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Urinary concentrations of environmental phenols and their associations with breast cancer incidence and mortality following breast cancer

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Abstract

Background: Environmental phenols, compounds used widely in personal care and consumer products, are known endocrine disruptors. Few epidemiologic studies have examined the association of phenol biomarkers with breast cancer incidence and, to our knowledge, none have considered associations with mortality following breast cancer. We examined seven urinary phenol biomarkers in association with breast cancer incidence and subsequent mortality, and examined effect measure modification by body mass index (BMI).

Methods: Participants included 711 women with breast cancer and 598 women without breast cancer who were interviewed for the population-based Long Island Breast Cancer Study Project. Among women with breast cancer, phenol biomarkers were quantified in spot urine samples

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collected on average within three months of a first diagnosis of primary *in situ* or invasive breast cancer in 1996-1997. Women with breast cancer were monitored for vital status using the National Death Index. After a median follow-up of 17.6 years, we identified 271 deaths, including 98 deaths from breast cancer. We examined creatinine-corrected phenol concentrations and the sum of parabens (Σparabens) in association with breast cancer incidence using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs), and with mortality using Cox regression to estimate hazard ratios (HRs) and 95% CIs. We evaluated multiplicative effect measure modification using cross-product terms in nested models.

Results: The highest (vs lowest) quintiles of urinary methylparaben, propylparaben, and Σparabens were associated with risk of breast cancer with ORs ranging from 1.31-1.50. Methylparaben, propylparaben, and Σparabens were also associated with all-cause mortality HRs ranging from 0.68-0.77. Associations for breast cancer incidence were more pronounced among women with BMI<25.0 kg/m^2 than among women with BMI≥25.0 kg/m^2; however, associations for mortality were more pronounced among women with BMI≥25 kg/m^2 than among women with BMI<25 kg/m^2.

Conclusions: Select parabens may have differential associations with risk of developing breast cancer and mortality following breast cancer.

Keywords

Breast cancer; environmental phenols; incidence; mortality; personal care products; parabens; BPA; triclosan

Introduction

Environmental and behavioral factors may play a role in the development of breast cancer,[1] the most frequently diagnosed cancer and the second-leading cause of cancer-related death among women in the United States (US).[2] Epidemiologic studies of environmental chemical exposures and breast cancer risk or mortality following breast cancer have focused primarily on associations with legacy persistent organic pollutants (POPs) and polycyclic aromatic hydrocarbons.[3-9] The role of other chemicals, including environmental phenols, on breast cancer risk and prognosis has received little scientific attention.[10] Although less environmentally and biologically persistent than the POPs,[11,12] as estrogen mimics, some environmental phenols may initiate or promote breast carcinogenesis.[13,14]

Many phenols are naturally occurring byproducts of plants and microorganisms; however, others are industrially synthesized for use in personal care and consumer products and pharmaceuticals.[15,16] The chemical 2,5-dichlorophenol, for example, is a metabolite of *p*-dichlorobenzene, a putative carcinogen and potent allergen used in mothballs and bathroom deodorizers.[17,18] Other synthetic chemicals in this class include bisphenol A (BPA), which is used in the production of plastics and food and beverage storage containers,[19] benzophenone-3, an ultraviolet (UV) filter and the active ingredient in many sunscreen lotions and cosmetics,[20] triclosan, a broad spectrum antibacterial agent added to soaps, toothpastes, and underarm deodorants,[21] and parabens, a group of alkyl esters of *p*-

hydroxybenzoic acid, which are used as preservatives in cosmetics and topical pharmaceutical preparations.[13,22]

Because environmental phenols or their precursors are commonly found in a wide range of conventional personal care and consumer products and may be found in "alternative" products that do not list specific chemical ingredients on the label,[23] human exposure may occur via oral, dermal, and inhalation routes,[14] with dermal exposures of greatest concern due to prolonged exposure and potential for migration into the bloodstream.[22] In the body, environmental phenols are quickly conjugated and excreted in urine; however, habitual use of personal care products results in continuous exposure. Quantification of environmental phenols in urine rather than in blood in which phenol concentrations may be ~50 times lower,[24] is therefore the preferred and most common and reliable method for assessing exposure in biomonitoring and epidemiologic studies,[25,26] which readily detect these chemical biomarkers.[27-32] Furthermore, some phenols are detected in human breast milk, [25,30,33-36] albeit at lower concentrations, suggesting their passage through breast epithelial cells.[37]

Few epidemiologic studies have examined environmental phenol sources of exposure or phenol biomarkers and breast cancer incidence[38-42] and, to our knowledge, no studies have examined whether urinary phenol biomarkers are associated with mortality following breast cancer. Herein, we examined the associations between seven select urinary environmental phenols and breast cancer incidence and subsequent mortality among participants in a population-based study of breast cancer conducted in the USA.

Methods

We used the case-control[43] and follow-up[44] resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of breast cancer which included 1,508 women with a first diagnosis of *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997 and 1,556 women without breast cancer (see Table 1 for descriptive characteristics of the LIBCSP participants). Institutional Review Board approval was obtained from all participating institutions and written informed consent was obtained prior to study participation. The analysis of blinded specimens by the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute any engagement in human subjects' research.

Case-Control Design

The case-control design of this LIBCSP ancillary study included 711 of the 1,508 women with breast cancer and 598 of the 1,556 women without breast cancer who had available data on urinary phenol metabolites and creatinine. The women with breast cancer were adult residents of Nassau and Suffolk Counties on Long Island, NY, with newly diagnosed breast cancer and were identified using rapid-case ascertainment, which involved active daily or weekly contact with local hospitals with confirmation by physicians and medical records, as previously reported.[43] Women without breast cancer were residents of the same two Long Island counties who were identified by Health Care Finance Administration rosters for those 65 years of age and older, and by random digit dialing for those under age 65, and were

frequency-matched to the expected distribution of women with breast cancer in 5-year age groups in 1996-1997. After providing written informed consent, the women with breast cancer, on average within three months of their breast cancer diagnoses, and the women without breast cancer were interviewed at home by trained interviewers using a structured questionnaire. At the time of the interview, 93% of women with breast cancer and 83% of women without breast cancer donated 25 mL spot urine for laboratory analyses. For the women with breast cancer, 79.1% of urine samples were collected prior to the initiation of chemotherapy.

Follow-up Design

The follow-up design of this LIBCSP ancillary study included 711 the 1,508 women with breast cancer with available data on urinary phenols and creatinine. These women with breast cancer were monitored for vital status using the National Death Index (NDI), a centralized database of death record information compiled from state vital statistics offices.[45] Women with breast cancer were followed-up from the time of diagnosis in 1996/1997 through December 31, 2014 to determine the date and cause of death, including death from breast cancer, identified using International Classification of Death codes 174.9 and C-50.9 listed on the death certificate.[44] Over a median follow-up of 17.6 years (range=0.4-18.4), we identified 271 deaths, including 98 from breast cancer, among the 711 women with breast cancer included here.

Quantification of urinary phenol concentrations

Details of the urine sample collection, processing, storage, and biomarker assays have been previously published.[44] In brief, stored samples were shipped overnight on dry ice from Columbia University to the National Center for Environmental Health at the CDC in two batches in 2007 and 2010. The first was batch analyzed in 2007, and included a random sample of 400 women with invasive breast cancer and 400 women without breast cancer from among those with available urine. The second batch was analyzed in 2010 and included 493 women with *in situ* disease or invasive breast cancer who had an available tumor specimen and had not been previously selected and 250 women without breast cancer randomly selected whose urine had not been previously analyzed.

At the CDC, using online solid phase extraction followed by high performance liquid chromatography-isotope dilution tandem mass spectrometry, samples were analyzed for the following seven environmental phenols: 2,5-dichlorophenol, benzophenone-3, BPA, methylparaben, propylparaben, butylparaben, and triclosan. Detection frequencies were >90% for 2,5 dichlorophenol, benzophenone-3, methylparaben, and propylparaben. BPA was detected in 82% of women. Butylparaben and triclosan were detected in 50% and 51% of women, respectively (Table 2). The coefficients of variation (SD/mean concentration) for the individual biomarkers based on masked quality control specimens (3% and 2% in batches 1 and 2, respectively; total n=34) from a single urine pool in all analysis batches ranged between 0.0% and 9.3% (median=2.9%) in both batches. The limits of detection (LODs) ranged from 0.2-2.3 μg/L (Table 2). Values below the LOD were imputed as the LOD divided by the square root of two.[46] To correct for urine dilution, concentrations (μg/L) were divided by creatinine for final units of micrograms per gram (μg/g) creatinine. After

excluding 234 women with missing creatinine (n=224) or with dilute urine as assessed by creatinine <10 mg/dL (n=10), the final analytic sample for this ancillary study comprised 711 women with breast cancer, including 112 women with *in situ* disease and 599 women with invasive breast cancer, and 598 women without breast cancer.

Other Covariates

Potential confounders of the associations between environmental phenols and breast cancer incidence and mortality were identified based on previous epidemiologic studies of breast cancer.[47,48] Characteristics assessed during the in-person interview included: demographics [age (continuous), income (<$24,999, $25,000-$49,999, ≥$50,000), education (<high school/high school graduate, college, post-college)]; reproductive factors [menopausal status (pre-, postmenopausal), age at menarche (≤12, >12 years), and parity and lactation history (nulliparous, parous/never lactated, parous/ever lactated)]; medical-related factors [family history of breast cancer (none or at least one first degree relative), pre-chemotherapy biospecimen collection (yes, no); exogenous hormone use [contraceptive use (ever, never), hormone replacement therapy use (ever, never)]; and lifestyle/behavioral factors [body mass index (BMI) in the year prior to diagnosis and at age 20 (<25.0, 25.0-29.9, ≥30.0 kg/m^2), and percent weight change since age 20 (weight loss and 0-19%, 20-39%, and ≥40% weight gain) and lifetime alcohol intake (non-drinkers, <15, 15-29, ≥30 grams per day)]. Estrogen receptor (ER) status of the first primary breast cancer was assessed by review of the medical record.

Statistical Analysis

In addition to examining the phenols individually, we combined the three parabens into a molar sum (Σparabens), computed as the creatinine-corrected molar sum of methylparaben, propylparaben, and butylparaben, and expressed as methylparaben, molecular weight 152. We categorized creatinine-corrected phenol concentrations of 2,5-dichlorophenol, benzophenone-3, BPA, methylparaben, propylparaben, and Σparabens into quintiles for use in primary analyses and tertiles for use in secondary analyses of effect measure modification. We categorized phenol concentrations based on the distributions in the women without breast cancer. Because butylparaben and triclosan were only detected in approximately half of the women, we categorized women with non-detectable concentrations into the lowest exposure group and women with detectable concentrations into quantiles based on the distributions in the women without breast cancer.

Prior to the case-control and follow-up analyses, we examined associations between urinary phenol biomarkers and the other covariates among women without breast cancer. We first examined Spearman correlations (ρ_s) between creatinine-corrected phenol concentrations and continuous covariates, and chi-square tests between quintiles of creatinine-corrected phenol concentrations and categorical covariates. Second, among the women with breast cancer, using generalized linear models, we regressed each of the phenol biomarkers on age and receipt of chemotherapy or hormone therapy treatments prior to urine sample collection separately to determine the impact of treatment on urinary phenol concentrations. Third, we compared age-adjusted means of ln-transformed creatinine-corrected urinary phenol

concentrations by tumor and treatment characteristics among the women with breast cancer to examine associations between phenols and breast tumor and treatment characteristics.

Case-Control Analyses

We compared continuous uncorrected and creatinine-corrected phenol concentrations between women with and without breast cancer using Wilcoxon rank-sum tests. Next, we examined multivariable associations between quintiles or quantiles (for butylparaben and triclosan) of creatinine-corrected phenol concentrations as well as ln-transformed concentrations and breast cancer incidence using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Logistic regression models were adjusted for the frequency matching factor, age (i.e., age-adjusted models), as well as other covariates that were statistically significantly correlated ($P<0.05$) with any of the phenols (i.e., multivariable-adjusted models).

In secondary analyses, using tertiles or quantiles (for butylparaben and triclosan) of creatinine-corrected phenol concentrations, we examined effect measure modification by BMI (<25.0 kg/m^2 vs ≥ 25.0 kg/m^2) by conducting BMI-stratified covariate-adjusted logistic regression analyses. We evaluated effect measure modification on the multiplicative scale by comparing the log-likelihood statistics from nested models with and without continuous cross-product terms for BMI and ln-transformed creatinine-corrected phenol concentrations.

Case-control analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Follow-up Analyses

We used Kaplan-Meier survival curves to examine the unadjusted associations between urinary phenol concentrations and all-cause and breast cancer-specific mortality up to 18 years following diagnosis. We examined the proportional hazards assumption by Schoenfeld residuals;[49] no violations of the proportional hazards assumption were evident. Next, using Cox regression to estimate hazard ratios (HRs) and 95% CIs, we examined age-adjusted and multivariable-adjusted associations between quintiles or quantiles (for butylparaben and triclosan) of ln-transformed urinary phenol concentrations and mortality.

In secondary analyses, using tertiles or quantiles (for butylparaben and triclosan) of creatinine-corrected phenol concentrations, we examined effect measure modification by BMI (<25.0 kg/m^2 vs ≥ 25.0 kg/m^2) by conducting BMI-stratified covariate-adjusted Cox regression analyses. Effect measure modification on the multiplicative scale was evaluated by comparing the log-likelihood statistics from nested models with and without continuous cross-product terms for BMI and ln-transformed creatinine-corrected phenol concentrations.

Follow-up analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Most women in the ancillary study reported here were postmenopausal (65.4%), self-identified as Caucasian (93.0%), and ranged in age from 22-96 years at reference, consistent

with the characteristics of the full sample of participants from the LIBCSP (Table 1). The mean age at diagnosis among the women with breast cancer was 59.0 years (SD=12.8). Among women with breast cancer, the median (interquartile range, IQR) creatinine was 76.4 (43.1-122.2) mg/dL and among women without breast cancer, the median (IQR) creatinine was 71.2 (42.1-120.7) mg/dL

Among women without breast cancer, Spearman correlations between urinary creatinine-corrected phenol concentrations and continuous covariates were generally weak, with the strongest correlations between 2,5-dichlorophenol and age at reference (ρ_s=0.23, P<0.01), butylparaben and age at menopause (ρ_s=0.18, *P*<0.01), and methylparabern and propylparaben and BMI at reference (both ρ_s=−0.16, *P*<0.01) (eTable S1). All phenols were associated with one or more covariate (all chi-square *P*<0.05), except oral contraceptive use and parity/lactation history (eTable S2). Among women with breast cancer, there were no differences in phenols concentrations by receipt of chemotherapy treatment or receipt of hormone therapy treatment prior to urine sample collection (all *P*>0.05) (eTable S3). Furthermore, among women with breast cancer, ln-transformed creatinine-corrected urinary phenol concentrations (μg/g creatinine) did not vary by tumor or treatment characteristics (eTable S4).

Case-Control Results

Among women without breast cancer, creatinine-corrected urinary phenol concentrations were highest for methylparaben (median=150 μg/g creatinine) and propylparaben (median=34.8 μg/g creatinine) while the lowest concentrations were for BPA (median=1.69 μg/g creatinine) and butylparaben (median=0.551 μg/g creatinine) (Table 2). Compared to women without breast cancer, women with breast cancer had higher median concentrations of methylparaben (160 vs. 150 μg/g creatinine) and propylparaben (median=39.9 vs. 34.8 μg/g creatinine); however, there were no statistically significant differences in the sample rankings based on Wilcoxon rank sum tests.

The associations between urinary phenol concentrations and breast cancer incidence are presented in Table 3. Among all women, the highest (vs lowest) quintiles of methylparaben, propylparaben, and Σparabens were associated with breast cancer ORs of 1.50 (95%CI=1.03-2.18), 1.31 (95%CI=0.90-1.90), and 1.35 (95%CI=0.93-1.97), respectively. Additionally, one ln-unit increases in methylparaben, propylparaben, and the Σparabens were associated with breast cancer ORs of 1.09 (95%CI=1.00-1.18), 1.06 (95%CI=1.00-1.13), and 1.09 (95%CI=1.00-1.18), respectively. There was little or no association between the remaining phenol biomarkers and breast cancer incidence.

Results of effect measure modification by BMI are presented in Table 4. Among women with BMI<25.0 kg/m^2, the highest (vs. lowest) tertiles of methylparaben, propylparaben, and the Σparabens were associated with breast cancer ORs of 1.47 (95%CI=0.95-2.25), 1.52 (95%CI=0.98-2.34), and 1.55 (95%CI=1.01-2.37), respectively, but not among women with BMI≥25.0 kg/m^2. Furthermore, among women with BMI<25.0 kg/m^2, one ln-unit increases in methylparaben, propylparaben, and Σparabens were associated with ORs of 1.13 (1.00-1.28), 1.12 (95%CI=1.02-1.24), and 1.13 (95%CI=0.99-1.27), respectively, but not among women with BMI≥25.0 kg/m^2.

Follow-up Results

From the Kaplan-Meier survival curves Figure 1, the highest (vs. lowest) quintiles of benzophenone-3, triclosan, methylparaben, propylparaben, butylparaben, and Σparabens were associated with lower all-cause mortality. Furthermore, the highest (vs. lowest) quintiles of 2,5-dichlorophenol, benzophenone-3, methylparaben, propylparaben, butylparaben, and Σparabens were associated with lower breast cancer-specific mortality (eFigure S1).

In multivariable-adjusted Cox models, the highest (vs. lowest) quintiles of methylparaben, propylparaben, butylparaben, and Σparabens were associated with all-cause mortality HRs of 0.71 (95%CI=0.48-1.05), 0.77 (95%CI=0.52-1.13), and 0.73 (95%CI=0.51-1.05), and 0.68 (95%CI=0.46-1.00) (Table 5). Additionally, one ln-unit increases of methylparaben, propylparaben, and Σparabens were associated with all-cause mortality HRs of 0.92 (95%CI=0.85-1.00), 0.93 (95%CI=0.87-0.99), and 0.92 (95%CI=0.85-1.00), respectively. The highest (vs. lowest) quintiles of benzophenone-3 and Σparabens were associated with breast cancer-specific mortality HRs of 0.52 (95%CI=0.25-1.08) and 0.74 (95%CI=0.39-1.42), respectively.

Results of effect measure modification by BMI for all-cause and breast cancer-specific mortality are presented in Table 6 and Table 7, respectively. Among women with BMI≥25.0 kg/m^2, the highest (vs. lowest) tertiles of triclosan, methylparaben, propylparaben, butylparaben, and Σparabens were associated with all-cause mortality HRs of 0.75 (95%CI=0.51-1.11), 0.74 (95%CI=0.50-1.09), 0.62 (95%CI=0.42-0.92), 0.64 (95%CI=0.42-0.99), and 0.70 (95%CI=0.47-1.03), respectively, but not among women with BMI<25.0 kg/m^2.

Discussion

In this study of urinary phenol biomarkers and breast cancer incidence and mortality, we observed 30-50% higher odds of developing breast cancer among women with the highest (vs. lowest) quintiles of parabens and these associations were more pronounced among women with BMI<25.0 kg/m^2 than among women with BMI≥25.0 kg/m^2. For mortality following breast cancer, we observed inverse associations between parabens and all-cause mortality, and contrary to our case-control results, associations were more pronounced among women with BMI≥25.0 kg/m^2 than among women with BMI<25.0 kg/m^2. While the confidence intervals were imprecise and included the null, the highest (vs. lowest) quintiles of benzophenone-3 and the parabens were inversely associated with breast cancer-specific mortality.

Few studies have examined associations between the use of personal care products and breast cancer development and, to our knowledge, no studies have considered mortality following breast cancer. Of the personal care products that have been examined in association with breast cancer incidence, particular attention has been placed on the association between deodorant use, a source of exposure to parabens and other chemicals,[13] due to observations of an increasing incidence of tumors in the upper, outer quadrant of the breast directly adjacent to the area of the breast where deodorants are applied.[50] Even so,

studies examining deodorant use and breast cancer development are limited. A recent review[38] identified two studies, one of which reported an inverse association,[51] and the other a small increase in risk of breast cancer development,[52] in association with deodorant use. Additionally, a recently published hospital-based case-control study reported an increase in breast cancer risk in association with use of underarm cosmetic products several times per day when women were under the age of 30.[42] However, the authors hypothesized that the association was due to the aluminum-based compounds found in the underarm cosmetic products.[42] Last, a study examining patterns of personal care product use reported an increased risk of breast cancer among frequent users of beauty and skincare products relative to infrequent users.[39]

At least two studies outside of the USA have examined biomarkers of BPA exposure in association with breast cancer development. The first, a small case-control study of Korean women (82 cases and 70 controls) reported higher serum BPA concentrations among cases compared to controls (median=0.61 vs. median=0.03 μg/L).[41] Measurement of BPA in serum, however, is likely unreliable for reasons of pharmacokinetics and external contamination,[26] and so results may not be directly comparable to the findings reported here. The second, a case-control study of Polish women (575 cases and 575 controls), reported an increase in postmenopausal breast cancer odds among women in the second quartile of urinary BPA (OR=1.70, 95% CI=0.91-1.17), but not for the third (OR=1.02, 95% CI=0.67-1.55) and fourth (OR=1.09, 95% CI=0.73-1.63) quartiles, compared to the first quartile.[40] These results are contrary to our findings reported here of a suggestive inverse association between BPA and breast cancer incidence. Differences in the distributions of BPA urinary concentrations, which were much lower in our study than in the study by Trabert et al., may be one reason for the discrepant findings. To our knowledge, no studies have examined 2,5-dichlorophenol, benzophenone-3, parabens, and triclosan in association with breast cancer development. Although previous studies reported an association between 2,5-dichlorophenol and earlier menarche in girls, which is known to increase a woman's risk of breast cancer,[53] in our study, we did not observe a positive association between urinary 2,5-dichlorophenol and breast cancer incidence.

Many environmental phenols are known endocrine disruptors,[14,54] and are thus biologically plausible breast carcinogens. Parabens are weakly estrogenic and increase ER-α and ER-β mRNA and protein expression and expression of the aromatase gene, inducing proliferation of MCF-7 human breast cancer cells and MCF-10A non-transformed breast epithelial cells *in vitro*.[37,55-57] Butylparaben has been shown to increase *c-Myc* RNA expression and ER-α-mediated breast cancer cell proliferation in human epidermal growth factor receptor (HER)-2 overexpressing BT-474 cells, synergistically in the presence of the HER ligand heregulin.[58] *In vivo*, parabens cause uterotrophic activity and up-regulate estrogen-responsive genes in the uteri of immature Sprague-Dawley rats at human exposure levels.[59] Although, estrogen-mediated mechanisms may be most relevant to breast carcinogenesis, parabens may also play a role in breast carcinogenesis through non-estrogen mediated mechanisms.[13] Propylparaben, for example, has been associated with the inhibition of apoptosis in MCF-7 breast cancer cells through the activation of PI3K/Akt pathway, measured as Akt phosphorylation,[60]

In this study, we report inverse associations between urinary parabens and all-cause mortality among a sample of women with breast cancer. The biological mechanisms by which parabens may be inversely associated mortality are unclear and require further investigation. However, two potential causal explanations are plausible. First, parabens have been shown to be peroxisome proliferator-activated receptor (PPAR) agonists,[61-63] which may result in anti-inflammatory effects through the inhibition of pro-inflammatory cytokines.[64] Second, parabens have also been shown to shown to exert anti-androgenic activity. In a cell-based study, at the highest concentrations tested, methyl-, butyl-, and propylparaben inhibited the transcriptional activity of testosterone.[65] High bioavailable testosterone levels have been associated with metabolic syndrome or its components in cross-sectional studies[66] and with greater risk of incident type 2 diabetes[67] and coronary heart disease events in prospective studies.[68,69] Thus, inhibition of testosterone by parabens may result in favorable mortality outcomes. Future studies should work to replicate our findings among a population-based sample of women without breast cancer in order to elucidate these associations.

Our BMI-stratified results suggest that exposure to phenols or their precursors and BMI may interact to increase the risk of breast cancer development. In postmenopausal women, with cessation of estrogen synthesis in the ovaries, the major pathway of estrogen production becomes the conversion of androstenedione into estrone in adipose tissue.[70,71] Additionally, postmenopausal obese women may have a higher proportion of bioavailable estrogen and testosterone due to lower levels of SHBG [72,73] Estrogens are well known breast carcinogens[74] and so it is conceivable that phenols may promote estrogen-initiated breast cancer, or that phenols may alter body weight,[75] thus impacting breast cancer risk. Additional research into the potential interactions between endocrine disrupting chemicals, obesity, and breast cancer is needed.

The strengths of our study include the large sample size and the use of biological samples from a population-based case-control study of breast cancer; however, this study had several limitations. First, among women with breast cancer, urine samples were collected after breast cancer diagnosis, but before initiation of chemotherapy for most participants. At-diagnosis phenol urinary concentrations may not reflect the etiologically relevant time period for breast cancer, which is hypothesized to be decades years prior to disease diagnosis for environmental pollutants;[1] however, because environmental phenols are estrogen mimics, concentrations measured shortly after diagnosis may be relevant to breast cancer progression as well as mortality following breast cancer. Furthermore, breast cancer or its treatments may impact phenol concentrations or women may alter their patterns of personal care product use after diagnosis. However, we observed higher concentrations of parabens among women with breast cancer compared to women without breast cancer and did not observe associations between chemotherapy treatment and phenol concentrations. It is unlikely women with breast cancer would increase their use of personal care products if they believed it was associated with their breast cancer diagnosis. Additionally, women with breast cancer were diagnosed in the mid- 1990s, before the onset of widespread public concern about endocrine disrupting chemicals in personal care products. Therefore, it is highly unlikely that women specifically changed their behavior with the intention of altering their chemical exposures. However, the hospital or medical settings could potentially be a source of

exposure to environmental phenols including those chemicals used in cleaning products such as antimicrobials,[23] which could result in higher biomarker levels among women with breast cancer as compared to women without breast cancer, potentially biasing our results. Additionally, we compared environmental phenol concentrations by receipt of chemotherapy treatment, but we did not consider specific chemotherapy regimens, and thus potential differences by chemotherapy type may have been masked. However, chemotherapy treatment at the time of the LIBCSP in the-mid-1990s was generally uniform consisting primarily of cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide and doxorubicin.[76] Second, some phenols show fair to good reproducibility over weeks or months, with intraclass correlations (ICCs) of 0.50-0.61 for 2,5-dichlorophenol, 0.62 for benzophenone-3, 0.42-0.61 for methylparaben, 0.32-0.55 for propylparaben, and 0.47-.058 for triclosan, but BPA shows poor reproducibility (ICC=0.24-0.27).[77-80] The fair reproducibility of most of these biomarkers suggests that concentrations from a single spot urine sample may allow for the moderately reliable ranking of women's exposure, but additional studies are needed that examine the ICCs over longer time periods. This may be especially relevant to our follow-up analyses that considered a single urinary measurement of phenol biomarkers in association with mortality up to 18 years following breast cancer diagnosis. Third, we included a subsample of the population-based LIBCSP sample. Although we observed little difference between the women included in this ancillary study and the parent LIBCSP, there remains a small potential for selection bias. Furthermore, as NHANES did not begin urinary biomonitoring of most of the environmental phenols we considered here until 2005-2006, we do not know whether the levels reported here are reflective of the general population at the time of participant enrollment into the LIBCSP in 1996-1997. Thus, the generalizability of our findings may be limited. Last, we cannot fully rule out residual and unmeasured confounding as a source of bias in this observational study. However, we examined a comprehensive list of covariates as potential confounders.

Conclusion

The results of our study support a hypothesized positive association between exposure to parabens and breast carcinogenesis. However, select parabens may have differential associations with the risk of developing breast cancer and mortality following breast cancer. Our results are consistent with laboratory evidence and thus biologically plausible; however, our findings should be interpreted with caution given that biospecimens were spot urine samples and collection among the women with breast cancer occurred after their diagnosis. Confirmation of our case-control results with a prospective study design is warranted, but if confirmed, our findings have implications about the widespread use of these chemicals in personal care and consumer products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Select parabens were associated with 30-50% higher odds of breast cancer
- BC incidence associations were more pronounced among women with low versus high BMI
- Select parabens were inversely associated with all-cause mortality
- Mortality associations were more pronounced among women with high versus low BMI

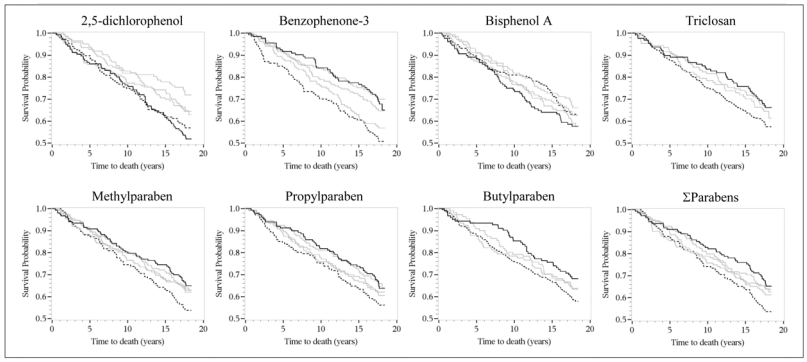

Figure 1.

Kaplan–Meier survival curves for all-cause mortality and creatinine-adjusted quintiles (Quintile 5, solid line vs. Quintile 1, dashed line) of urinary environmental phenols among LIBCSP women diagnosed with breast cancer in 1996–1997 (n=711). The x-axis shows times to death in years; the y-axis shows proportion of participants alive.

Table 1.

Distribution of select characteristics among the LIBCSP women by breast cancer status, comparing the ancillary study sample with available values of urinary concentrations of creatinine-corrected phenols and the parent-study sample.

	Women with Breast Cancer		Women without Breast Cancer	
	Phenols Sample (*n*=711)	Parent Study Sample (*n*=1,508)	Phenols Sample (*n*=598)	Parent Study Sample (*n*=1,556)
Age at reference (years)				
<50	196 (27.6%)	407 (27.0%)	197 (32.9%)	499 (32.1%)
50–64	259 (36.4%)	582 (38.6%)	250 (41.8%)	617 (39.7%)
≥65	256 (36.0%)	519 (34.4%)	151 (25.2%)	440 (28.3%)
Income				
<$24,999	154 (21.7%)	286 (19.0%)	104 (17.4%)	295 (19.0%)
$25,000–$49,999	227 (32.0%)	488 (32.4%)	172 (28.8%)	475 (30.6%)
≥$50,000	328 (46.3%)	730 (48.5%)	321 (53.8%)	784 (50.5%)
Missing	2	4	1	2
Education				
<HS/HS graduate	340 (47.9%)	721 (48.0%)	240 (40.2%)	676 (43.6%)
College	261 (36.8%)	551 (36.7%)	263 (44.0%)	651 (41.9%)
Post-college	109 (15.3%)	230 (15.3%)	94 (15.8%)	225 (14.5%)
Missing	1	6	1	4
Menopausal status				
Premenopausal	226 (32.6%)	472 (31.9%)	211 (37.1%)	503 (33.7%)
Postmenopausal	468 (67.4%)	1,006 (68.1%)	357 (62.9%)	990 (66.3%)
Missing	17	30	30	63
HRT use				
Never	506 (71.3%)	1,096 (72.9%)	439 (73.4%)	1,159 (74.5%)
Ever	204 (28.7%)	408 (27.1%)	159 (26.6%)	396 (25.5%)
Missing	1	4	0	1
Age at menarche (years)				
≤12	311 (44.1%)	658 (44.0%)	274 (46.0%)	677 (43.8%)
>12	394 (55.9%)	837 (56.0%)	321 (54.0%)	870 (56.2%)
Missing	6	13	3	9
Oral Contraceptive use				
Never	406 (57.2%)	848 (56.3%)	304 (50.8%)	840 (54.0%)
Ever	304 (42.8%)	657 (43.7%)	294 (49.2%)	715 (46.0%)
Missing	1	3	0	1
Parity/lactation history				
Nulliparous	92 (12.9%)	198 (13.1%)	70 (11.7%)	171 (11.0%)
Parous/never lactated	375 (52.7%)	830 (55.0%)	302 (50.5%)	832 (53.5%)
Parous/ever lactated	244 (34.3%)	480 (31.8%)	226 (37.8%)	553 (35.5%)
Family history of breast cancer				

	Women with Breast Cancer		Women without Breast Cancer	
	Phenols Sample (*n*=711)	**Parent Study Sample (*n*=1,508)**	**Phenols Sample (*n*=598)**	**Parent Study Sample (*n*=1,556)**
None	564 (82.1%)	1,166 (79.8%)	498 (84.7%)	1,321 (87.0%)
First degree	123 (17.9%)	295 (20.2%)	90 (15.3%)	197 (13.0%)
Missing	24	47	10	38
BMI at reference (kg/m^2)				
<25.0	316 (44.6%)	683 (45.8%)	309 (52.2%)	750 (49.1%)
25.0-29.9	220 (31.0%)	476 (31.9%)	160 (27.0%)	455 (29.8%)
≥30.0	173 (24.4%)	332 (22.3%)	123 (20.8%)	323 (21.1%)
Missing	2	17	6	28
BMI at age 20 (kg/m^2)				
<25.0	653 (93.0%)	1,377 (93.0%)	534 (90.2%)	1,397 (91.2%)
≥25.0	49 (7.0%)	103 (7.0%)	58 (9.8%)	135 (8.8%)
Missing	9	28	6	24
Lifetime alcohol intake (g/day)				
Non-drinkers	263 (37.0%)	598 (39.7%)	225 (37.7%)	605 (39.0%)
<15	339 (47.7%)	691 (45.8%)	289 (48.4%)	735 (47.3%)
15-29	71 (10.0%	147 (9.7%)	48 (8.0%)	119 (7.7%)
≥30	38 (5.3%)	72 (4.8%)	35 (5.3%)	94 (6.1%)
Stage				
In situ	112 (15.8%)	235 (15.6%)	–	–
Invasive	599 (84.2%)	1,273 (84.4%)	–	–
Tumor size				
≤2cm	279 (73.6%)	622 (75.5%)	–	–
>2cm	100 (26.4%)	202 (24.5%)	–	–
Missing	332	684	–	–
ER status				
Negative	115 (23.8%)	264 (26.7%)	–	–
Positive	368 (76.2%)	726 (73.3%)	–	–
Missing	228	518	–	–
Radiation therapy				
No	192 (38.4%)	401 (39.1%)	–	–
Yes	308 (61.6%)	625 (60.9%)	–	–
Missing	211	482	–	–
Chemotherapy				
No	297 (59.6%)	599 (58.6%)	–	–
Yes	201 (40.4%)	423 (41.4%)	–	–
Missing	213	486	–	–
Hormone therapy				
No	188 (38.1%)	393 (39.0%)	–	–
Yes	306 (61.9%)	616 (61.0%)	–	–
Missing	217	499	–	–

Long Island Breast Cancer Study Project (LIBCSP) population-based women without breast cancer were frequency matched by age to women diagnosed with breast cancer between August 1, 1996 and July 31, 1997.

Table 2.

Distribution of urinary biomarker concentrations among the ancillary study sample of LIBCSP women.

Biomarker	LOD	n (%) <LOD	Median uncorrected urinary concentrations (µg/L)[a]			Median creatinine-corrected urinary concentrations (µg/g creatinine)[a]		
			With Breast Cancer (n=893)	No Breast Cancer (n=650)	*P*[b]	With Breast Cancer (n=711)	No Breast Cancer (n=598)	*P*[b]
2,5-dichlorophenol	0.2	3 (0.2)	7.50	8.30	0.55	9.95	10.4	0.26
Benzophenone-3	0.4	115 (7.5)	8.60	10.1	0.39	11.5	11.9	0.40
Bisphenol A	0.4	282 (18.3)	1.20	1.30	0.41	1.53	1.69	0.13
Triclosan	2.3	759 (49.2)	2.40	2.40	0.52	5.18	5.77	0.64
Methylparaben	1.0	7 (0.5)	104	100	0.24	160	150	0.37
Propylparaben	0.2	35 (2.3)	25.6	22.4	0.13	39.9	34.8	0.36
Butylparaben	0.2	779 (50.5)	<LOD	0.200	0.31	0.440	0.551	0.06
Creatinine						76.4	71.2	0.57

Long Island Breast Cancer Study Project (LIBCSP) population-based women without breast cancer were frequency matched by age to women diagnosed with breast cancer between August 1, 1996 and July 31, 1997.

LOD, limit of detection (in µg/L)

[a] Values <LOD were imputed as LOD/√2.

[b] *P*-value for Wilcoxon rank-sum test.

Table 3.

Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between urinary phenol concentrations (μg/g creatinine) and breast cancer incidence among the ancillary study sample of LIBCSP women (n=1,309).

Biomarker (μg/g creatinine)	Median in Women without Breast Cancer	Breast Cancer/ No Breast Cancer	Age-Adjusted	Multivariable-Adjusted[a]	
			OR (95% CI)	OR (95% CI)	P_{Trend}
2,5-dichlorophenol					
0.648-4.28	3.03	147/119	1.00	1.00	
4.30-7.62	5.93	163120	1.07 (0.76-1.50)	1.20 (0.84-1.72)	
7.63-14.9	10.4	122/120	0.81 (0.57-1.16)	0.86 (0.59-1.25)	
15.1-45.0	24.1	143120	0.92 (0.65-1.30)	0.95 (0.66-1.37)	
46.0-9,159	171	136/119	0.81 (0.57-1.15)	0.92 (0.63-1.33)	
Ln(2,5-dichlorophenol)			0.93 (0.86-0.99)	0.94 (0.87-1.00)	0.06
Benzophenone-3					
<LOD-2.13	1.11	147/119	1.00	1.00	
2.14-6.98	3.76	151/120	1.07 (0.76-1.51)	1.10 (0.77-1.58)	
7.20-23.7	11.9	137/120	1.02 (0.72-1.44)	1.01 (0.70-1.46)	
23.9-184	65.0	142/120	1.05 (0.74-1.49)	1.17(0.81-1.70)	
185-26,184	774	133/119	0.99 (0.70-1.40)	1.10(0.76-1.61)	
Ln(Benzophenone-3)			0.99 (0.95-1.04)	1.01 (0.96-1.06)	0.73
Bisphenol A					
<LOD-0.950	0.627	174/119	1.00	1.00	
0.958-1.38	1.16	132/120	0.76 (0.54-1.07)	0.76 (0.53-1.09)	
1.38-2.04	1.69	135/120	0.78 (0.56-1.10)	0.76 (0.53-1.09)	
2.05-3.63	2.66	142/120	0.82 (0.59-1.16)	0.80 (0.56-1.15)	
3.63-388	5.72	128/119	0.74 (0.52-1.04)	0.75 (0.52-1.08)	
Ln(Bisphenol A)			0.90 (0.81-1.02)	0.91 (0.80-1.02)	0.11
Triclosan					
<LOD	–	334/294	1.00	1.00	
LOD-10.4	5.58	142/101	1.35 (1.00-1.83)	1.31 (0.96-1.80)	
10.5-33.8	16.0	107/102	1.02 (0.74-1.40)	1.02 (0.72-1.44)	
34.0-1,715	79.1	128/101	1.19 (0.87-1.62)	1.18 (0.86-1.63)	ND[b]
Methylparaben					
1.04-31.2	15.0	126/119	1.00	1.00	
32.2-100	62.3	147/120	1.16 (0.82-1.65)	1.34 (0.93-1.95)	
102-209	150	132/120	1.03 (0.72-1.47)	1.24 (0.85-1.81)	
215-412	303	153/120	1.20 (0.85-1.70)	1.48 (1.02-2.15)	
414-3,174	658	153/119	1.21 (0.86-1.72)	1.50 (1.03-2.18)	
Ln(Methylparaben)			1.04 (0.96-1.12)	1.09(1.00-1.18)	0.04
Propylparaben					
<LOD-5.21	1.63	142/119	1.00	1.00	

Biomarker (μg/g creatinine)	Median in Women without Breast Cancer	Breast Cancer/ No Breast Cancer	Age-Adjusted	Multivariable-Adjusted[a]	
			OR (95% CI)	OR (95% CI)	P_{Trend}
5.27-20.3	9.90	120/120	0.85 (0.60-1.21)	0.97 (0.67-1.41)	
20.6-54.2	34.8	153/120	1.08 (0.77-1.52)	1.27 (0.89-1.83)	
54.4-125	80.6	147/120	1.04 (0.73-1.46)	1.16 (0.81-1.67)	
128-3,116	216	149/119	1.07 (0.76-1.51)	1.31 (0.90-1.90)	
Ln(Propylparaben)			1.03 (0.97-1.09)	1.06 (1.00-1.13)	0.06
Butylparaben					
<LOD	–	370/288	1.00	1.00	
LOD-1.06	0.553	107/103	0.85 (0.62-1.17)	0.96 (0.69-1.33)	
1.10-6.52	2.50	111/104	0.86 (0.63-1.17)	0.85 (0.61-1.19)	
6.55-173	18.9	123/103	0.96 (0.71-1.31)	1.03 (0.74-1.42)	ND[b]
Σparabens[c]					
2.57-42.7	19.4	132/119	1.00	1.00	
42.7-133	80.7	142/120	1.05 (0.74-1.49)	1.21 (0.84-1.75)	
133-279	191	132/120	1.00 (0.69-1.41)	1.21 (0.83-1.76)	
280-550	395	159/120	1.18 (0.84-1.67)	1.39 (0.97-2.01)	
551-3,766	897	146/119	1.09 (0.77-1.55)	1.35 (0.93-1.97)	
Ln(ΣParabens)			1.04 (0.96-1.12)	1.09 (1.00-1.18)	0.05

Long Island Breast Cancer Study Project (LIBCSP) population-based women without breast cancer were frequency matched by age to women diagnosed with breast cancer between August 1, 1996 and July 31, 1997.

CI, confidence interval; ND, not determined; OR, odds ratio

[a]Adjusted for age (continuous in years), education (<HS/HS graduate, College, and Post-college), menopausal status (pre- vs post-menopausal), hormone replacement therapy use (never vs ever), age at menarche (≤12 vs >12 years of age), parity/lactation history (Nulliparous, Parous/never lactated, Parous/ever lactated), family history of breast cancer (None vs First degree), body mass index (<25.0, 25.0-29.9, and ≥30.0 kg/m^2), and lifetime alcohol intake (non-drinkers, <15, 15-29, ≥30 grams per day).

[b]Not determined due to high proportions <LOD.

[c]ΣParabens: Creatinine-corrected molar sum of paraben metabolites: methylparaben, propylparaben, and butylparaben (expressed as methylparaben, molecular weight 152).

Table 4.

BMI-stratified odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between urinary phenol concentrations (μg/g creatinine) and breast cancer incidence among the ancillary study sample of LIBCSP women (*n*=1,301).

	Body Mass Index (BMI)				
	BMI <25.0 kg/m^2 (*n*=625)		BMI ≥25.0 kg/m^2 (n=676)		
Biomarker (μg/g creatinine)	**With Breast Cancer/ No Breast Cancer**	**OR (95% CI)[a]**	**With Breast Cancer/ No Breast Cancer**	**OR (95% CI)[a]**	***p*Interaction**
2,5-dichlorophenol					0.14
0.648-6.41	130/111	1.00	136/86	1.00	
4.42-20.9	99/102	0.87 (0.59-1.29)	117/96	0.79 (0.52-1.20)	
21.0-9,149	87/96	0.77 (0.51-1.16)	140/101	0.77 (0.51-1.16)	
Ln(2,5-dichlorophenol)		0.92 (0.83-1.03)		0.95 (0.86-1.04)	
Benzophenone-3					0.50
<LOD-4.55	86/97	1.00	153/100	1.00	
4.71-44.1	104/96	1.17 (0.75-1.81)	147/102	1.05 (0.71-1.55)	
44.5-26,184	125/116	1.17 (0.77-1.77)	93/81	0.91 (0.60-1.39)	
Ln(Benzophenone-3)		1.01 (0.95-1.08)		0.99 (0.92-1.06)	
Bisphenol A					0.15
<LOD-1.23	119/99	1.00	139/97	1.00	
1.24-2.44	105/101	0.80 (0.53-1.19)	124/97	0.93 (0.63-1.39)	
2.45-388	92/109	0.65 (0.44-0.98)	130/89	1.07 (0.71-1.60)	
Ln(Bisphenol A)		0.78 (0.66-0.93)		1.04 (0.87-1.24)	
Triclosan					ND[b]
<LOD	137/164	1.00	196/125	1.00	
LOD-15.9	94/76	1.63 (1.08-2.45)	94/75	0.94 (0.63-1.42)	
16.0-1,715	85/69	1.46 (0.97-2.22)	103/83	0.86 (0.58-1.27)	
Methylparaben					0.50
1.04-73.3	71/84	1.00	151/113	1.00	
73.7-267	106/107	1.27 (0.82-1.98)	135/92	1.13 (0.76-1.67)	
270-3,174	139/118	1.47 (0.95-2.25)	107/78	1.02 (0.68-1.53)	
Ln(Methylparaben)		1.13 (1.00-1.28)		1.04 (0.93-1.16)	
Propylparaben					0.20
<LOD-12.4	64/83	1.00	140/115	1.00	
12.9-67.7	109/100	1.57 (1.00-2.47)	144/97	1.43 (0.97-2.10)	
68.2-3,116	143/126	1.52 (0.98-2.34)	109/71	1.29 (0.85-1.96)	
Ln(Propylparaben)		1.12 (1.02-1.24)		1.00 (0.92-1.09)	
Butylparaben					ND[b]
<LOD	135/133	1.00	233/152	1.00	
LOD-2.49	80/83	0.98 (0.65-1.48)	81/70	0.88 (0.58-1.32)	
2.51-173	101/93	1.00 (0.68-1.48)	79/61	0.88 (0.58-1.34)	

	Body Mass Index (BMI)				
	BMI <25.0 kg/m^2 (*n*=625)		BMI ≥25.0 kg/m^2 (n=676)		
Biomarker (μg/g creatinine)	**With Breast Cancer/ No Breast Cancer**	**OR (95% CI)[a]**	**With Breast Cancer/ No Breast Cancer**	**OR (95% CI)[a]**	$p_{Interaction}$
Σparabens[c]					0.43
2.57-97.1	68/85	1.00	161/112	1.00	
100-353	103/103	1.30 (0.83-2.03)	128/96	0.94 (0.64-1.39)	
354-3,766	145/121	1.55 (1.01-2.37)	104/75	0.97 (0.64-1.46)	
Ln(Σparabens)		1.13 (0.99-1.27)		1.03 (0.93-1.15)	

CI, confidence interval; ND, not determined; OR, odds ratio

Long Island Breast Cancer Study Project (LIBCSP) population-based women without breast cancer were frequency matched by age to women diagnosed with breast cancer between August 1, 1996 and July 31, 1997.

CI, confidence interval; ND, not determined; OR, odds ratio

[a] Adjusted for age (continuous in years), education (<HS/HS graduate, College, and Post-college), menopausal status (pre- vs post-menopausal), hormone replacement therapy use (never vs ever), age at menarche (≤12 vs >12 years of age), parity/lactation history (Nulliparous, Parous/never lactated, Parous/ever lactated), family history of breast cancer (None vs First degree), and lifetime alcohol intake (non-drinkers, <15, 15-29, ≥30 grams per day).

[b] Not determined due to high proportions <LOD.

[c] ΣParabens: Creatinine-corrected molar sum of paraben metabolites: methylparaben, propylparaben, and butylparaben (expressed as methylparaben, molecular weight 152).

Table 5.

Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between urinary phenol concentrations (μg/g creatinine) and all-cause and breast cancer-specific mortality among the ancillary study sample of LIBCSP women with breast cancer (*n*=711).

	All-Cause Mortality					Breast Cancer-Specific Mortality				
Biomarker (μ/g creatinine)	**Deaths (*n*=271)**	**Censored (n=440)**	**Age-adjusted HR (95% CI)**	**Multivariable-adjusted HR (95% CI)[a]**	**P_{Trend}**	**Deaths (*n*=98)**	**Censored (n=605)**	**Age-adjusted HR (95% CI)**	**Multivariable-adjusted HR (95% CI)[a]**	**P_{Trend}**
2,5-dichlorophenol										
0.648-4.28	63	84	1 (Reference)	1 (Reference)		23	123	1 (Reference)	1 (Reference)	
4.30-7.62	58	105	0.82 (0.57-1.17)	0.86 (0.59-1.25)		24	136	0.93 (0.52-1.65)	0.90 (0.49-1.62)	
7.63-14.9	34	88	0.64 (0.42-0.97)	0.67 (0.44-1.03)		13	106	0.64 (0.33-1.27)	0.64 (0.32-1.28)	
15.1-45.0	51	92	0.75 (0.52-1.09)	0.76 (0.52-1.10)		18	124	0.76 (0.41-1.40)	0.68 (0.36-1.28)	
46.0-9,159	65	71	0.87 (0.62-1.24)	0.92 (0.65-1.32)		20	116	0.91 (0.49-1.66)	0.84 (0.45-1.56)	
Ln(2,5-dichlorophenol)			0.95 (0.89-1.02)	0.96 (0.89-1.03)	0.25			0.95 (0.84-1.08)	0.94 (0.83-1.07)	0.35
Benzophenone-3										
<LOD-2.13	72	75	1 (Reference)	1 (Reference)		27	117	1 (Reference)	1 (Reference)	
2.14-6.98	65	86	0.97 (0.69-1.35)	0.96 (0.68-1.36)		22	129	0.75 (0.43-1.33)	0.74 (0.41-1.32)	
7.20-23.7	41	96	0.69 (0.47-1.01)	0.77 (0.52-1.13)		15	120	0.55 (0.29-1.04)	0.63 (0.33-1.21)	
23.9-184	50	92	0.89 (0.62-1.29)	0.92 (0.63-1.34)		23	117	0.83 (0.47-1.46)	0.90 (0.50-1.62)	
185-26,184	43	90	0.75 (0.51-1.10)	0.84 (0.57-1.25)		11	121	0.41 (0.20-0.83)	0.52 (0.25-1.08)	
Ln(Benzophenone-3)			0.97 (0.93-1.02)	0.99 (0.94-1.04)	0.67			0.91 (0.84-1.00)	0.95 (0.86-1.04)	0.25
Bisphenol A										
<LOD-0.950	64	110	1 (Reference)	1 (Reference)		26	145	1 (Reference)	1 (Reference)	
0.958-1.38	44	88	0.97 (0.66-1.43)	0.96 (0.65-1.41)		16	116	0.80 (0.43-1.48)	0.78 (0.41-1.47)	
1.38-2.04	50	85	1.13 (0.78-1.64)	1.10 (0.75-1.60)		16	119	0.79 (0.42-1.47)	0.77 (0.41-1.44)	
2.05-3.63	59	83	1.22 (0.85-1.73)	1.16 (0.81-1.67)		22	119	1.06 (0.60-1.88)	1.03 (0.57-1.85)	
3.63-388	54	74	1.27 (0.88-1.83)	1.27 (0.87-1.83)		18	106	1.00 (0.55-1.82)	0.93 (0.50-1.73)	
Ln(Bisphenol A)			1.12 (0.98-1.27)	1.12 (0.98-1.28)	0.09			1.03 (0.83-1.29)	1.02 (0.82-1.28)	0.85
Triclosan										
<LOD	141	193	1 (Reference)	1 (Reference)		50	282	1 (Reference)	1 (Reference)	
LOD-10.4	48	94	0.95 (0.68-1.32)	0.95 (0.68-1.33)		18	122	0.84 (0.49-1.44)	0.90 (0.52-1.55)	
10.5-33.8	39	68	0.96 (0.67-1.36)	0.94 (0.65-1.36)		15	92	0.93 (0.52-1.66)	0.96 (0.53-1.73)	

Biomarker (μ/g creatinine)	All-Cause Mortality					Breast Cancer-Specific Mortality				
	Deaths (*n*=271)	Censored (n=440)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]	P_{Trend}	Deaths (*n*=98)	Censored (n=605)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]	P_{Trend}
34.0-1,715	43	85	0.88 (0.62-1.24)	0.91 (0.64-1.29)	ND[b]	15	109	0.77 (0.43-1.38)	0.82 (0.45-1.47)	ND[b]
Methylparaben										
1.04-31.2	58	68	1 (Reference)	1 (Reference)		23	103	1 (Reference)	1 (Reference)	
32.2-100	54	93	0.79 (0.55-1.15)	0.82 (0.56-1.19)		18	126	0.66 (0.34-1.22)	0.74 (0.39-1.38)	
102-209	50	82	0.80 (0.55-1.16)	0.83 (0.56-1.22)		17	113	0.69 (0.37-1.30)	0.75 (0.39-1.42)	
215-412	56	97	0.74 (0.51-1.06)	0.76 (0.52-1.12)		21	129	0.72 (0.40-1.31)	0.80 (0.43-1.50)	
414-3,174	53	100	0.68 (0.47-0.98)	0.71 (0.48-1.05)		19	134	0.65 (0.35-1.18)	0.83 (0.44-1.56)	
Ln(Methylparaben)			0.91 (0.84-0.99)	0.92 (0.85-1.00)	0.05			0.92 (0.81-1.05)	0.96 (0.84-1.11)	0.59
Propylparaben										
<LOD-5.21	62	80	1 (Reference)	1 (Reference)		25	117	1 (Reference)	1 (Reference)	
5.27-20.3	47	73	0.88 (0.60-1.29)	0.84 (0.57-1.24)		22	96	1.01 (0.57-1.79)	1.02 (0.57-1.82)	
20.6-54.2	58	95	0.86 (0.60-1.23)	0.84 (0.59-1.22)		16	134	0.58 (0.31-1.09)	0.58 (0.31-1.09)	
54.4-125	51	96	0.69 (0.48-1.00)	0.65 (0.44-0.96)		17	127	0.62 (0.34-1.15)	0.61 (0.31-1.17)	
128-3,116	53	96	0.75 (0.52-1.08)	0.77 (0.52-1.13)		18	131	0.64 (0.35-1.17)	0.87 (0.45-1.65)	
Ln(Propylparaben)			0.93 (0.88-0.99)	0.93 (0.87-0.99)	0.03			0.91 (0.83-1.01)	0.94 (0.84-1.05)	0.28
Butylparaben										
<LOD	153	217	1 (Reference)	1 (Reference)		56	309	1 (Reference)	1 (Reference)	
<LOD-1.06	39	68	1.00 (0.70-1.43)	1.01 (0.71-1.44)		15	91	0.93 (0.53-1.65)	1.06 (0.59-1.89)	
1.10-6.52	40	71	0.87 (0.61-1.23)	0.84 (0.59-1.21)		14	96	0.81 (0.45-1.45)	0.86 (0.47-1.58)	
6.55-173	39	84	0.73 (0.51-1.03)	0.73 (0.51-1.05)	ND[b]	13	109	0.66 (0.36-1.21)	0.78 (0.42-1.44)	ND[b]
Σparabens[c]										
2.57-42.7	61	71	1 (Reference)	1 (Reference)		25	107	1 (Reference)	1 (Reference)	
42.7-133	51	91	0.74 (0.51-1.07)	0.77 (0.53-1.14)		18	121	0.66 (0.36-1.21)	0.76 (0.41-1.41)	
133-279	51	81	0.86 (0.59-1.25)	0.89 (0.61-1.32)		19	111	0.76 (0.42-1.37)	0.81 (0.44-1.49)	
280-550	58	101	0.74 (0.52-1.06)	0.77 (0.53-1.12)		19	137	0.61 (0.33-1.10)	0.67 (0.35-1.26)	
551-3,766	50	96	0.64 (0.44-0.93)	0.68 (0.46-1.00)		17	129	0.57 (0.31-1.06)	0.74 (0.39-1.42)	
Ln(ΣParabens)			0.91 (0.84-0.99)	0.92 (0.85-1.00)	0.06			0.90 (0.79-1.03)	0.95 (0.82-1.09)	0.45

CI, confidence interval; ND, not determined; HR, hazard ratio

Long Island Breast Cancer Study Project (LIBCSP) women with breast cancer were diagnosed between August 1, 1996 and July 31, 1997 and monitored for vital status from diagnosis through December 31, 2014.

[a] Adjusted for age at diagnosis (continuous in years), education (<HS/HS graduate, College, and Post-college), menopausal status (pre- vs post-menopausal), hormone replacement therapy use (never vs ever), parity/lactation history (nulliparous, parous/never lactated, and parous/ever lactated), and body mass index (<25.0, 25.0-29.9, and ≥30.0 kg/m^2).

[b] Not determined due to high proportions <LOD.

[c] ΣParabens: Creatinine-corrected molar sum of paraben metabolites: methylparaben, propylparaben, and butylparaben (expressed as methylparaben, molecular weight 152).

Table 6.

BMI-stratified Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between urinary phenol concentrations (μg/g creatinine) and all-cause mortality among the ancillary study sample of LIBCSP women with breast cancer (*n*=709).

	BMI <25.0 kg/m^2(*n*=316)			BMI ≥25.0 kg/m^2 (*n*=393)			
Biomarker (μ/g creatinine)	**Deaths (*n*=101)**	**Censored (n=215)**	**Multivariable-adjusted HR (95% CI)[a]**	**Deaths (*n*=169)**	**Censored (n=224)**	**Multivariable-adjusted HR (95% CI)[a]**	***p*Interaction**
2,5-dichlorophenol							0.38
0.648-6.41	48	82	1 (Reference)	57	79	1 (Reference)	
4.42-20.9	22	77	0.53 (0.32-0.89)	50	67	1.20 (0.81-1.78)	
21.0-9,149	31	56	0.80 (0.50-1.27)	62	78	0.96 (0.66-1.38)	
Ln(2,5-dichlorophenol)			0.93 (0.82-1.06)			0.98 (0.90-1.07)	
Benzophenone-3							0.95
<LOD-4.55	35	51	1 (Reference)	79	74	1 (Reference)	
4.71-44.1	30	74	0.82 (0.50-1.37)	52	95	0.89 (0.62-1.27)	
44.5-26,184	36	89	0.87 (0.53-1.41)	38	55	1.02 (0.68-1.53)	
Ln(Benzophenone-3)			0.98 (0.91-1.06)			0.99 (0.92-1.06)	
Bisphenol A							0.41
<LOD-1.23	36	83	1 (Reference)	58	81	1 (Reference)	
1.24-2.44	35	70	1.16 (0.72-1.87)	47	77	0.85 (0.57-1.26)	
2.45-388	30	62	1.29 (0.78-2.12)	64	66	1.28 (0.89-1.84)	
Ln(Bisphenol A)			1.05 (0.84-1.32)			1.17 (0.99-1.37)	
Triclosan							ND[b]
<LOD	48	89	1 (Reference)	93	103	1 (Reference)	
LOD-15.9	31	63	1.30 (0.80-2.09)	40	54	1.02 (0.70-1.49)	
16.0-1,715	22	63	0.88 (0.52-1.49)	36	67	0.75 (0.51-1.11)	
Methylparaben							0.96
1.04-73.3	26	45	1 (Reference)	72	79	1 (Reference)	
73.7-267	29	77	0.65 (0.37-1.12)	54	81	0.78 (0.54-1.12)	
270-3,174	46	93	0.77 (0.47-1.28)	43	64	0.74 (0.50-1.09)	
Ln(Methylparaben)			0.93 (0.80-1.08)			0.90 (0.81-1.00)	
Propylparaben							0.55
<LOD-12.4	22	42	1 (Reference)	67	73	1 (Reference)	
12.9-67.7	34	75	1.04 (0.59-1.80)	60	84	0.81 (0.57-1.15)	
68.2-3,116	45	98	0.87 (0.51-1.46)	42	67	0.62 (0.42-0.92)	
Ln(Propylparaben)			0.96 (0.85-1.07)			0.92 (0.85-0.99)	
Butylparaben							ND[b]
<LOD	48	87	1 (Reference)	104	129	1 (Reference)	
LOD-2.49	22	58	0.89 (0.53-1.49)	37	44	1.00 (0.68-1.46)	
2.51-173	31	70	0.83 (0.51-1.32)	28	51	0.64 (0.42-0.99)	
Σparabens[c]							0.82

Biomarker (μ/g creatinine)	BMI <25.0 kg/m^2(*n*=316) Deaths (*n*=101)	Censored (n=215)	Multivariable-adjusted HR (95% CI)[a]	BMI ≥25.0 kg/m^2 (*n*=393) Deaths (*n*=169)	Censored (n=224)	Multivariable-adjusted HR (95% CI)[a]	$P^{Interaction}$
2.57-97.1	25	43	1 (Reference)	74	87	1 (Reference)	
100-353	29	74	0.69 (0.40-1.21)	56	72	0.90 (0.63-1.28)	
354-3,766	47	98	0.80 (0.49-1.32)	39	65	0.70 (0.47-1.03)	
Ln(Σparabens)			0.94 (0.81-1.09)			0.90 (0.81-0.99)	

CI, confidence interval; ND, not determined; HR, hazard ratio

Long Island Breast Cancer Study Project (LIBCSP) women with breast cancer were diagnosed between August 1, 1996 and July 31, 1997 and monitored for vital status from diagnosis through December 31, 2014.

[a]Adjusted for age at diagnosis (continuous in years), education (<HS/HS graduate, College, and Post-college), menopausal status (pre- vs post-menopausal), hormone replacement therapy use (never vs ever), and parity/lactation history (nulliparous, parous/never lactated, and parous/ever lactated).

[b]Not determined due to high proportions <LOD.

[c]ΣParabens: Creatinine-corrected molar sum of paraben metabolites: methylparaben, propylparaben, and butylparaben (expressed as methylparaben, molecular weight 152).

Table 7.

BMI-stratified Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between urinary phenol concentrations (μg/g creatinine) and breast cancer-specific mortality among the ancillary study sample of LIBCSP women with breast cancer (*n*=701).

	BMI <25.0 kg/m^2 (*n*=313)			BMI ≥25.0 kg/m^2 (*n*=388)			
Biomarker (μ/g creatinine)	**Deaths (*n*=33)**	**Censored (n=280)**	**Multivariable-adjusted HR (95% CI)[a]**	**Deaths (*n*=65)**	**Censored (n=323)**	**Multivariable-adjusted HR (95% CI)[a]**	**$P_{Interaction}$**
2,5-dichlorophenol							0.62
0.648-6.41	17	111	1 (Reference)	25	109	1 (Reference)	
4.42-20.9	7	91	0.49 (0.20-1.20)	20	95	1.04 (0.57-1.91)	
21.0-9,149	9	78	0.78 (0.34-1.78)	20	119	0.78 (0.42-1.44)	
Ln(2,5-dichlorophenol)			0.90 (0.71-1.16)			0.97 (0.83-1.12)	
Benzophenone-3							0.16
<LOD-4.55	9	77	1 (Reference)	29	121	1 (Reference)	
4.71-44.1	12	90	1.02 (0.42-2.50)	21	124	0.80 (0.44-1.46)	
44.5-26,184	12	112	0.83 (0.33-2.06)	15	78	0.94 (0.49-1.81)	
Ln(Benzophenone-3)			0.96 (0.83-1.11)			0.92 (0.82-1.04)	
Bisphenol A							0.33
<LOD-1.23	11	108	1 (Reference)	25	111	1 (Reference)	
1.24-2.44	14	90	1.33 (0.59-2.99)	13	111	0.54 (0.27-1.07)	
2.45-388	8	82	1.05 (0.42-2.64)	27	101	1.20 (0.68-2.10)	
Ln(Bisphenol A)			0.85 (0.55-1.30)			1.11 (0.85-1.44)	
Triclosan							ND[b]
<LOD	12	123	1 (Reference)	38	158	1 (Reference)	
LOD-15.9	11	83	1.56 (0.66-3.69)	18	74	1.02 (0.57-1.82)	
16.0-1,715	10	74	1.46 (0.61-3.49)	9	91	0.43 (0.20-0.89)	
Methylparaben							0.22
1.04-73.3	8	62	1 (Reference)	28	122	1 (Reference)	
73.7-267	7	98	0.40 (0.14-1.18)	21	112	0.83 (0.47-1.48)	
270-3,174	18	120	1.07 (0.46-2.52)	16	89	0.82 (0.43-1.54)	
Ln(Methylparaben)			1.05 (0.79-1.38)			0.91 (0.77-1.08)	
Propylparaben							0.52
<LOD-12.4	8	56	1 (Reference)	27	112	1 (Reference)	
12.9-67.7	8	98	0.52 (0.19-1.41)	24	116	0.84 (0.48-1.46)	
68.2-3,116	17	126	0.89 (0.38-2.10)	14	95	0.60 (0.30-1.17)	
Ln(Propylparaben)			0.94 (0.76-1.16)			0.93 (0.82-1.05)	
Butylparaben							ND[b]
<LOD	14	120	1 (Reference)	42	187	1 (Reference)	
LOD-2.49	9	70	1.01 (0.43-2.39)	14	67	1.00 (0.54-1.85)	
2.51-173	10	90	0.80 (0.34-1.88)	9	69	0.63 (0.30-1.30)	
Σparabens[c]							0.28

Biomarker (μ/g creatinine)	BMI <25.0 kg/m^2 (*n*=313) Deaths (*n*=33)	Censored (n=280)	Multivariable-adjusted HR (95% CI)[a]	BMI ≥25.0 kg/m^2 (*n*=388) Deaths (*n*=65)	Censored (n=323)	Multivariable-adjusted HR (95% CI)[a]	$P_{Interaction}$
2.57-97.1	8	59	1 (Reference)	30	129	1 (Reference)	
100-353	8	94	0.49 (0.17-1.36)	21	105	0.86 (0.49-1.53)	
354-3,766	17	127	0.95 (0.40-2.24)	14	89	0.70 (0.36-1.35)	
Ln(Σparabens)			1.01 (0.76-1.32)			0.90 (0.76-1.07)	

CI, confidence interval; ND, not determined; HR, hazard ratio

Long Island Breast Cancer Study Project (LIBCSP) women with breast cancer were diagnosed between August 1, 1996 and July 31, 1997 and monitored for vital status from diagnosis through December 31, 2014.

[a]Adjusted for age at diagnosis (continuous in years), education (<HS/HS graduate, College, and Post-college), menopausal status (pre- vs post-menopausal), hormone replacement therapy use (never vs ever), and parity/lactation history (nulliparous, parous/never lactated, and parous/ever lactated).

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