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Environmental estrogen-like endocrine disrupting chemicals and breast cancer

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ABSTRACT

Background: Estrogen-mimicking endocrine disruptors (EEDs) such as polychlorinated biphenyls (PCBs), bisphenol A (BPA), and phthalates have been found ubiquitously throughout our environment. Although exposure to EEDs has the ability to interfere with endocrine control of reproductive function and development in both humans and wildlife, inconsistent reports have made it difficult to draw conclusions concerning the hypothesized increased risk of breast cancer associated with EEDs.

Objectives: The purpose of this study was to examine the cross-sectional relationship between exposure to PCBs, BPA or phthalates; and risk of breast cancer in U.S. women using the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) data between 1999 and 2004.

Methods: We analyzed data from female participants (20 years of age and older) collected by NHANES between 1999 and 2004 for exposure assessment based on lipid adjusted serum levels of 6 individual PCB congeners (PCB 074, 099, 118, 138, 153, and 180), the sum of dioxin-like PCBs (074 and 118), and the sum of non-dioxin-like PCBs (099 + 138 + 153 + 187). Levels of urinary BPA and seven phthalate metabolites mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-ethyl phthalate (MEP), mono-(3-caroxypropyl) phthalate (MCPP), mono-benzyl phthalate (MZP), and three metabolites of di (2-ehtylhexyl) phthalate (DEHP): [mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)] were obtained from the 2003–2010 yearly survey cycles in participants aged 6 years and older. Assessments of EEDs or their metabolites were analyzed in conjunction with medical and reproductive health questionnaire data. Age, race/ethnicity, age at menarche, body mass index (BMI; kg/m^2), and lactation were considered as potential confounders in our final models. Geometric means (GM) were calculated to compare PCB, BPA or phthalate concentrations in women who self-reported a breast cancer diagnosis versus women who self-reported never being diagnosed with breast cancer. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the association between PCB, BPA or phthalate measurements and breast cancer.

Results: In age, race/ethnicity, and BMI adjusted models, PCB138 was the only congener found to be significantly associated with breast cancer [OR of 3.16; 95% CI: 1.14–8.76]. We also found the sum of non-dioxin-like PCBs to be significantly associated with breast cancer [OR of 1.14; 95% CI: 1.00–1.29]. Risk of breast cancer, however, was not found to be significantly associated with phthalate, phthalate metabolites, and BPA in unadjusted or adjusted logistic regression models.

Conclusions: Our results suggest a link between environmental exposures to PCB 138 and breast cancer. There were no significant associations between phthalates or BPA and breast cancers. These findings should be interpreted with caution because of the use of cross-sectional self-reported data and a small sample size of breast cancer subjects. Nonetheless, our finding emphasizes a need of comprehensive environmental molecular epidemiologic study to determine the potential role of environmental exposures to PCBs, phthalates, and BPA in the development of breast cancer.

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1. Introduction

There is a general agreement that human populations are constantly exposed to a wide variety of environmental estrogen-like endocrine disrupting chemicals. Endocrine disrupting effects of some of the environmental estrogen-like chemicals in humans through experimental animal data and epidemiological studies have been widely recognized (Roy et al., 1997, 1998; Liehr et al., 1998; Faroon and Olson, 2000; Burantrevedh and Roy, 2001; Bergman et al., 2012; Munn and Goumenou, 2013). Only a limited number of estrogen-mimicking endocrine disruptors (EEDs), such as diethylstilbestrol (DES), polychlorinated biphenyls (PCBs), bisphenol A (BPA), and phthalates have been studied extensively to assess the endocrine disrupting effects and biological consequences of these effects in experimental models and in humans. Reproductive abnormalities reported in female rodents include increased uterine and ovarian weights and malformations at very high phthalate levels, delayed onset of puberty and modified morphology of the mammary gland (Moral et al., 2008). We have shown that bisphenol A (BPA) is oxidized to bisphenol-o-quinone by the cytochrome P450 activation system (Atkinson and Roy, 1995a). Administration of a single dose or multiple doses of 200 mg/kg of BPA to CD1 male rats produced in vivo DNA adducts matching the profile of dGMP-bisphenol-o-quinone. Covalent modifications in DNA by in vivo exposure of BPA are suspected to be a factor in the induction of endocrine toxicity (Atkinson and Roy, 1995b). In female rodents, BPA exposure was shown to cause alterations in the mammary gland development, changes in gene expression of the mammary gland, and an increased expression of estrogen receptor-α (ERα) and progesterone receptors (Moral et al., 2008; Colerangle and Roy 1997; Muñoz-de-Toro et al., 2005; Newbold et al., 2009; Signorile et al., 2010; Cabaton et al., 2011). Estrogen is a major risk factor of breast cancer (Roy and Singh, 2004; Okoh et al., 2011, 2013; DeSantis et al., 2014; Bodicoat et al., 2014; Ferlay et al., 2015). The contribution of unopposed estrogens to the risk for breast cancer allows for a perception of health concerns among the public about EEDs found in food, personal care products or as environmental contaminants. In the last decade, exposure to multiple EEDs such as PCBs, phthalates, and BPA have been detected in 90% of blood and urine samples collected (Calafat et al., 2008; Woodruff et al., 2011; Silva et al., 2004). Exposure to PCBs, BPA, or phthalates during early development of the breast, endometrium, and prostate may alter their development possibly contributing to the susceptibility to complex chronic diseases through effects on stem cells. The role of EEDs in the etiology of some human cancers and reproductive health hazards has been implicated, but the linkage between these two processes is highly controversial (Burantrevedh and Roy, 2001).

While there are studies which link PCBs, BPA, and phthalate exposure to an increased risk of breast cancer, there have also been inconsistent study findings that reported no association between these EEDs and increased breast cancer risk. Studies pertaining to PCBs and breast cancer are controversial. While some studies reported no significant associations (Wolff et al., 2000; Pavuk et al., 2003; Itoh et al., 2009) or inverse associations (Charlier et al., 2004; Cohn et al., 2012) other studies have found an increased breast cancer risk when analyzing total PCB exposure or specific individual PCB congeners (Recio-Vega et al., 2011; Demers et al., 2002; Muscat et al., 2003; Zhang et al., 2004; Millikan et al., 2000; Li et al., 2004, Roy et al., 2015). Charlier et al., 2004 found concentrations of PCB 138 (1.25 vs. 0.94 ppb; $p = 0.0068$), PCB 153 (1.63 vs. 0.63; $p < 0.0001$), and total PCBs (7.08 vs. 5.10 ppb; $p = 0.012$) to be significantly higher in cases when compared to controls. Millikan et al., 2000 did not find any associations with total PCBs and breast cancer among all participants (OR = 1.09; 95% CI, 0.79–1.52) or white women (OR = 1.03; 95% CI, 0.68–1.56), but did find a slightly elevated risk for African-American women (OR = 1.74; 95% CI, 1.00–3.01). Recio-Vega et al., 2011 found the GM of total PCBs to be significantly higher in cases than controls (5.26 vs. 3.33 ppb) (OR = 1.09; 95% CI, 1.01–1.14) as well as an increased risk of breast cancer among PCBs grouped by structure-activity relationships and 8 individual PCB congeners (nos. 118, 128, 138, 170, 180, 195, 206, and 209) and Muscat et al., 2003 found that PCB concentrations in the highest tertile for PCB congener 118 (RR = 4.0; 95%, CI 1.32–4.9) and total PCBs (RR = 2.9; 95% CI, 1.02–8.2) were related to an increased risk of breast cancer recurrence in women with non-metastatic breast cancer. Stronger associations were reported between PCB exposure and breast cancer risk in studies that considered genetic polymorphism of the CYP 1A1 enzyme and menopausal status (Zhang et al., 2004; Li et al., 2004; Moysich et al., 1998, 1999). CYP1A1-M2 genetic variants were found to modify the association between PCB exposure and breast cancer in post-menopausal Caucasian women, while CYP1A1-M3 genotypes were found to modify this association in African American women (Zhang et al., 2004; Li et al., 2004). Limited studies have shown a relationship between phthalate exposure and breast cancer (López-Carrillo et al., 2010) and BPA exposure and breast cancer (Yang et al., 2009).

The purpose of this study was to use the National Health and Nutrition Examination Survey (NHANES) data to assess the association of breast cancer with exposure to PCBs, BPA, and phthalates which are three selected classes of EEDs commonly found in the environment. In this study, we examined the relationship between 6 individual PCB congeners, the sum of dioxin-like PCBs, and the sum of non-dioxin-like PCBs with self-reported breast cancer in female subjects participating in the NHANES between the years 1999–2004. Data on the Urinary BPA measurements were obtained from the 2003–2004, 2005–2006, 2007–2008, and 2009–2010 survey cycles in survey participants aged 6 years and older. The objectives of this study were to: 1) describe the mean PCB, phthalates (metabolites of phthalates), and BPA levels in women (≥20 years of age) diagnosed with breast cancer compared to women not diagnosed with breast cancer; and 2) assess the association between higher body burdens of PCBs, phthalates, phthalate metabolites, BPA and increased risk of breast cancer.

2. Methods

2.1. Study design and population

NHANES is an ongoing cross-sectional survey designed to be nationally representative of the non-institutionalized U.S. civilian population. Conducted annually since 1999 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC), NHANES uses a complex multi-stage sampling design where approximately 5000 survey participants a year complete in-home interviews and physical examinations in mobile examination units (CDC, 2012, 2013a, b, 2014). All participants provided written informed consent and all procedures were approved by the National Center for Health Statistics (NCHS) Institutional Review Board (CDC, 2012, 2013a, b, 2014). We merged data from the 1999–2000, 2001–2002, and 2003–2004 survey cycles. We limited our analysis to women 20–85 years of age who completed the reproductive and medical health questionnaires in a face-to-face interview at a mobile examination center.

2.2. Medical health questionnaire

Self-reported cancer status was obtained through the medical questionnaires in participants' 20 years of age and older who