WTSB2YR, was calculated as 1/6 * WTSB2YR. Statistical analyses were performed using R version 4.1.2, with a two-sided *P*-value < 0.05 considered significant.

Results

Characteristics of study populations

In the sample of 4,993 female adults, 154 women were identified as having breast cancer, accounting for 3.08% of the study population. The characteristics of the population, both with and without breast cancer, are presented in Table 1.

The mean age of participants with breast cancer was significantly older than those without (*P*<0.001). Regarding racial differences, the breast cancer group had a higher proportion of non-Hispanic whites (*P*=0.008). No significant differences were observed between the two groups in terms of educational level, marital status, PIR, BMI, smoking status, alcohol consumption status, and urinary creatinine concentration.

The distribution of exposure chemicals

Table 2 presents the lower limit of detection (LLOD), detection frequency, mean, geometric medians (GM), and the 25th, 50th, 75th, and 95th percentiles of all chemical exposures. The detection frequencies of BPA, BP3, TCS, PrPB, and MePB all exceeded 75%, representing 90.9%, 96.6%, 75.1%, 97.8%, and 99.4%, respectively. BePB and EtPB were excluded from further analysis due to their low detection frequencies (52.1% and 58.9%). BP3 and MePB exhibited the highest mean concentrations among the study population, at 381.36 ng/ml and 342.84 ng/ml, respectively. The results of the Spearman rank analysis indicated significant correlations among all chemical substances, with correlation coefficients ranging from 0.13 to 0.81 (Fig. 2).

Table 1: Characteristics of the study population (N=4993)

Characteristics	Total (N=4993)	Breast cancer		*P* value
		No (N=4839)	Yes (N=154)	
Age (Mean, SD)	47.91 (17.72)	47.29 (17.52)	67.29 (11.83)	<0.001
Race/ethnicity (*n*, %)				0.008
Non-Hispanic white	1995 (40.0)	1913 (39.5)	82 (53.2)	
Non-Hispanic black	1139 (22.8)	1106 (22.9)	33 (21.4)	
Other Hispanic	526 (10.5)	513 (10.6)	13 (8.4)	
Mexican American	807 (16.2)	790 (16.3)	17 (11.0)	
Other Race	526 (10.5)	517 (10.7)	9 (5.8)	
Educational level (*n*, %)				0.405
<high school	1249 (25.0)	1212 (25.0)	37 (24.1)	
Completed high school	1126 (22.6)	1083 (22.4)	43 (27.9)	
Some college	1517 (30.4)	1472 (30.4)	45 (29.2)	
College degree or more	1101 (22.0)	1072 (22.2)	29 (18.8)	
Marital status (*n*, %)				0.980
Married or living with a partner	2751 (55.1)	2666 (55.1)	85 (55.2)	
Single	2242 (44.9)	2173 (44.9)	69 (44.8)	
Family income-to-poverty ratio (*n*, %)				0.165
≤1.30	1821 (36.5)	1773 (36.6)	48 (31.2)	
> 1.30	3172 (63.5)	3066 (63.4)	106 (68.8)	
Body mass index (kg/ m ^{2}) (*n*, %)				0.992
<25	1545 (30.9)	1498 (31.0)	47 (30.5)	
25-30	1425 (28.5)	1381 (28.5)	44 (28.6)	
≥30	2023 (40.5)	1960 (40.5)	63 (40.9)	
Smoking status (*n*, %)				0.140
Yes	1763 (35.3)	1700 (35.1)	63 (40.9)	
No	3230 (64.7)	3139 (64.9)	91 (59.1)	
Alcohol consumption status (*n*, %)				0.102
Yes	3008 (60.2)	2925 (60.4)	83 (53.9)	
No	1985 (39.8)	1914 (39.6)	71 (46.1)	
Urinary creatinine (mg/dl), median (IQR)	94.00 (94.00)	94.00 (94.00)	90.50 (83.25)	0.233

Table 2: Distribution of the chemical exposures of the study population from NHANES 2005-2016 (N=4993).

Chemicals	LLOD	Detection per-centage (%)	Mean	GM	Percentile			
					25th	50th	75th	95th
BPA (ng/ml)	0.2-0.4	90.9	3.31	1.46	0.70	1.40	3.00	8.90
BP3 (ng/ml)	0.4	96.6	381.36	24.18	5.10	17.80	101.00	1740.28
TCS (ng/ml)	1.7-2.3	75.1	98.14	11.91	1.70	7.90	43.70	535.40
PrPB (ng/ml)	0.1-0.2	97.8	88.33	17.49	4.30	22.40	80.60	360.58
BuPB (ng/ml)	0.1-0.2	52.1	5.04	0.47	0.14	0.14	1.60	24.78
EtPB (ng/ml)	1.0	58.9	28.84	3.63	0.71	1.90	13.50	138.62
MePB (ng/ml)	1.0	99.4	342.84	105.03	34.00	120.00	359.00	1310.00

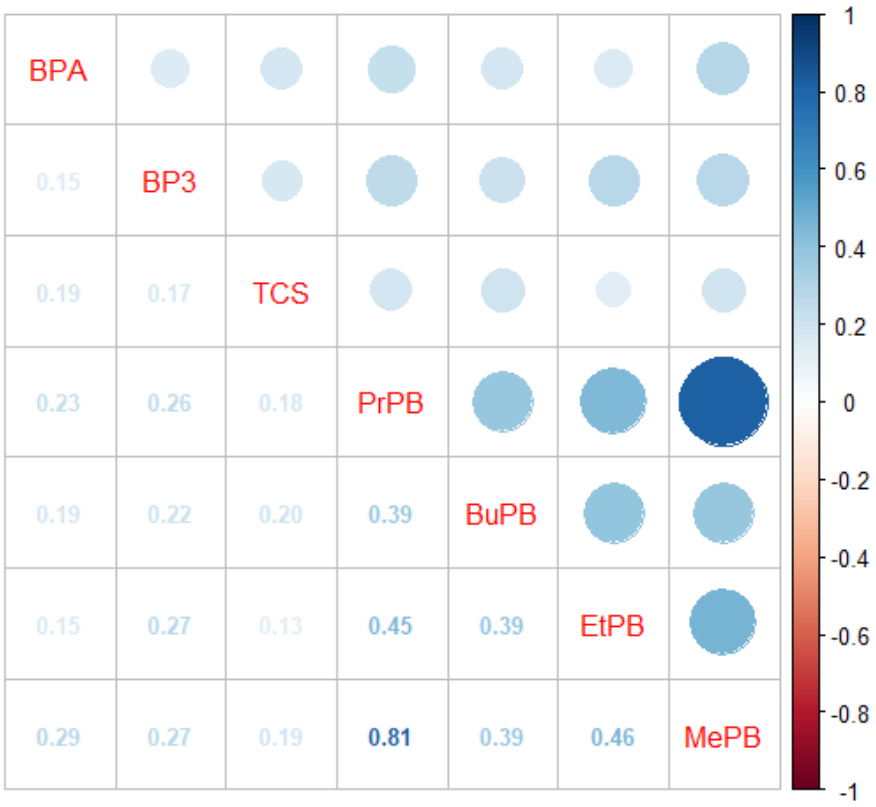

Fig. 2: Spearman correlations between concentrations of urinary chemicals of each other in the study participants (N=4993)

Association between individual exposure chemicals and breast cancer

Table 3 presents the association between individual phenols and parabens and breast cancer using the weighted logistic model. In Model 1, compared to the first quantile of TCS, the incidence of breast cancer for the third and fourth quantiles were 2.34 and 1.78, respectively. The linear model further confirmed the positive association between TCS and breast cancer. Urinary concentration of MePB was positively associated with the incidence of breast cancer in the linear model. No significant associations were found between the other chemicals and breast cancer in Model 1. After adjusting for all potential confounders, the third quantile of TCS remained positively associated with breast cancer, with an OR of 2.12. Meanwhile, PrPB exhibited a negative association with breast cancer, with an OR value of 0.48 for the highest quantile compared to the lowest quantile.

Table 3: The weighted regression model of association between individual chemicals and breast cancer

Chemicals	Q1	Q2		Q3		Q4		Linear model	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BPA									
Model 1	1.00	0.90 (0.60-1.35)	0.609	0.79 (0.42-1.49)	0.470	0.85 (0.45-1.62)	0.626	0.94 (0.80-1.11)	0.486
Model 2	1.00	0.80 (0.48-1.36)	0.418	0.60 (0.26-1.35)	0.221	0.62 (0.28-1.39)	0.253	0.89 (0.75-1.05)	0.164
BP3									
Model 1	1.00	1.25 (0.66-2.37)	0.494	1.38 (0.76-2.51)	0.286	1.55 (0.90-2.69)	0.118	1.07 (0.99-1.16)	0.091
Model 2	1.00	1.23(0.63-2.40)	0.543	1.31(0.67-2.57)	0.436	1.40 (1.79-2.50)	0.256	1.05 (0.97-1.14)	0.205
TCS									
Model 1	1.00	1.25(0.68-2.31)	0.475	2.34 (1.35-4.07)	0.003	1.78 (1.03-3.07)	0.040	1.09 (1.01-1.18)	0.023
Model 2	1.00	1.14(0.62-2.10)	0.679	2.12 (1.23-3.65)	0.008	1.62 (0.93-2.82)	0.092	1.08 (0.99-1.18)	0.846
PrP									
Model 1	1.00	0.94 (0.52-1.72)	0.848	0.68 (0.39-1.16)	0.160	0.60 (0.31-1.17)	0.138	0.95 (0.85-1.06)	0.324
Model 2	1.00	0.93 (0.50-1.72)	0.812	0.60 (0.34-1.07)	0.090	0.48 (0.23-0.98)	0.048	0.91 (0.81-1.03)	0.137
MeP									
Model 1	1.00	0.99 (0.53-1.87)	0.983	0.93(0.49-1.78)	0.832	0.79 (0.38-1.65)	0.530	1.25 (1.03-1.50)	0.023
Model 2	1.00	0.94 (0.49-1.78)	0.841	0.83 (0.43-1.60)	0.579	0.65 (0.31-1.34)	0.248	1.21 (0.99-1.47)	0.055

Model 1 was adjusted for age and race only.
Model 2 accounted for age, race, educational level, marital status, PIR, BMI, alcohol consumption status, smoking status, survey cycle, and urinary creatinine concentrations

Association of all phenols and parabens with breast cancer by WQS regression

The mean weights of each phenol and paraben in the two models are displayed in Fig. 3.

In the positive model, urinary BP3 contributed the most weight to the WQS index (weight = 0.308), whereas in the negative model, MePB accounted for the majority of the WQS index (weight = 0.290). The results of the WQS regression between WQS indices (representing the joint effect of multiple chemicals) and breast cancer are presented in Table 4.

Table 4: Correlations of WQS indices with breast cancer

Model	OR	95% CI	*P*-value
Positive model	1.09	0.65-1.84	0.736
Negative model	0.95	0.57-1.58	0.834

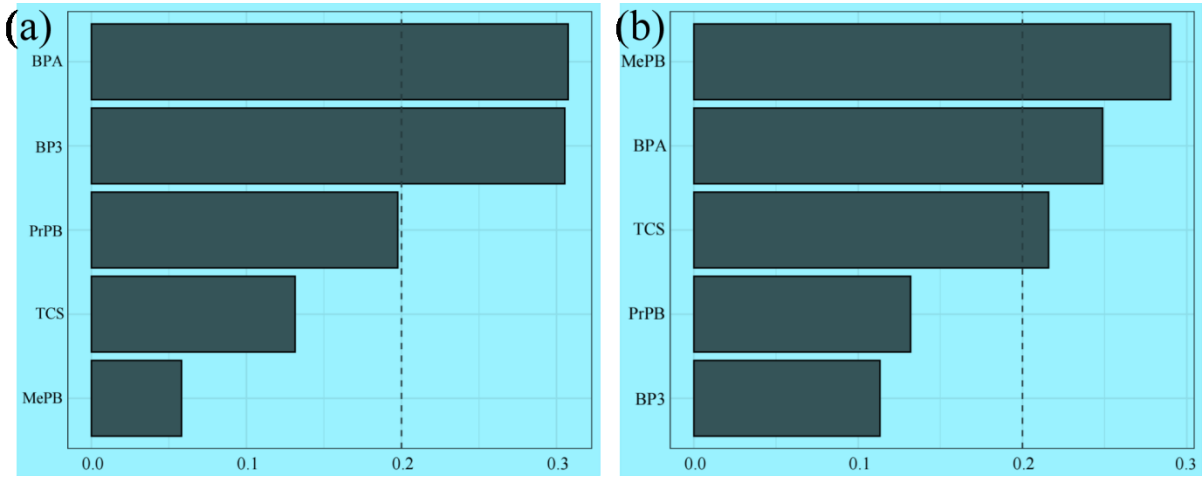

Fig. 3: Mean weights of each chemical in the WQS regression model in both the (a) positive model and (b) negative model. The red line indicates the mean weight was significant

Discussion

The present study investigated the association between urinary concentrations of phenols and parabens and breast cancer among U.S. female adults. Our primary findings indicated that TCS was positively associated with the risk of breast cancer (*P* for Q3 = 0.008), while PrPB demonstrated a negative association with the risk of breast cancer (*P* for Q4 = 0.048). No significant associations were found between co-exposure to multiple chemicals and the risk of breast cancer in both the positive and negative models (*P* = 0.736 and *P* = 0.834).

Our study found a positive association between TCS and breast cancer, consistent with previous research. A case-control study of 302 breast cancer patients also reported a positive link between urinary TCS and breast cancer risk (34). Several biological factors may contribute to exacerbating the toxic effects of TCS exposure on breast cancer. TCS may exacerbate toxic effects on breast cancer through several mechanisms: it can infiltrate human breast tissue and affect breast epithelial cell proliferation and motility (35). Furthermore, TCS has been identified as a xenoestrogen-promoting proliferation and anti-apoptosis in cancer cells (36). Another possible explanation is that oxidative stress and relative telomere length may mediate the adverse effect of TCS on breast cancer (34). Additionally, TCS exposure might affect breast cancer cell growth by altering energy metabolism (37). In conclusion, our findings support the association between TCS and breast cancer, and further research is needed to explore this relationship in greater depth.

Conversely, our study found an inverse association between PrPB and breast cancer among the total study population. Anna et al. also observed that urinary total parabens exhibited an inverse association with the risk of breast cancer (29). However, conflicting findings exist, with some studies suggesting a positive association between paraben exposure and breast cancer. A cohort study of 711 women found positive associations between MePB, PrPB, and total parabens with breast cancer risk, with odds ratios ranging from 1.30 to 1.50 (26). Subsequent research further supported this positive association (27). Parabens are widely recognized as hormone disruptors, and the complex effects of parabens on hormones and their receptors may contribute to breast carcinogenesis (19). The disparities in the carbon chain length of parabens could lead to variations in both toxicity profiles and antiandrogenic activities (38). Consequently, these distinctions may provide a plausible explanation for the differential impacts of PrPB and MePB on breast cancer. Additionally, differences in study populations, regions, and detection methods for chemical sub-

stances could explain the conflicting results. Collectively, there is a wide range of inconsistencies in the current research regarding the relationship between parabens exposure and breast cancer. Although our negative results possess a certain degree of reliability and representativeness, high-quality studies are still needed in the future to further explore this issue.

No significant associations were found between mixed pollutants exposure and breast cancer in this study. The WQS regression model, which integrates the effects of multiple exposures, is known to be more sensitive than single-chemical models (39, 40). Despite the lack of significant results in our study, the WQS model remains a valuable tool for exploring the health impacts of combined chemical exposures. Future research with larger samples could provide further insights into the effects of mixed exposures from personal care products on breast cancer.

Our study has several strengths. Firstly, we utilized NHANES data from 4,993 participants across six survey cycles. NHANES's standardized protocols and quality control enhance the reliability of our results, and the large sample size strengthens the statistical power of our analyses. The nationally representative nature of NHANES makes our findings broadly applicable to the U.S. adult population. Secondly, this study is among the few that explore the association between co-exposure to phenols and parabens and breast cancer, offering new insights. However, there are limitations. The cross-sectional nature of the data prevents causal inference between chemical exposure and breast cancer. Additionally, self-reported breast cancer status may affect accuracy, and future research should rely on clinical diagnoses. Lastly, future studies should consider additional confounders, such as dietary intake and reproductive factors, which might influence the risk of breast cancer related to environmental exposures.

Conclusion

This study suggests a positive association between TCS and breast cancer, and a negative association between PrPB and breast cancer. These results highlight the need to consider phenols and parabens as potential factors influencing breast cancer risk. Further high-quality research is needed to explore the relationship between these chemicals and breast cancer, as well as the underlying mechanisms involved.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The author declares that there is no conflict of interest.

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