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# Prepubertal and Pubertal Endocrine-Disrupting Chemical Exposure and Breast Density among Chilean Adolescents

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## Abstract

**Background:** During puberty, mammary tissue undergoes rapid development, which provides a window of heightened susceptibility of breast composition to the influence of endogenous and exogenous hormones. Exposure to endocrine disrupting chemicals (EDCs) may affect breast development and composition and the risk of developing breast cancer in adulthood.

**Methods:** We evaluated the associations between breast density and urinary concentrations of phenols and phthalates collected at Tanner 1 (B1) and Tanner 4 (B4) in 200 Chilean girls. Total breast volume (BV), fibroglandular volume (FGV), and percent dense breast (%FGV) were evaluated at B4 using dual x-ray absorptiometry. Generalized estimating equations were used to analyze the association between concentrations of EDC biomarkers across puberty and breast density.

**Results:** The geometric mean %FGV was 7% higher among girls in the highest relative to the lowest tertile of monocarboxyisooctyl phthalate (1.07; 95% CI: 1.01–1.14). Monoethyl phthalate concentrations at B4 were positively associated with FGV (highest vs lowest tertile: 1.22; 95% CI: 1.06–1.40). Bisphenol A displayed a u-shaped association with FGV; girls in the middle tertile had at least 10% lower FGV than girls in the lowest or highest tertiles. Monocarboxyisononyl phthalate showed a non-linear association with BV. No other statistically significant associations were observed.

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**Conclusions:** Our results suggest that the developing breast tissue is susceptible to select EDCs during childhood and adolescence.

**Impact:** This study may spur further investigations into environmental influences on breast development during puberty, and how shifts in pubertal breast density track through the life course to modify breast cancer risk.

### Keywords

puberty; breast density; phenols; phthalates; endocrine disrupting chemicals

## INTRODUCTION

High mammographic density is strongly associated with increased breast cancer risk (1–3). A greater proportion of dense breast tissue is indicative of relatively more collagen, epithelial and stromal cells relative to fat (4). Increasing age, parity, and menopause are all associated with reductions in breast density, reflecting a shift in the relative abundance of these cell types (5).Greater body fatness during childhood and adolescence has been associated with decreased adult breast density (6,7). Total breast volume of young women, estimated by cup size, has also been associated with breast cancer risk (8,9). Results from these studies suggest that breast density is modifiable, but largely dependent on initial peak density established during adolescence (10). Furthermore, it is during this period of rapid development and cell proliferation that the susceptibility of mammary tissue to carcinogens is suspected to be the greatest (11–13).

Pubertal breast development follows a coordinated surge in adrenal hormones preceding the reactivation of hypothalamic-pituitary-ovarian axis, and production of estrogen from the ovaries (14). Accordingly, during this period of rapid hormone-sensitive development, mammary tissue may be particularly susceptible to endocrine disrupting chemicals (EDCs), which have the potential to interfere with the action of the body’s endogenous hormones (15). Phenols and phthalates are two classes of pervasive EDCs found in plastics, personal care products, adhesives, detergents, pharmaceuticals, and building materials (16–18). Despite their ubiquity, there are surprisingly few investigations into the potential impact of these compounds on human breast development and subsequent cancer risk. One prior longitudinal study of girls from the United States reported no association between childhood phthalate biomarkers in urine and the age of breast development (thelarche) (19). Within the same cohort, phenol urinary biomarkers demonstrated a more complicated relations with age at thelarche. While benzophenone-3 was associated with earlier thelarche, 2,5-dichlorophenol and triclosan were associated with later development (20). Only one study has investigated the potential association between phthalate exposure and breast cancer risk. In a case-control study of Mexican women, urinary concentrations of monoethyl phthalate (MEP) were associated with increased odds of premenopausal breast cancer, whereas monobenzyl phthalate (MBzP) and mono(3-carboxypropyl) phthalate (MCPP) were associated with lower odds (21).

These prior studies suggest that pubertal breast development might be sensitive to EDC exposure. However, no studies have explored how breast composition responds to EDC

exposure during childhood and adolescence. To address these gaps in knowledge, we investigated the association between childhood and adolescent EDC urinary biomarkers and pubertal breast density in a longitudinal cohort of girls in Santiago, Chile. This study provides unique insight into the potential influence of early life exposures on determinants of breast cancer risk.

## MATERIALS AND METHODS

### Study Population

Our study population was the longitudinal Growth and Obesity Cohort Study (GOCS) in Santiago, Chile. Initiated in 2006, children ages 2.6 to 4.0 years were recruited from public nursery schools of six counties in Santiago who met the following inclusion criteria: 1) singletons born in 2002–2003 and with birthweight between 2500 and 4500g, and 2) absence of physical (e.g. skin burn), medical (e.g. brain tumor) or endocrine diseases (e.g. hyperthyroidism, hyperprolactinemia) that can alter the growth and/or onset of puberty. Of 1,498 eligible participants, 1,195 (~80%) agreed to participate in the study. No significant differences in age, gender, and birth anthropometry were identified between the final participants and those not enrolled. The GOCS children are representative of the low to middle-income families served by the public nursery schools. Two trained dietitians collected anthropometry measurements approximately every 6 months after 2006. Based on height (cm) and weight (kg) measured at each clinic visit, sex and age-adjusted BMI Z-scores were calculated using the Centers for Disease Control and Prevention (CDC) growth charts. Of the 515 girls who participated in the original cohort, 389 girls had follow-up information through B4 and consented to have breast density measured using dual x-ray absorptiometry. Due to the limits in available funds, the current study was restricted to a subset of 200 randomly sampled girls with urine samples collected at both Tanner 1 (B1) and Tanner 4 (B4), and with breast density measurements performed at B4. Among the 389 girls with breast density measurements, total breast volume, fibroglandular volume, and percent dense breast adjusting for BMI Z-score at B4 did not significantly differ between those included and excluded from the current analysis. The study protocol was conducted in accordance with the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the Institute of Nutrition and Food Technology, University of Chile and the Institutional Review Board of the Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA. Informed written consent was obtained from all parents or guardians of children before the start of data collection.

### Breast Density Measurements

Breast density was measured at B4, when total fibroglandular volume is assumed to reach its peak (22). Breast development was assessed by visual inspection using the Tanner rating scale approximately every 6 months (23). After confirming the absence of pregnancy by a urine test, DXA was used to measure dense tissue volume (absolute fibroglandular volume) of the breast. The UCSF DXA breast scanning protocol was developed by Shepherd *et al.*, in the Department of Radiology and Biomedical Imaging, University of California, San Francisco (version 5) (24). Each breast was scanned using the Prodigy DXA system software (version 13.6, series 200674; GE Healthcare). A quality control phantom

containing reference breast density materials was scanned throughout the study to assure a stable calibration. This approach has been shown to have high validity and precision for measuring breast density in girls at different Tanner stages (22). The radiation dose from DXA is exceedingly small; DXA is commonly used to measure whole body percent fat and body mass in pediatric studies (25). Total projected breast area was manually delineated on each image and breast fibroglandular volume (FGV; $cm^3$) and total volume (BV; $cm^3$) was estimated using a two-compartment model of adipose and fibro-glandular tissue with software developed by Shepherd at the University of California (26). Percent FGV (%FGV) was defined as the proportion FGV relative to BV times 100. We averaged the values of the left and right breast for all analyses.

## EDC Measurements

Fasting spot urine samples were collected between 10 AM and 12 PM in polypropylene sterile cups, immediately vortexed, and aliquoted, and stored at −20 °C until analysis. Previous evaluations indicate that the integrity of the specimens and stability of the biomarkers are not compromised under these conditions (27,28) Concentrations of 26 phenols and phthalates biomarkers were quantified in urines collected at B1 and B4 from 200 girls (400 urine samples). Biomarker measurements were performed at the CDC using described analytical methods; each analytic batch includes reagent blanks and low- and high-concentration quality control materials, which are evaluated using standard statistical probability rules (29,30). Concentrations below the limit of detection (LOD) were given an imputed value equal to LOD/sqrt(2). Dilution adjustment was performed using the formula $P_c=P[(1.015–1)/(SG-1)]$, where $P_c$ is the specific gravity-corrected biomarker concentration, P is the observed biomarker concentration, SG is the specific gravity of the urine sample, and 1.015 is the median SG of the study population (31,32). The analysis of blinded specimens by the CDC laboratory was determined not to constitute engagement in human subjects' research.

## Statistical Analysis

Generalized estimating equations (GEE) were used to jointly estimate the influence of EDC biomarker concentrations at B1 and B4 on breast density measurements, including: total breast volume, absolute FGV, and percent FGV. This non-conventional application of GEE models allows for the simultaneous modeling of the associations with B1 and B4 EDC biomarker concentrations, with a working independence assumption and model based standard errors (33,34). Breast density measurements were log-transformed prior to analysis. Time-varying associations between EDC biomarker concentrations and breast density were investigated by evaluating the significance of the interaction between biomarker concentrations and Tanner stage at biomarker measurement on breast density. Reported associations were stratified by Tanner stage if significant statistical interaction was detected (Wald test; $p<0.05$). To account for potential non-linear associations, we modeled tertiles of EDC biomarker concentrations, with tertile cut-points stratified by Tanner stage. Multivariate Wald tests were used to assess whether breast composition was significantly different between any tertile of EDC biomarker concentrations ("overall test"). Significant trends across categories were evaluated by modeling the log-transformed median biomarker concentration within tertiles as a continuous variable. All models were adjusted for age at

B1 EDC biomarker measurement, age at B4 EDC biomarker measurement, BMI Z-score at B1, and BMI Z-score at B4. Models were additionally adjusted for maternal education as an indicator of socio-economic status, which has been related to both exposure profile and breast density (35–38). Associations between breast density measurements and biomarker concentrations were reported as the relative change in geometric mean and 95% confidence interval (CI) by exponentiating the associations with log-transformed breast density measurement. Least-square means were used to visualize the absolute change in breast density measurements between tertiles of EDC biomarker concentrations in adjusted GEE models. For significant (overall test, $p<0.05$) non-monotonic associations between EDC biomarker concentration and breast density, we additionally modeled urinary biomarker concentrations continuously, including a main effect and interaction with each of the other quantified biomarkers (dichotomized by mean). For models significantly improved by the inclusion of another EDC biomarker and the relevant interaction term (multivariate Wald test, $p<0.01$), we reported the stratum-specific associations. All statistical analyses were performed in R Version 3.3.1 and figures were generated using ggplot2 (39).

## RESULTS

Urinary concentrations of 26 phenol and phthalate biomarkers were quantified in 200 Chilean adolescent girls at breast Tanner stages B1 and B4 as previously described (40). Data analysis was restricted to the subset of 21 biomarkers that were detected in at least 75% of the girls at both time points. In this subset of the ongoing Growth and Obesity Cohort Study (GOCS), urine samples were obtained during B1 between the ages of 6.7 and 9.6 years, with a median collection age of 7.9 years. Urine B4 samples were collected between the ages of 9.4 and 13.1 years, with a median age of 11.2 years (40). The time between EDC biomarker measurements in this cohort ranged from 2 to 5 years. Correlations between B1 and B4 EDC biomarker concentrations in these girls were moderate to weak, reflecting changes in exposure profiles over time (40). On average, biomarker concentrations at B4 were slightly lower than at B1, paralleling a similar trend observed among adolescent U.S. girls of the same age participating in the National Health and Nutrition Examination Survey (40). Furthermore, the correlation between individual biomarkers varied by Tanner stage (Supplemental Figures 1 and 2). Approximately 90% of the girls reached menarche after the first visit establishing B4 (n=179). No EDC biomarker, measured at Tanner 1 or Tanner 4, was significantly ($p<0.05$) associated with the occurrence of menarche prior to the first observed visit of B4. The median BMI Z-score at B1 urine collection was −0.1 (range: (−2.6, 2.1), and 0.1 (range: −2.1, 2.3) at breast density measurement. Approximately 23% of the mothers had post-secondary education (40).

### Total Breast Volume

Monocarboxyisononyl phthalate (MCNP) was the only biomarker significantly associated with total breast volume (BV), adjusting for age and BMI Z-score at biomarker measurement, as well as maternal education (overall test, $p<0.05$; Table 1). While BV among girls in the middle tertile was not significantly different from those in the lowest, volume was 10% greater in the highest tertile compared to the middle tertile (1.10; 95% CI: 1.02, 1.18; Table 1 and Figure 1a). We hypothesized that this non-monotonic u-shaped

association may indicate an interaction between MCNP and another EDC on BV. Therefore, we analyzed the influence of adding a main effect and interaction with each of the other biomarkers. Adding dichotomized (relative to the median) MEP concentrations and an interaction with continuous MCNP concentrations significantly improved model fit ($p<0.01$, multivariate Wald tests; Supplemental Table 1). Among girls with high MEP concentrations, a one log(ng/ml) increase in MCNP was associated with a 6% increase in BV (1.06; 95% CI: 1.01, 1.10). We additionally detected a significant trend across tertiles of 2,4-dichlorophenol concentrations; girls in the highest tertile had 9% lower geometric mean breast volume than girls in the lowest tertile (0.91; 95% CI: 0.84, 0.99). However, the overall test of whether BV significantly varied between categories of 2,4-dichlorophenol concentrations was not significant.

### Fibroglandular Volume

A few distinct biomarkers were associated with dense breast volume (FGV), including MEP, mono-isobutyl phthalate (MiBP), and bisphenol A (BPA; Table 2 and Table 3 and Figure 1b). For MEP and MiBP, the association with FGV was modified by the time of biomarker measurement (Table 3). Concentrations of MEP were moderately correlated between the two Tanner stages (Spearman $\rho= 0.325$) (40). However, MEP specific gravity-adjusted geometric mean concentration was nearly 20 ng/ml higher at B1 than B4 (40). Concentrations of MiBP did not significantly differ between Tanner stages, and were moderately correlated between B1 and B4 (Spearman $\rho= 0.279$) (40). After stratifying by Tanner stage at biomarker measurement, tertiles of MiBP concentration were not significantly associated with FGV (overall test; Table 3). Distinctly, B4 MEP concentrations had a positive association with FGV (trend test, $p=0.004$). Girls with MEP concentrations in the highest tertile at B4 had a 22% higher geometric mean volume than girls with MEP levels in the first tertile (1.22; 95% CI: 1.06, 1.40). In contrast, BPA had a clear non-linear association with dense volume across Tanner stages. Girls in the middle tertile of BPA concentrations had at least 10% lower FGV than girls in either the lowest or highest tertiles (Table 2). BPA significantly interacted with MEP to influence dense volume, potentially contributing to this non-monotonic association ($p<0.01$, multivariate Wald tests for added biomarker and interaction; Supplemental Table 1). BPA was only significantly associated with FGV among girls with relatively low concentrations of MEP. A one log(ng/ml) increase in BPA was associated with a 7% decrease in geometric mean FGV among those with low concentrations of MEP (0.93; 95% CI: 0.87, 1.00).

### Percent Fibroglandular Volume

While MCNP was only significantly associated with BV, we observed a similarly shaped trend with dense volume. Conversely, MEP and BPA were only associated with FGV. Considering this discordance, we would expect MEP and BPA to be associated with percent dense breast (%FGV). In both cases, the association with %FGV was similar to the association with dense volume (Table 4 and Table 5; Figure 1c). An increase in B4 concentrations of MEP were associated with greater %FGV (Table 5). Paralleling the FGV association, girls with concentrations of BPA in the middle tertile had significantly lower %FGV than girls in the highest or lowest tertiles (Table 4). Percent FGV also had a significant relationship with monocarboxyisooctyl phthalate (MCOP; Table 4). Compared to

girls in the first tertile, those in the highest tertile of MCOP concentrations had 7% higher %FGV (1.07; 95% CI: 1.01, 1.14). While the associations between this biomarker and FGV were not significant, the association trended in the same direction as with %FGV. The association between MCOP and %FGV was significantly modified by the occurrence of menarche prior to breast density measurement (Yes/No; Supplemental Table 2). The analysis restricted to girls that attained menarche after breast density measurement trended in a similar direction. However, the overall test of whether %FGV varied between MCOP tertiles was no longer significant. Monomethyl phthalate (MMP) similarly demonstrated a positive association with %FGV (trend p=0.032). However, the overall test that tertiles of MMP concentration improved model fit for %FGV did not reach significance.

## DISCUSSION

This is the first investigation of the impact of childhood and adolescent exposure to phenols and phthalates on pubertal breast density. While the correlations between the EDC biomarkers measured at B1 and B4 were low, the associations between these biomarkers and breast density were relatively consistent over time. The only two exceptions were the diethyl phthalate (DEP) metabolite, MEP, and the diisobutyl phthalate biomarker, MiBP. Only B4 biomarker concentrations of MEP were significantly associated with FGV. We speculate that the mechanism of action of MEP may depend on a threshold level of specific endogenous hormones, such as estradiol. *In vitro*, DEP causes significant proliferation of human breast cancer cell lines through activation of estrogen-receptor alpha (41,42). Based on recombinant yeast screen assays, DEP has been shown to have weak estrogenic potential (43).

A few biomarkers demonstrated a non-linear association with breast volume and density, including BPA and MCNP. Non-monotonic dose-response relationships are relatively commonplace among *in vitro* and *in vivo* experimental studies of the health effects of EDC exposure (44). There are a number of mechanisms that may contribute to these phenomena, including multiple target receptors with different binding affinities and opposing action, stimulating negative feedback, and receptor desensitization. In the case of BPA and MCNP, these non-monotonic associations reflected a significant interaction with another biomarker on breast composition, notably MEP. MCNP was only positively associated with BV among girls with high concentrations of MEP relative to the median. The relationship between FGV and BPA was inverted among girls with low concentrations of MEP. Concentrations of BPA and MEP, and MCOP and MEP were not correlated in this population, suggesting disparate routes of exposure. A common source of DEP, the parent compound of MEP is personal care product use (45,46). Given this unique exposure route, the observed statistical interactions with MEP may reflect unmeasured confounding by an element of hygiene routine. To address this question, future studies could be useful to disentangle specific routes of EDC exposure for Latina girls, which may greatly vary from U.S. or European populations.

Prior studies have suggested that childhood and adolescent levels of exogenous and endogenous sex hormones are associated with breast density. Compared to women who started hormonal contraceptives at older ages (22–28 years), initiation of hormonal contraceptive use between the ages of 12–17 years has been associated with higher young

adult breast density (47). Prior to menarche, higher serum levels of dehydroepiandrosterone sulfate and sex hormone-binding globulin have also been positively associated with young adult breast density (48). This earlier study did not report a significant association with adolescent levels of estrogens, progesterone, androstenedione, or testosterone before or after menarche (48). Currently, little is known about how EDCs may interact with endogenous hormone levels in adolescent girls. One small study of 84 girls in Copenhagen found mono-n-butyl phthalate (MBP) was inversely associated (albeit not significantly) with adrenal androgens at age 13 (49). In our study, MBP was not significantly associated with breast density measurements. Research to assess whether endogenous hormone levels may interact with both phenol and phthalate biomarkers during puberty would increase our understanding of the potential implications for breast development.

Only one prior cross-sectional study has examined the association between EDC biomarker concentrations and breast density (50). This earlier study found a positive association between serum BPA and MEP and %FGV among approximately 250 postmenopausal women. A major criticism of this prior study was the use of serum biomarkers, which are more sensitive to contamination (51). However, these influences were likely to result in non-differential measurement error, and were postulated to bias associations towards the null. Urinary concentrations of MEP were associated with increased odds of breast cancer among Mexican women (21). Mirroring these findings, we report a positive association between B4 MEP urinary concentrations and adolescent breast density. In contrast, BPA had a non-monotonic association with breast density in our study, possibly reflecting an interaction with MEP concentrations. Both of the prior investigations were restricted to a subset of the phenols and phthalates biomarkers evaluated in this study. Therefore, it is possible that some of the additional associations observed in the present study would have been observed at other ages. Alternatively, breast tissue may have specific windows of susceptibility to certain EDCs.

One limitation of our study was the use of a single urine measurement at each developmental stage to estimate EDC exposure given the short half-life of these biomarkers. Nevertheless, due to chronic and repetitive exposures, prior longitudinal assessments have suggested that relative EDC exposures over several months (to possibly a year) can be reasonably estimated based on a single spot sample (51–54). Potential measurement error in exposure is compensated by our longitudinal assay of urinary phenol and phthalate biomarker concentrations. Puberty reflects a period of rapid physical and social change that may influence both exposure profile and modulate the impact of these compounds on developing mammary tissue. Another strength is the focus on Latina girls. A study of similarly aged U.S. girls showed differences in the urinary biomarker concentrations of phenols and phthalates by race/ethnicity (55). In addition to disparities in exposure profile, the U.S. cohort also reported an earlier age of thelarche among Hispanic girls compared to non-Hispanic white girls, indicating potential biological differences in breast development (56). The consequential drawback is that the findings of our study may not be generalizable to all race/ethnicities. Concentrations of BPA in this population were lower than similarly aged U.S. girls (57,58), but only slightly lower than a cohort of girls in Mexico City (59). In contrast, concentrations of MEP were much higher in this cohort compared to U.S. girls (58), with a similar distribution detected in the Hispanic study (59). These discrepancies

highlight potential differences in exposure profile between populations. Finally, we recommend cautious interpretation of the weaker pairwise comparisons of breast composition between tertiles of the many EDC biomarkers quantified. In our discussion of the results, we have chosen to highlight the stronger associations that are less likely due to chance. We encourage replication of these analyses in independent cohorts to validate these findings and to appraise population-specific sensitivities.

Higher estrogenic activity in childhood has previously been associated with early breast development in the GOCS cohort (60). Given these prior findings were independent of central activation or peripheral estrogen conversion associated with obesity, it was postulated that this estrogenic activity may reflect EDC action (60). This study suggests that the developing breast tissue of Latina girls is responsive to exogenous hormones during childhood and adolescence. Future studies would be useful to assess whether these shifts in pubertal breast density track through the life course to modify breast cancer risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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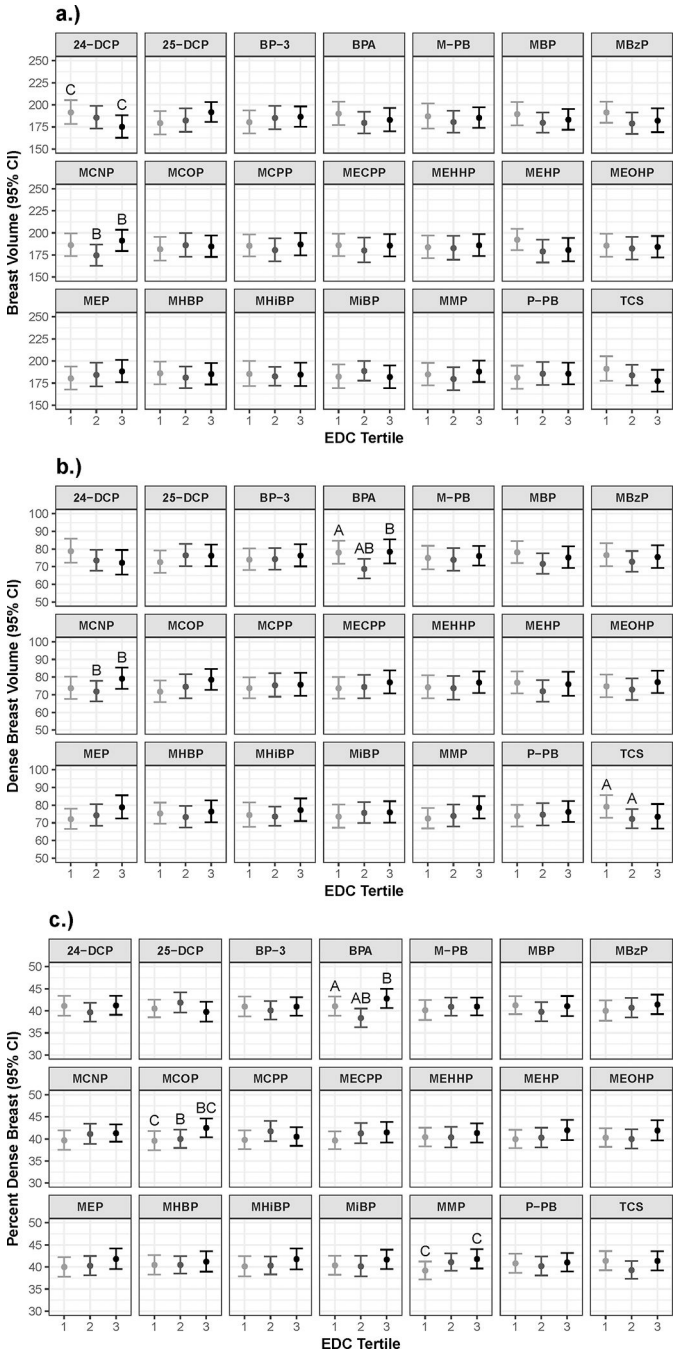


**Figure 1.**

Changes in breast density associated with urinary phenol and phthalate biomarker concentrations. T1= lowest tertile; T2=middle tertile, T3=highest tertile. Plotting the least-square means and associated 95% CI of a.) breast volume, b.) fibroglandular volume, and c.) %FGV between tertiles of biomarker concentrations based on GEE models adjusting for age at B1 biomarker measurement, age at B4 biomarker measurement, BMI z-score at B1, BMI z-score at B4, and maternal education. Significant difference ($p<0.05$) between: tertiles T1

and T2 indicated by A, tertiles T2 and T3 indicated by B, and tertiles T1 and T3 indicated by C.

**Table 1.**

Relative shift in geometric mean (95% CI) breast volume between tertiles of each phenol and phthalate biomarker across B1 and B4[a]

| EDC | Overall Test[b] (p-value) | Middle vs Lowest Tertile (ref) | Highest vs Lowest Tertile (ref) | Highest vs Middle Tertile (ref) | Trend[c] (p-value) |
|---|---|---|---|---|---|
| 2,4-dichlorophenol | 0.108 | 0.97 (0.89, 1.05) | 0.91 * (0.84, 0.99) | 0.94 (0.86, 1.03) | 0.032 * |
| 2,5-dichlorophenol | 0.198 | 1.02 (0.93, 1.11) | 1.07 (0.99, 1.16) | 1.05 (0.97, 1.13) | 0.057 |
| Benzophenone-3 | 0.695 | 1.03 (0.95, 1.11) | 1.03 (0.96, 1.12) | 1.01 (0.94, 1.09) | 0.380 |
| BPA | 0.356 | 0.95 (0.88, 1.02) | 0.96 (0.88, 1.05) | 1.02 (0.94, 1.11) | 0.448 |
| Methyl paraben | 0.679 | 0.97 (0.89, 1.05) | 0.99 (0.91, 1.08) | 1.03 (0.95, 1.11) | 0.804 |
| MBP | 0.329 | 0.95 (0.88, 1.02) | 0.97 (0.90, 1.04) | 1.02 (0.95, 1.10) | 0.453 |
| MBzP | 0.184 | 0.93 (0.87, 1.01) | 0.95 (0.87, 1.04) | 1.02 (0.94, 1.10) | 0.243 |
| MCNP | 0.043 * | 0.94 (0.86, 1.02) | 1.03 (0.96, 1.10) | 1.10 * (1.02, 1.18) | 0.369 |
| MCOP | 0.852 | 1.03 (0.94, 1.12) | 1.02 (0.94, 1.10) | 0.99 (0.91, 1.08) | 0.706 |
| MCPP | 0.708 | 0.97 (0.90, 1.06) | 1.01 (0.94, 1.09) | 1.04 (0.95, 1.13) | 0.766 |
| MECPP | 0.735 | 0.97 (0.89, 1.05) | 1.00 (0.92, 1.08) | 1.03 (0.94, 1.13) | 0.936 |
| MEHHP | 0.919 | 0.99 (0.91, 1.08) | 1.01 (0.93, 1.09) | 1.02 (0.93, 1.11) | 0.741 |
| MEHP | 0.077 | 0.92 * (0.85, 1.00) | 0.93 (0.86, 1.01) | 1.01 (0.93, 1.11) | 0.108 |
| MEOHP | 0.908 | 0.98 (0.91, 1.07) | 0.99 (0.92, 1.07) | 1.01 (0.93, 1.09) | 0.855 |
| MEP | 0.600 | 1.02 (0.94, 1.12) | 1.04 (0.96, 1.14) | 1.02 (0.94, 1.11) | 0.296 |
| MHBP | 0.767 | 0.97 (0.90, 1.05) | 1.00 (0.92, 1.07) | 1.02 (0.95, 1.10) | 0.902 |
| MHiBP | 0.915 | 0.99 (0.91, 1.06) | 1.00 (0.91, 1.09) | 1.01 (0.94, 1.09) | 0.949 |
| MiBP | 0.517 | 1.04 (0.96, 1.12) | 1.00 (0.91, 1.09) | 0.96 (0.89, 1.04) | 0.967 |
| MMP | 0.544 | 0.97 (0.90, 1.05) | 1.02 (0.94, 1.10) | 1.05 (0.96, 1.13) | 0.716 |
| Propyl paraben | 0.811 | 1.02 (0.94, 1.11) | 1.02 (0.94, 1.11) | 1.00 (0.92, 1.08) | 0.582 |
| Triclosan | 0.226 | 0.96 (0.89, 1.04) | 0.93 (0.85, 1.01) | 0.96 (0.89, 1.04) | 0.070 |

[a] Estimating average association across B1 and B4 EDC measurements using a multivariable GEE model adjusting for age at B1 EDC measurement, age at B4 EDC measurement, BMI z-score at B1, BMI z-score at B4, and maternal education

[b] Overall test whether EDC category improves model fit (multivariate Wald test)

[c] Trend evaluated by modeling the log(median) concentration within tertiles as a continuous variable

* p<0.05,

** p<0.01,

*** p<0.001

**Table 2.**

Relative shift in geometric mean (95% CI) fibroglandular volume between tertiles of each phenol and phthalate biomarker across B1 and B4[a]

| EDC | Overall Test[b] (p-value) | Middle vs Lowest Tertile (ref) | Highest vs Lowest Tertile (ref) | Highest vs Middle Tertile (ref) | Trend[c] (p-value) |
|---|---|---|---|---|---|
| 2,4-dichlorophenol | 0.269 | 0.93 (0.84, 1.03) | 0.92 (0.82, 1.03) | 0.98 (0.88, 1.10) | 0.152 |
| 2,5-dichlorophenol | 0.578 | 1.05 (0.95, 1.17) | 1.05 (0.94, 1.17) | 1.00 (0.91, 1.10) | 0.382 |
| Benzophenone-3 | 0.811 | 1.00 (0.91, 1.11) | 1.03 (0.93, 1.14) | 1.03 (0.93, 1.13) | 0.433 |
| BPA | 0.008** | 0.88** (0.80, 0.97) | 1.01 (0.90, 1.12) | 1.14* (1.03, 1.26) | 0.879 |
| Methyl paraben | 0.824 | 0.99 (0.88, 1.10) | 1.01 (0.92, 1.12) | 1.03 (0.94, 1.13) | 0.876 |
| MBP | 0.169 | 0.92 (0.84, 1.00) | 0.96 (0.87, 1.06) | 1.05 (0.96, 1.15) | 0.497 |
| MBzP | 0.582 | 0.95 (0.86, 1.05) | 0.99 (0.88, 1.10) | 1.04 (0.94, 1.14) | 0.763 |
| MCNP | 0.080 | 0.97 (0.88, 1.08) | 1.07 (0.97, 1.18) | 1.10* (1.01, 1.20) | 0.120 |
| MCOP | 0.189 | 1.04 (0.93, 1.16) | 1.09 (0.99, 1.21) | 1.05 (0.95, 1.16) | 0.073 |
| MCPP | 0.854 | 1.02 (0.92, 1.13) | 1.03 (0.93, 1.13) | 1.00 (0.90, 1.12) | 0.616 |
| MECPP | 0.719 | 1.01 (0.91, 1.12) | 1.05 (0.94, 1.16) | 1.04 (0.92, 1.16) | 0.374 |
| MEHHP | 0.708 | 0.99 (0.89, 1.11) | 1.04 (0.93, 1.15) | 1.04 (0.94, 1.16) | 0.489 |
| MEHP | 0.237 | 0.91 (0.82, 1.01) | 0.98 (0.88, 1.08) | 1.07 (0.95, 1.20) | 0.715 |
| MEOHP | 0.554 | 0.98 (0.88, 1.08) | 1.03 (0.93, 1.15) | 1.06 (0.96, 1.17) | 0.549 |
| MEP | 0.194 | 1.03 (0.93, 1.14) | 1.09 (0.99, 1.21) | 1.06 (0.96, 1.17) | 0.065 |
| MHBP | 0.687 | 0.97 (0.88, 1.08) | 1.01 (0.92, 1.11) | 1.04 (0.95, 1.14) | 0.772 |
| MHiBP | 0.588 | 0.99 (0.89, 1.10) | 1.04 (0.93, 1.16) | 1.05 (0.96, 1.15) | 0.516 |
| MiBP | 0.802 | 1.03 (0.93, 1.14) | 1.03 (0.93, 1.15) | 1.00 (0.91, 1.10) | 0.489 |
| MMP | 0.252 | 1.02 (0.93, 1.12) | 1.08 (0.98, 1.20) | 1.06 (0.96, 1.17) | 0.116 |
| Propyl paraben | 0.812 | 1.01 (0.91, 1.12) | 1.03 (0.94, 1.14) | 1.02 (0.93, 1.12) | 0.468 |
| Triclosan | 0.130 | 0.91* (0.83, 1.00) | 0.93 (0.83, 1.04) | 1.02 (0.92, 1.13) | 0.218 |

[a]Estimating average association across B1 and B4 EDC measurements using a multivariable GEE model adjusting for age at B1 EDC measurement, age at B4 EDC measurement, BMI z-score at B1, BMI z-score at B4, and maternal education

[b]Overall test whether EDC category improves model fit (multivariate Wald test)

[c]Trend evaluated by modeling the log(median) concentration within tertiles as a continuous variable

*p<0.05,

**p<0.01,

***p<0.001

**Table 3.**

Relative shift in geometric mean (95% CI) fibroglandular volume between tertiles of MEP and MiBP concentrations stratified by Tanner stage at EDC measurement[a]

| EDC | Tanner Stage | Overall Test[b] (p-value) | Middle vs Lowest Tertile (ref) | Highest vs Lowest Tertile (ref) | Highest vs Middle Tertile (ref) | Trend[c] (p-value) |
|---|---|---|---|---|---|---|
| MEP | | | | | | |
| | B1 | 0.590 | 1.06 (0.92, 1.22) | 0.99 (0.85, 1.14) | 0.93 (0.81, 1.07) | 0.752 |
| | B4 | 0.006** | 1.00 (0.88, 1.15) | 1.22** (1.06, 1.40) | 1.21** (1.06, 1.39) | 0.004** |
| MiBP | | | | | | |
| | B1 | 0.214 | 0.90 (0.78, 1.04) | 1.01 (0.87, 1.16) | 1.12 (0.97, 1.29) | 0.942 |
| | B4 | 0.075 | 1.17* (1.02, 1.35) | 1.06 (0.92, 1.22) | 0.90 (0.79, 1.04) | 0.377 |

[a]Estimating Tanner stage-specific association between EDC metabolite and fibroglandular volume using a multivariable GEE model adjusting for age at B1 EDC measurement, age at B4 EDC measurement, BMI z-score at B1, BMI z-score at B4, and maternal education, including an interaction between EDC tertile and Tanner stage; restricted to subset of association for which the interaction with Tanner stage was significant ($p<0.05$)

[b]Overall test whether EDC category improves model fit (Likelihood ratio test)

[c]Trend evaluated by modeling the log(median) concentration within tertiles as a continuous variable

*$p<0.05$,

**$p<0.01$,

***$p<0.001$

**Table 4.**

Relative shift in geometric mean (95% CI) percent fibroglandular volume between tertiles of each phenol and phthalate biomarker across B1 and B4[a]

| EDC | Overall Test[b] (p-value) | Middle vs Lowest Tertile (ref) | Highest vs Lowest Tertile (ref) | Highest vs Middle Tertile (ref) | Trend[c] (p-value) |
|---|---|---|---|---|---|
| 2,4-dichlorophenol | 0.369 | 0.96 (0.90, 1.03) | 1.00 (0.94, 1.07) | 1.04 (0.98, 1.10) | 0.872 |
| 2,5-dichlorophenol | 0.221 | 1.03 (0.97, 1.10) | 0.98 (0.92, 1.05) | 0.95 (0.89, 1.01) | 0.410 |
| Benzophenone-3 | 0.707 | 0.98 (0.92, 1.04) | 1.00 (0.94, 1.07) | 1.02 (0.96, 1.08) | 0.779 |
| BPA | 0.003** | 0.93* (0.88, 1.00) | 1.04 (0.98, 1.11) | 1.12*** (1.05, 1.19) | 0.210 |
| Methyl paraben | 0.802 | 1.02 (0.95, 1.09) | 1.02 (0.96, 1.09) | 1.00 (0.95, 1.05) | 0.635 |
| MBP | 0.422 | 0.96 (0.91, 1.02) | 1.00 (0.93, 1.06) | 1.03 (0.97, 1.10) | 0.848 |
| MBzP | 0.612 | 1.02 (0.95, 1.09) | 1.04 (0.97, 1.11) | 1.02 (0.96, 1.08) | 0.363 |
| MCNP | 0.408 | 1.04 (0.97, 1.11) | 1.04 (0.98, 1.11) | 1.00 (0.95, 1.06) | 0.203 |
| MCOP | 0.039* | 1.01 (0.95, 1.07) | 1.07* (1.01, 1.14) | 1.06* (1.00, 1.12) | 0.022* |
| MCPP | 0.354 | 1.05 (0.98, 1.12) | 1.02 (0.96, 1.08) | 0.97 (0.91, 1.03) | 0.664 |
| MECPP | 0.305 | 1.04 (0.98, 1.10) | 1.05 (0.98, 1.12) | 1.00 (0.94, 1.07) | 0.195 |
| MEHHP | 0.726 | 1.00 (0.94, 1.06) | 1.02 (0.96, 1.09) | 1.02 (0.96, 1.09) | 0.486 |
| MEHP | 0.265 | 1.00 (0.93, 1.07) | 1.04 (0.98, 1.12) | 1.05 (0.98, 1.12) | 0.168 |
| MEOHP | 0.343 | 0.99 (0.93, 1.05) | 1.04 (0.97, 1.11) | 1.05 (0.98, 1.12) | 0.229 |
| MEP | 0.352 | 1.01 (0.94, 1.08) | 1.05 (0.98, 1.12) | 1.04 (0.98, 1.11) | 0.172 |
| MHBP | 0.787 | 1.00 (0.94, 1.07) | 1.02 (0.96, 1.09) | 1.02 (0.96, 1.08) | 0.566 |
| MHiBP | 0.412 | 1.00 (0.94, 1.07) | 1.04 (0.97, 1.12) | 1.04 (0.98, 1.10) | 0.264 |
| MiBP | 0.432 | 0.99 (0.93, 1.07) | 1.03 (0.97, 1.10) | 1.04 (0.98, 1.11) | 0.336 |
| MMP | 0.083 | 1.05 (0.99, 1.11) | 1.07* (1.01, 1.13) | 1.02 (0.96, 1.08) | 0.032* |
| Propyl paraben | 0.785 | 0.98 (0.92, 1.05) | 1.00 (0.95, 1.07) | 1.02 (0.96, 1.08) | 0.727 |
| Triclosan | 0.125 | 0.95 (0.89, 1.01) | 1.00 (0.94, 1.07) | 1.05 (0.99, 1.12) | 0.853 |

[a]Estimating average association across B1 and B4 EDC measurements using a multivariable GEE model adjusting for age at B1 EDC measurement, age at B4 EDC measurement, BMI z-score at B1, BMI z-score at B4, and maternal education

[b]Overall test whether EDC category improves model fit (multivariate Wald test)

[c]Trend evaluated by modeling the log(median) concentration within tertiles as a continuous variable

*p<0.05,

**p<0.01,

***p<0.001

**Table 5.**

Relative shift in geometric mean (95% CI) percent fibroglandular volume between tertiles of MEP concentrations stratified by Tanner stage at EDC measurement[a]

| EDC | Tanner Stage | Overall Test[b] (p-value) | Middle vs Lowest Tertile (ref) | Highest vs Lowest Tertile (ref) | Highest vs Middle Tertile (ref) | Trend[b] (p-value) |
|---|---|---|---|---|---|---|
| MEP | | | | | | |
| | B1 | 0.742 | 1.03 (0.94, 1.12) | 1.00 (0.91, 1.09) | 0.97 (0.89, 1.06) | 0.875 |
| | B4 | 0.026* | 0.99 (0.91, 1.07) | 1.10* (1.01, 1.20) | 1.12* (1.02, 1.22) | 0.024* |

[a]Estimating Tanner stage-specific association between EDC metabolite and percent fibroglandular volume using a multivariable GEE model adjusting for age at B1 EDC measurement, age at B4 EDC measurement, BMI z-score at B1, BMI z-score at B4, and maternal education, including an interaction between EDC tertile and Tanner stage; restricted to subset of association for which the interaction with Tanner stage was significant ($p<0.05$)

[b]Overall test whether EDC category improves model fit (Likelihood ratio test)

[c]Trend evaluated by modeling the log(median) concentration within tertiles as a continuous variable

*$p<0.05$,

**$p<0.01$,

***$p<0.001$