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Environmental phenols and pubertal development in girls

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ABSTRACT

Environmental exposures to many phenols are documented worldwide and exposures can be quite high (>1 μM of urine metabolites). Phenols have a range of hormonal activity, but knowledge of effects on child reproductive development is limited, coming mostly from cross-sectional studies. We undertook a prospective study of pubertal development among 1239 girls recruited at three U.S. sites when they were 6–8 years old and were followed annually for 7 years to determine age at first breast or pubic hair development. Ten phenols were measured in urine collected at enrollment (benzophenone-3, enterolactone, bisphenol A, three parabens (methyl-, ethyl-, propyl-), 2,5-dichlorophenol, triclosan, genistein, daidzein). We used multivariable adjusted Cox proportional hazards ratios (HR (95% confidence intervals)) and Kaplan–Meier survival analyses to estimate relative risk of earlier or later age at puberty associated with phenol exposures. For enterolactone and benzophenone-3, girls experienced breast development 5–6 months later, adjusted HR 0.79 (0.64–0.98) and HR 0.80 (0.65–0.98) respectively for the 5th *vs* 1st quintiles of urinary biomarkers (μg/g-creatinine). Earlier breast development was seen for triclosan and 2,5-dichlorophenol: 4–9 months sooner for 5th *vs* 1st quintiles of urinary concentrations (HR 1.17 (0.96–1.43) and HR 1.37 (1.09–1.72), respectively). Association of breast development with enterolactone, but not the other three phenols, was mediated by body size. These phenols may be antiadipogens (benzophenone-3 and enterolactone) or thyroid agonists (triclosan and 2,5-dichlorophenol), and their ubiquity and relatively high levels in children would benefit from further investigation to confirm these findings and to establish whether there are certain windows of susceptibility during which exposure can affect pubertal development.

1. Introduction

During the past 20 years, a new generation of environmental contaminants has emerged, including metabolites of chemicals used widely in commerce and derived from a variety of sources (Wolff, 2006). Human exposure exists universally, as documented by detection of urinary metabolites around the world (CDC, 2009; Moos et al., 2014; Philippat et al., 2012; Engel et al., 2014; Nahar et al., 2012; Xue et al., 2015). Reported urinary biomarkers include more than a dozen phenols, which may be a parent compound or metabolite, including phytoestrogen polyphenols that are dietary in origin. Biological effects have been seen in a variety of experimental models, potentially related to several hormonal mechanisms in humans including thyroid agonists and obesogens (Witorsch and Thomas, 2010). Structural homology with agents of known function suggests that varying responses exist for different phenols including possible mechanisms for common urinary phenols (Fig. 1). Several polyphenols resemble antiobesogens and aromatase inhibitors, and agents with a chorophenol moiety are similar to thyroid hormone (Buzdar and Howell, 2001; Gross and Staels, 2007; Okada-Iwabu et al., 2013).

Puberty is a reproductive milestone that signals the onset of maturity, and early puberty is likely a risk for metabolic disease and breast cancer (Biro and Wolff, 2011; Bodicoat et al., 2014). Action of environmental agents during puberty may be an indirect pathway to later disease. In particular, hormonal effects of environmental agents are relevant to

Abbreviations: BMI, Body mass index; B1, B2, breast stage 1, 2; PH1, 2, pubic hair stage 1,2; LOD, limit of detection; CDC, Centers for Disease Control and Prevention.

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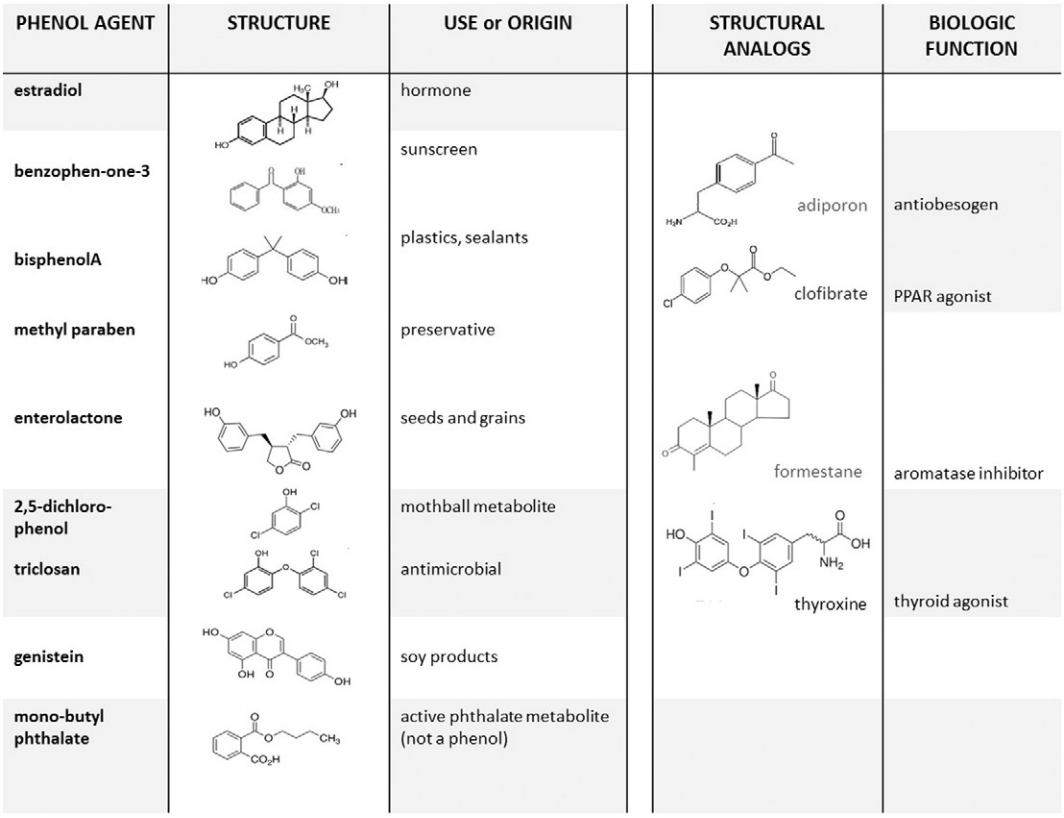

Fig. 1. Chemical structures of environmental phenols, examples of representative sources, and possible mechanistic parallels for converse associations with hormonal outcomes, including adiponectin agonists or aromatase inhibitors. (Buzdar and Howell, 2001; Okada-Iwabu et al., 2013). In addition, enterolactone is derived from lignans and both genistein and daidzein are isoflavone phytoestrogens mainly found in soy products and legumes.

breast development as well as changes in body size or obesity. Both earlier and later pubertal milestones have been seen with a number of phenols, mainly in cross-sectional studies (Biro and Wolff, 2011; Buttke et al., 2012). We reported previously on exposures to ten phenols among girls in the Breast Cancer and Environment Research Program (BCERP) Puberty Study when girls in the cohort were <10 years of age (Wolff et al., 2010). In this new analysis, we have investigated timing of pubertal onset across 7 years of follow-up, during which stage 2 of breast or pubic hair was reached by >85% of girls. Thus, we can now examine associations of exposures measured at enrollment in relation to actual ages for these benchmarks across the window of development, and with respect to changes in body size during this period.

2. Materials and methods

2.1. Study design and data collection

The BCERP Puberty Study is a cohort that has followed girls enrolled starting in 2004. This report includes data collected through 2012 (up to seven years' follow-up). Study sites included Icahn School of Medicine at Mount Sinai (MSSM) that recruited black or Hispanic girls mainly from East Harlem in New York City; Cincinnati Children's Hospital (Cincinnati) recruited from the greater Cincinnati metropolitan area; and Kaiser Permanente Northern California (KPNC) that recruited members of the KPNC Health Plan in the San Francisco Bay Area. Eligible girls were 6–8 years of age without serious endocrine medical conditions. Informed consent was obtained from parent or guardian administered by the institutional IRBs. The Centers for Disease Control and Prevention (CDC) IRB approved the urine specimen analysis, which had no personal identifiers. For this report, we used demographic, anthropometric, and pubertal assessments and urinary phenol metabolites for which complete protocols and analytic methods have been described previously along with quality control measures (Biro et al., 2010; Wolff et al., 2010). As detailed there, we obtained age at stage 2, the first appearance of breast (B2) or pubic hair (PH2) development (*vs* stage 1, B1 or PH1, no development), as well as age- and sex-specific body mass index percentiles (BMI% at the last B1 or PH1 visit) calculated using the CDC growth charts (CDC, 2000). Urine specimens collected at enrollment were analyzed using well-established analytic methods at the CDC National Center for Environmental Health laboratory that were available for 10 metabolites that represent several families of phenols (benzophenone-3, enterolactone, bisphenol A, methyl-, ethyl-, propyl-parabens, 2,5-dichlorophenol, triclosan, genistein, and daidzein). We summed the paraben metabolites based on molecular weight, expressed as propyl paraben (molecular weight 180.2 g/mol). Phenols were detected in >80% of samples except for butyl paraben (48%). Concentrations below the limit of detection (LOD) were assigned the value LOD/√2. Concentrations (ln-μg/L) were normalized for urine dilution in linear models using ln-creatinine as a covariate or, in models with quintiles, using cutpoints based on creatinine-corrected biomarkers (μg/g-creatinine). There were 1170 girls with at least one exposure biomarker and pubertal stage information. The urinary phenol assays were the same as those reported earlier (Wolff et al., 2010), with a few analyses that were added at a later date; see Suppl Table 1 for a summary.

2.2. Statistical analyses

Analyses were performed with SAS (version 9.4; SAS Institute, Inc). We modeled relative risk for age when girls advanced from B1 to B2 or PH1 to PH2 using Cox Proportional Hazards models to compute Hazard ratios (HR) and 95% confidence intervals (CI) in relation to phenol exposures. More details on the Cox methods and handling of censored pubertal age values are given in (Wolff et al., 2014). We obtained