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Association between Exposure to Estrogenic Endocrine Disruptors - Polychlorinated Biphenyls, Phthalates, and Bisphenol A and Gynecologic Cancers- Cervical, Ovarian, Uterine Cancers

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Abstract

Introduction: Estrogen is a driver in the growth and progression of gynecologic cancers (cervical, ovarian, and uterine). A number of estrogenically active chemicals are suspected to contribute in the development of gynecologic lesions, including an increased risk of estrogen-dependent cancer in women. Humans are exposed to estrogenic endocrine disruptors (EEDs), such as- polychlorinated biphenyls (PCBs), phthalates and bisphenol A (BPA). Therefore, we examined the cross-sectional relationship between exposure to PCBs, phthalates, and BPA and gynecologic cancers (cervical, ovarian, and uterine).

Methods: We analyzed data from female participants (20 years of age and older) who provided blood and urine samples for the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010. Exposure was examined based on lipid adjusted serum levels of 6 individual PCB congeners (74, 99, 118, 138, 153, and 180), the sum of dioxin-like PCBs (074 and 118), the sum of non-dioxin-like PCBs (099+138+153+187), 8 urinary phthalate metabolites (MNP, MEP, MEHP, MBzP, MCPP, MEHHP, MEOHP, and MIB), the sum of DEHP metabolites (MHP+MHH+MOH), the sum of total phthalates, and urinary BPA in conjunction with data obtained from the medical and reproductive health questionnaires. We calculated geometric means to compare EEDs concentrations in women who self-reported a cervical, ovarian, or uterine cancer diagnosis *vs.* women who self-reported never being diagnosed with cancer. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between exposure to EEDs and r gynecologic cancers. We also evaluated age, race/ethnicity, body mass index (BMI; kg/m^2), and age at menarche as potential confounding variables in our final models.

Results: Separate analyses showed weighted geometric mean (GM) levels of individual PCB congeners to be significantly higher among women with ovarian cancer, and uterine cancer when compared to the rest of the study population. Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was found to be significantly higher and BPA was higher among women with ovarian cancer compared to women never diagnosed with any gynecologic cancer. After adjusting for age, race, BMI, and age at menarche, we found that PCB 138 was significantly associated with cervical cancer, and uterine cancer [odds ratios of 3.05, 95% CI: 1.21-7.69; and 5.83, 95% CI: 1.63-20.9], respectively. PCB 74 and 118 however, were significantly associated with ovarian cancer with an odds ratios of 6.47, 95% CI: 1.23-3.41 (for PCB 74) and 6.68, 95% CI: 1.39-32.3 (for PCB 118). We also found the sum of non-dioxin-like PCBs to be significantly associated with uterine cancer (OR of 1.12, 95% CI: 1.03-1.23) and the sum of dioxin-like PCBs to be significantly associated with ovarian cancer (OR of 2.02, 95% CI: 1.06-3.85). We did not find significant associations between urinary phthalates and BPA and gynecologic cancers.

Conclusions: Our findings point to a possible association between environmental exposure to PCBs and an increased risk of cervix, ovarian and uterine cancer. However, these findings should be interpreted cautiously because of self-reported cross sectional data and a limited sample size of gynecologic cancers.

Keywords: NHANES; PCBs; Phthalates; BPA; EDC; Gynecologic cancers

Introduction

Based on 2009-2013 survey, NCI SEER 2016 estimates that the number of new cases of gynecologic cancers- cervical, endometrial and ovarian was 7.5, 25.4 and 11.9 per 100,000 women per year, respectively [1]. However, in terms of deaths, ovarian cancer leads to more deaths than uterine and cervical cancers. To prevent new incidence of gynecologic cancers, it is important to understand the associated environmental and molecular risk factors. In most cases, the exact cause of these cancers is not known. Genetics can only account for 5-10% of gynecologic cancer risks and the rest possibly can be attributed to hormonal and environmental influences.

Epidemiologic studies support unopposed elevated levels of estrogen exposure including endocrine-active chemicals and their

association with increased risk of developing cervical, ovarian and endometrial cancers [2-8]. A recent report by the United Nations Environment Program (UNEP) and WHO highlighted the increasing rates of endocrine-related cancers over the past 40-50 years in conjunction with approximately 800 chemicals that are suspected to act as endocrine disruptors [9,10]. Many of these chemicals are used in a variety of consumer products; therefore, exposure to endocrine disrupting chemicals among general population is widespread. Human exposure to endocrine disrupting chemicals may result from inhalation from air, absorption through the skin, and most commonly through the ingestion of contaminated food and water [11]. Human populations are constantly exposed to a wide variety of estrogenic endocrine disruptors (EEDs). Exposure to multiple EEDs, such as polychlorinated biphenyls (PCBs), phthalates, and bisphenol A (BPA) have been detected in 90% of blood and urine samples collected [12-14] in various human studies during the last decade.

The role of EEDs, in the etiology of some of the human gynecologic cancers and reproductive health hazards, has been implicated, although the linkage between these two processes is highly controversial [2-8]. In rodent experimental models, neonatal exposure to DES, dioxin-like compounds, 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153); 2,3',4,4',5-pentachlorobiphenyl (PCB118); hydroxylated polychlorinated biphenyls BPA affects the adult uterine response to hormone and induces reproductive lesions including uterotrophy, uterine hyperplasia and cancer, cervicovaginal (CV) tract carcinomas [15,16]. Animal studies have linked PCB exposure to decreased sperm fertilizing ability in mice [17], changes in the uterine myometrium [18], and exhibited a significant dose-dependent relationship in the prevalence and severity of endometriosis in rhesus monkeys [19]. Among various phthalates, di (2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP) and butylbenzyl phthalate (BBP) have been studied for their endocrine disrupting effects. Phthalates were shown to produce anti-androgenic effects by suppressing testosterone and oestrogen production. At very high phthalate levels, reproductive abnormalities were reported in rodent females which included increased uterine and ovarian weights, and delayed onset of puberty [20]. In our earlier study [21], we have shown that bisphenol A (BPA) is oxidized to bisphenol-o-Quinone by cytochrome P450 activation system. Administration of a single dose or multiple doses of 200 mg/kg of BPA to CD1 male rats produced *in vivo* DNA adducts with matching dGMP-bis-phenol-o-Quinone profile. Further, covalent modifications in DNA by *in vivo* exposure of BPA are suspected to be a factor in the induction of endocrine toxicity [21]. In rodent females, BPA exposure has shown to cause alterations in the mammary gland development, changes in gene expression of the mammary gland and many other gynecological cancer related disorders and impairments. For example, BPA exposure has also been shown to cause cystic ovaries, endometrial hyperplasia, adenomyosis, leiomyomas, atypical hyperplasia, stromal polyps, ductal hyperplasias and carcinoma, a decline in fertility and fecundity, decreased wet weight of the vagina, decreased volume of the endometrial lamina propria, and an increased expression of estrogen receptor-α (ERα) and progesterone receptors [20,22-27]. Estrogen is a major driver in the growth and progression of gynecologic cancers (cervix, ovary, and uterus) [2-4,28-30]. PCBs, BPA, and phthalates are extensively studied estrogenically active chemicals, and therefore, our objective of this study was to use the available National Health and Nutrition Examination Survey (NHANES) data (1999-2010) to assess the association of gynecologic cancers (cervix, ovarian, and uterine) with exposure to these three selected classes of EEDs: PCBs, BPA, and phthalates.

Methods

Study design and population

We obtained blood serum concentrations of individual PCB congeners (6 individual PCB congeners, the sum of dioxin-like PCBs, and the sum of non-dioxin-like PCBs) and urinary phthalates and bisphenols data from the NHANES (http://www.cdc.gov/nchs/nhanes/index.htm) as described by Marissa et al. [8].

Gynecologic cancers data collection

We included female NHANES participants of 25 to 85 years of age who completed the physical exam, reproductive questionnaire, and medical health questionnaire and provided a response for "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" Women who answered "yes" were subsequently asked "What kind of cancer was it?"

A total of 8,315 women who provided a response in the 1999-2004 survey cycles to for "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" question. After removing the observations that did not include PCB data, our PCB study population consisted of 2,072 participants: 27 reported a cervical cancer diagnosis, 11 reported an ovarian cancer diagnosis and 26 reported a uterine cancer diagnosis and women who did not report a cancer diagnosis ranged from 1955 to 1962 depending on the PCB congener being evaluated.

Our phthalate study population consisted of women of 20 to 85 years of age who provided a response in the 2003-2010 survey years to "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" question. After removing creatinine observations that were <30 mg/dL and >300 mg/dL our study populations consisted of 3,003 participants of whom 28 reported a cervical cancer diagnosis, 20 reported an ovarian cancer diagnosis, 27 reported a uterine cancer diagnosis and 2,731 reported no cancer diagnosis.

Our BPA study population consisted of women of 20 to 85 years of age provided a response in the 2005-2010 survey cycles to for "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" question. After removing creatinine observations that were <30 mg/dL and >300 mg/dL our study populations consisted of 2,202 participants of whom 16 reported a cervical cancer diagnosis, 16 reported an ovarian cancer diagnosis, 22 reported a uterine cancer diagnosis, and 2,070 reported no cancer diagnosis.

Statistical analysis

Due to a small number of cervical, ovarian, and uterine cancer cases, we conducted logistic regression analyses using the following two groups: Level of detection (LOD) to 50th percentile (reference) *vs.* ≥ 50th percentile. We also conducted separate analyses on females with serum PCB, phthalate, and BPA levels >LOD where gynecologic cancers cases were compared with non-cancer cases. Significance was set at $p < 0.05$. As described in our recent paper [8], using PROC SURVEYLOGISTIC, we derived unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) to evaluate the association between exposure to EEDs and cervical cancer, ovarian cancer, or uterine cancer. We conducted separate analyses for the sum of dioxin-like and non-dioxin-like PCBs and individual PCB

congeners and gynecologic cancers. Due to a small number of cervical, ovarian, and uterine cancer cases, ORs and 95% CIs were calculated using the following group: <LOD to 50th percentile *vs.* ≥ 50th percentile. The reference group for each PCB congener is defined as those participants whose serum concentrations were <LOD to 50th percentile.

Covariates

The following potential confounders were either self-reported in the questionnaire interviews or taken as a laboratory measurement. The demographic variables of age at interview (20-59 years, 60-74 years, and ≥ 75 years), race (white *vs.* other) were obtained during the NHANES home interview [8]. Reproductive variables including age at menarche (<12 years, 12-14 years, ≥ 15 years), parity (0, 1, ≥ 2), oral contraceptive use (yes/no) and lactation (yes/no) as well as lifestyle variables including smoking (yes/no) and alcohol use (yes/no) were obtained from health questionnaires completed in the mobile examination center. Body mass index (<25 kg/m^2, 25 to <30 kg/m^2 and ≥ 30 kg/m^2) was obtained through the body measurement component in the mobile examination center [23]. For all EEDs, ORs and 95% CIs are reported for three models: unadjusted; age and race/ethnicity adjusted; and age, race/ethnicity, BMI, and age at menarche adjusted. Parity and oral contraceptive use, and lactation were not included in the models because of the extent of missing data. Smoking history and alcohol consumption were not significant predictors of gynecologic cancer risk and therefore were also not presented in the final models.

Results

PCB Descriptive Statistics

The study population included 2,008 female participants of 20 years of older age with available PCB data and who completed the medical conditions questionnaire and provided a response to "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" question. Women who answered "yes" were subsequently asked, "What kind of cancer was it?" question. Among the women who reported no cancer or a gynecological cancer: 1,965 (91.5%) reported never being diagnosed with cancer, 43 (2.14%) reported being diagnosed with cervical cancer, 11 (0.56%) reported being diagnosed with ovarian cancer, and 26 (1.31%) reported being diagnosed with uterine cancer (Table 1). Study participants were fairly evenly distributed between the two races: 48.6% were of non-Hispanic white ethnicity group and 51.4% were classified the group 'Other'. The majority of participants were 20-59 years of age at the time of interview (65.9%) (Table 1). The mean age at the time of interview was 45.6 years for the women who reported to have never been diagnosed with cancer, 47.5 years, 52.0 years, and 52.4 years for women who reported being diagnosed with cervical cancer, ovarian cancer, and uterine cancer, respectively. The mean age at diagnosis was 30.6 years, 41.9 years, and 53.2 years for women diagnosed with cervical cancer, ovarian cancer, and uterine cancer, respectively (Table 1). BMI was normal (<25 kg/m^2) for 35.5%, overweight (25 to <30 kg/m^2) for 28.6%, and obese (≥ 30 kg/m^2) for 39.0% of study participants. The majority of study participants reported an age of menarche of 12-14 years (64%), ≥ 2 live births (71.4%), responded yes to breastfeeding (57.6%), responded yes to oral contraceptive use (58.8%), responded no to a history of smoking (57.8%), and yes to alcohol consumption (54.5%) (Table 1).

	Cervical Cancer	Ovarian Cancer	Uterine Cancer
Variables	n (%)	n(%)	n(%)
Total Population (n, %)	27 (1.36%)	11 (0.56%)	26 (1.31%)
Age at interview (years; mean ± se)	47.5 ± 2.61	52.0 ± 3.75	52.4 ± 5.17
Age at diagnosis (years; mean ± se)	30.6 ± 1.14	41.9 ± 1.97	53.2 ± 1.52
Race/Ethnicity[1]			
Non-Hispanic white	19 (0.95%)	6 (0.30%)	17 (0.85%)
Other	8 (0.40%)	5 (0.25%)	9 (0.45%)
Age (years)			
20-59	18(0.90%)	7 (0.35%)	11 (0.55%)
60-74	6 (0.30%)	3 (0.15%)	11 (0.55%)
≥ 75	3 (0.15%)	1 (0.05%)	4 (0.20%)
Age at menarche (years)			
<12 years	10 (0.56%)	2 (0.11%)	7 (0.39)
12-14 years	14 (0.79%)	6 (0.34%)	14 (0.78%)
≥ 15 years	0 (0.00%)	2 (0.11%)	4 (0.22%)
Parity (no. of live births)			
0	3 (0.19%)	1 (0.07%)	1 (0.06%)
1	4 (0.26%)	2 (0.13%)	5 (0.32%)
>2	16(1.04%)	6 (0.39%)	18 (1.16%)
BMI (kg/m^2)			
Normal weight (18.5 to <25)	16 (0.80%)	4 (0.20%)	12 (0.60%)
Overweight (25 to <30)	16 (0.80%)	4 (0.20%)	8 (0.40%)
Obese (≥ 30)	9 (0.45%)	3 (0.15%)	8 (0.40%)
Breastfed			
Yes	12 (0.85%)	5 (0.36%)	13 (0.92%)
No	8 (0.57%)	3 (0.21%)	10 (0.71%)
Oral Contraceptive Use			
Yes	18 (0.98%)	6 (0.33%)	12 (0.66%)
No	6 (0.33%)	4 (0.22%)	14 (0.76%)
Ever Smoked			
Yes	13 (0.65%)	7 (0.35%)	16 (0.80%)
No	14 (0.70%)	4 (0.20%)	10 (0.50%)
Alcohol Use			
Yes	10 (0.55%)	7 (0.38%)	17 (0.93%)
No	15 (0.85%)	3 (0.16%)	9 (0.49%)

Estimated percent distribution after applying NHANES sampling weights.

Table 1: Descriptive statistics for gynecological cancer status and selected covariates among women ≥ 20 years of age with serum PCB measurements, NHANES 1999-2004. No cancer cases in total Population (n,%) 1965 (91.5%) Age at interview (years; mean ± se) 45.6 ± .42.

Phthalate and BPA descriptive statistics

The study population included 3,003 female participants of 20 years of age and older age with available phthalate and/or BPA data and who completed the medical conditions questionnaire and provided a response for "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" question.Women who answered "yes" were subsequently asked, "What kind of cancer was it?" and "What was your age at diagnosis?" question. Among the 3,003 participants, 2,731 (90.4%) reported never being diagnosed with cancer, 28 (0.65%) reported being diagnosed with cervical cancer, 20 (0.47%) reported being diagnosed with ovarian cancer, and 27 (0.63%) reported being diagnosed with uterine cancer (Table 2). The mean age at diagnosis was 30.5 years, 46.3 years, and 52.3 years for women diagnosed with cervical cancer, ovarian cancer, and uterine cancer, respectively (Table 2). BMI was normal (<25 kg/m^2) for 28.3%, overweight (25 to <30 kg/m^2) for 28.6%, and obese (≥ 30 kg/m^2) for 39.3% of study participants. The majority of study participants reported age of menarche at 12-14 years (62.1%), ≥ 2 live births (74.0%), responded yes to breastfeeding (54.9%), and responded yes to oral contraceptive use (63.4%), responded no to a history of smoking (58.4%), and yes to alcohol consumption (57.1%) (Table 2).

Variables	Cervical Cancer n(%)	Ovarian Cancer n(%)	Uterine Cancer n(%)
Total Population (n,%)	28 (0.65%)	20 (0.47%)	27 (0.63%)
Age at interview (years; mean ± se)	48.1 ± 2.71	56.1 ± 5.09	58.3 ± 3.10
Age at diagnosis (years; mean ± se)	30.5 ± 0.76	46.3 ± 1.42	52.3 ± 2.04
Race/Ethnicity[1]			
Non-Hispanic white	18 (0.65%)	9 (0.33%)	20 (0.73%)
Other	10 (0.36%)	11 (0.40%)	7 (0.25%)
Age (years)			
20-59	24 (0.87%)	11 (0.40%)	8 (0.29%)
60-74	3 (0.11%)	6 (0.22%)	11 (0.40%)
≥ 75	1 (0.04%)	5 (0.18%)	8 (0.29%)
Age at menarche (years)			
<12 years	1 (0.04%)	4 (0.16%)	5(0.20%)
12-14 years	18 (0.73%)	10 (0.41%)	17 (0.69%)
≥ 15 years	3 (0.12%)	3 (0.12%)	5 (0.20%)
Parity (no. of live births)			
0	1 (0.05%)	0 (0.00%)	0 (0.00%)
1	4 (0.20%)	4 (0.20%)	1 (0.21%)
>2	4 (0.20%)	11 (0.55%)	4 (0.82%)
BMI (kg/m2)			
Normal weight (18.5 to <25)	7 (0.26%)	3 (0.11%)	6 (0.22%)
Overweight (25 to <30)	7 (0.26%)	12 (0.44%)	6 (0.22%)
Obese (≥30)	14 (0.51%)	5 (0.18%)	15 (0.55%)
Breastfed			
Yes	15 (0.77%)	7 (0.36%)	11 (0.56%)
No	10 (0.51%)	8 (0.41%)	15 (0.77%)
Oral Contraceptive Use			
Yes	21(0.84%)	7 (0.28%)	15 (0.60%)
No	5 (0.20%)	10 (0.40%)	12 (0.48%)
Ever Smoked			
Yes	21 (0.76%)	6 (0.22%)	13 (0.47%)
No	7 (0.25%)	14 (0.51%)	14 (0.51%)
Alcohol Use			
Yes	19 (0.76%)	6 (0.24%)	14 (0.56%)
No	7 (0.28%)	11 (0.44%)	13 (0.52%)

Table 2: Descriptive statistics for gynecological cancer status and selected covariates among women ≥ 20 years of age with urinary phthalate and bisphenol a measurements, NHANES 2003-2010. Estimated percent distribution after applying NHANES sampling weights. Total Population with no cancer (n, %) 2731 (90.4%) Age at interview (years; mean ± se) 45.3 ± .40

Geometric mean[1]**(ng/g) (GSE,n)**			
PCB Metabolites[2]	**Cervical Cancer**	**Ovarian Cancer**	**Uterine Cancer**
PCB 074	9.58 (1.21, 27)	30.0 (1.32, 11)[b]	10.8 (1.21, 26)
PCB 099	6.82 (1.16, 26)	51.9 (1.32, 11)[b]	7.24 (1.21, 25)
PCB 118	12.2 (1.25, 27)	38.9 (1.38, 11)[b]	11.1 (1.32, 26)
PCB 138	12.2 (1.25, 27)	22.3 (1.36, 11)[b]	30.9 (1.14, 26)[b]
PCB 153	12.2 (1.25, 27)	12.2 (1.42, 11)[b]	40.9 (1.15, 26)[b]
PCB 180	23.8 (1.17, 27)	16.6 (1.28, 11)	30.3 (1.20, 26)[b]
Phthalate Metabolites[3]			
MBP	1.92 (1.04, 28)	1.93 (1.04, 20)	2.03 (1.07, 27)

MEP	2.86 (1.04, 28)	1.93 (1.04, 20)	3.10 (1.16, 27)[b]
MEHP	1.20 (1.05, 28)	1.36 (1.05, 20)	1.07 (1.07, 27)
MBzP	1.51 (1.05, 28)	1.68 (1.07, 20)	1.46 (1.08, 27)
MCCP	1.18 (1.05, 28)	1.26 (1.09, 20)	1.20 (1.04, 27)
MEHHP	1.88 (1.05, 28)	2.32 (1.25, 20)[b]	1.93 (1.08, 27)
MEOHP	1.77 (1.05, 28)	2.03 (1.28, 20)	1.72 (1.08, 27)
MIB	1.39 (1.04, 28)	1.46 (1.06, 20)	1.46 (1.09, 27)
DEHP4	3.34 (1.17, 28)	6.55 (2.08, 20)	3.53 (1.23, 27)
Total Phthalates5	54.6 (1.31, 28)	102 (1.54, 20)	56.8 (1.22, 27)
Bisphenol A[6]			
BPA	1.17 (1.08, 16)	1.23 (1.08, 16)	1.09 (1.06, 22)

Table 3: Geometric Mean of serum PCB or urinary phthalate levels (ng/g) by gynecological cancer status for women ≥ 20 years of age. [1]Geometric means calculated after applying NHANES sampling weights. [2]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g); NHANES 1999-2004. PCB metabolites in no cancer cases (GM, SE and n): PCB 074-8.08 (1.03, 1960), PCB099-5.99 (1.03, 1958), PCB118- 9.49 (1.03, 1960), PCB-138, 20.9 (1.03, 1961) PCB153-28.8 (1.02, 1962), PCB 180-19.5 (1.02, 1955). [3]Log transformed and creatinine corrected urinary phthalate metabolites (ng/mg); NHANES 2003-2010. Phthalate Metabolites in no cancer cases (GM, SE and n). MBP-1.93 (1.01, 2723), MEP- 2.83 (1.01, 2723), MEHP- 1.19 (1.01, 2723), MBzP- 1.54 (1.01, 2723)d, MCCP-1.21 (1.01, 2723), MEHHP-1.90 (1.01, 2723), MEOHP-1.72 (1.01, 2723), MIB-1.46 (1.01, 2723), DEHP4-3.86 (1.03, 2723), Total Phthalates 5-58.0 (1.04, 2723), [4]DEHP=Sum of MEHP, MEHHP and MEOHP. [5]Total Phthalates=Sum of MBP, MEP, MEHP, MBzP, MCCP, MEHHP, MEOHP and MIB. 6Log transformed and creatinine corrected urinary BPA measurements (ng/g); NHANES 2005-1010. BPA in no cancer cases (GM, SE and n). 1.16 (1.01, 2070) c PCB or phthalate levels significantly higher in women with cancer *vs.* women without cancer; [a]$p<0.0001$, [b]$p<0.05$. BPA significantly higher in women without cancer *vs.* women with breast cancer, [c]$p<0.05$. MBzP is significantly higher in women without cancer *vs.* women diagnosed with breast cancer, [d]$p<0.05$.

Table 3 presents GMs+GSEs of EEDs by gynaecologic cancer status. PCB 74, 99, 118, 138, and 153 were significantly higher in women diagnosed with uterine cancer and PCB 138, 153, and 180 were significantly higher in women diagnosed with uterine cancer compared to women never diagnosed with cancer. None of the PCB congeners were significantly higher in women diagnosed with cervical cancer (Table 3 and Figure 1). MHH was significantly higher in women diagnosed with ovarian cancer compared to women never diagnosed with cancer (Table 3 and Figure 2). MHP was the only phthalate found to be significantly higher among women with a gynaecologic cancer compared to women never diagnosed with cancer. Women diagnosed with a gynaecologic cancer did not have significantly higher levels of BPA compared to women never diagnosed with cancer (Table 3).

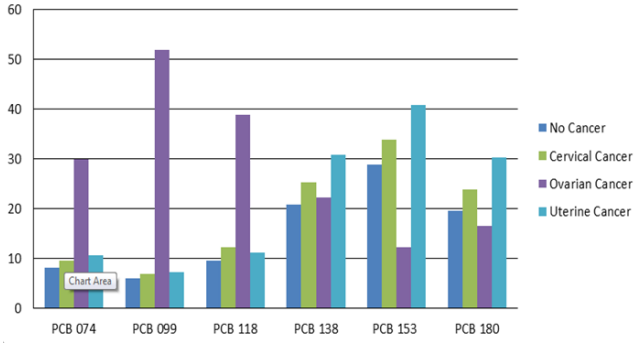

Figure 1: Geometric Mean PCB levels (ng/g) by cancer status for women ≥ 20 years of age, NHANES 1999-2004.

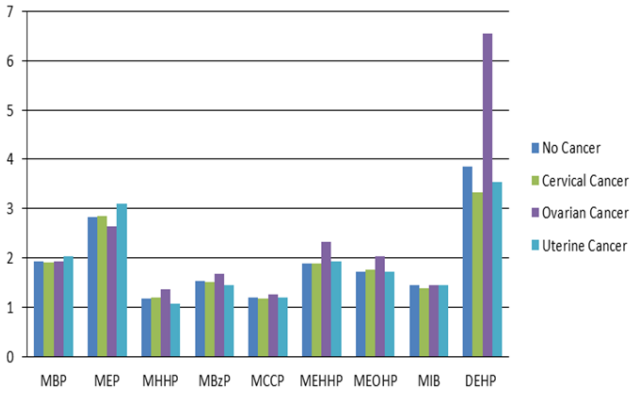

Figure 2: Geometric mean urinary phthalate levels (ng/mg) in women ≥ 20 years of age, NHANES 2003-2010.

GM of EED levels were also examined by cancer status in women with individual PCB concentrations with >LOD (Table 4). PCB 74, 99, 118, 138, and 153 were significantly higher in women diagnosed with ovarian cancer, and PCB 138 was significantly higher in women diagnosed with uterine cancer compared to women never diagnosed with cancer. For women with phthalate concentrations >LOD, GM levels did not differ between women diagnosed with a gynecologic cancer and women never diagnosed with cancer (Table 4). When observations <LOD were removed, BPA became significantly higher in women diagnosed with cervical cancer compared to women never diagnosed with cancer (Table 4).

Geometric mean1 (ng/g) (GSE,n)			
	Cervical Cancer	**Ovarian Cancer**	**Uterine Cancer**
PCB Metabolites[2]			
PCB 074	10.7 (1.25, 24)	21.8 (1.19, 9)[a]	10.9 (1.21, 23)

PCB 099	7.61 (1.21, 21)	20.1 (1.21, 8)[b]	8.50 (1.22, 19)
PCB 118	14.4 (1.29, 24)	30.9 (1.25, 9)[a]	12.9 (1.25, 23)
PCB 138	28.2 (1.22, 24)	47.5 (1.38, 9)[b]	31.5 (1.14, 25)[b]
PCB 153	37.7 (1.21, 25)	63.4 (1.35,9)[b]	41.3 (1.15, 25)
PCB 180	25.0 (1.17, 25)	37.7 (1.36, 9)	30.9 (1.21, 24)
Phthalate Metabolites[3]			
MBP	1.92 (1.04, 28)	1.93 (1.04, 20)	2.03 (1.08, 27)
MEP	2.86 (1.04, 28)	2.64 (1.05, 20)	3.10 (1.16, 27)[b]
MEHP	1.45 (1.06, 18)	1.55 (1.27, 16)	1.16 (1.04, 19)
MBzP	1.51 (1.05, 28)	1.68 (1.07, 20)	1.46 (1.05, 27)
MCCP	1.19 (1.05, 28)	1.26 (1.09, 20)	1.20 (1.05, 27)
MEHHP	1.88 (1.06, 28)	2.32 (1.25, 20)	1.93 (1.04, 27)
MEOHP	1.77 (1.05, 28)	2.03 (1.28, 20)	1.72 (1.08, 27)
MIB	1.43 (1.04, 28)	1.46 (1.06, 20)	1.46 (1.06, 27)
Bisphenol A[6]			
BPA	1.27 (1.05, 14)[a]	1.30 (1.08, 15)	1.09 (1.06, 22)

Table 4: Geometric Mean PCB or urinary phthalate levels (ng/g) by gynecological cancer status for women ≥ 20 years of age with concentrations above the LOD. [1]Geometric means calculated after applying NHANES sampling weights. [2]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g); NHANES 1999-2004. PCB metabolite levels in no cancer cases (GM, SE n). PCB 074-9.87 (1.03, 1484), PCB 099-7.24 (1.02, 1334), PCB 118-11.7 (1.03, 1534), PCB 138 -23.6 (1.03, 1594), PCB 153-31.8 (1.03, 1651), PCB 180- 23.3 (1.03, 1600). [3]Log transformed and creatinine corrected phthalate metabolites (ng/mg); NHANES 2003-2010. Phthalate metabolite in no cancer cases (GM, SE n). MBP-1.93 (1.01, 2718), MEP- 2.83 (1.01, 2722), MEHP- 1.34 (1.01, 1913), MBzP- 1.55 (1.01, 2704), MCCP- 1.22 (1.01, 2677), MEHHP- 1.90 (1.01, 2719), MEOHP- 1.72 (1.01, 2714), MIB-1.48 (1.01, 2695). [4]Log transformed and creatinine corrected urinary BPA measurements (ng/g); NHANES 2005-1010. BPA (GM, SE n). 1.18 (1.01, 1959) PCB, BPA, or phthalate levels significantly higher in women with cancer *vs.* women without cancer; [a]$p<0.0001$, [b]$p<0.05$

Estimated ORs and 95% confidence intervals (CI) for the risk of having cervical, ovarian, or uterine cancers cancer and the six individual PCB congeners are shown in Tables 5-8. Estimated ORs and 95% CIs for the risk of having cervical cancer and the six individual PCB congeners are shown in Table 6. In unadjusted models, PCBs were significantly associated with cervical cancer risk for subjects in the second group (≥ 50th percentile) when compared to the reference group (<LOD to 50th percentile) for PCB congeners 138 and 153 (Table 5). After adjusting for age and race/ethnicity, PCB138 was the only congener found to be significantly associated with cervical cancer (OR of 3.12; 95% CI: 1.32-8.74) (Table 6). In addition, PCB138 remained significantly associated with cervical cancer (OR of 3.05, 95% CI: 1.21-7.69) when adjusted for age, race/ethnicity, BMI, lactation, and age at menarche (Table 6).

Analyte[1]	No Cases	No. Non cases	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
PCB 074					
<LOD to 50%	4	1047	1.00	1.00	1.00
≥ 50%	39	1047	5.82 (2.56-13.1)[a]	1.62 (0.48-5.38)	1.95 (0.31-12.4)
PCB 099					
<LOD to 50%	12	1172	1.00	1.00	1.00
≥ 50%	31	787	3.09 (1.60-5.98)b	1.40 (0.66-2.94)	1.52 (0.62-3.74)
PCB 118					
<LOD to 50%	6	999	1.00	1.00	1.00
≥ 50%	37	999	4.34 (1.95-9.70)b	1.38 (0.40-4.78)	1.54 (0.29-8.35)
PCB 138					
<LOD to 50%	4	1068	1.00	1.00	1.00
≥ 50%	39	891	7.35 (3.10-17.5)a	3.14 (1.14-8.62)b	2.52 (1.06-5.99)b
PCB 153					

<LOD to 50%	4	1078	1.00	1.00	1.00
≥ 50%	39	882	9.20 (2.30-36.8)b	3.94 (0.58-26.6)	3.15 (0.53-18.6)
PCB 18					
<LOD to 50%	4	1148	1.00	1.00	1.00
≥ 50%	39	806	10.6 (3.03-37.1)b	4.33 (0.79-23.6)	3.45 (0.76-15.6)

Table 5: Estimated ORs (95% CIs) of gynecological cancer by concentration of lipid adjusted PCBs, among women ≥ 20 years of age, NHANES 1999-200.4. [1]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g). [2]Adjusted for age and race/ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 40/1754 in 074; 40/1753 inO99; 40/1755 in 118; 40/1756 in 138 and 153; 40/1749 in 180. Significance [a]p<0.0001, [b]p<0.05.

Analyte[1]	No Cases	Noncases	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
PCB 074					
<LOD to 50%	12	1048	1.00	1.00	1.00
≥ 50%	15	912	1.26 (0.55-2.87)	1.01 (0.37-2.77)	0.87 (0.28-2.70)
PCB 099					
<LOD to 50%	13	11721	1.00	1.00	1.00
≥ 50%	13	787	1.52 (0.81-2.83)	1.53 (0.81-2.88)	1.40 (0.72-2.74)
PCB 118					
<LOD to 50%	11	1000	1.00	1.00	1.00
≥ 50%	16	960	1.47 (0.57-3.77)	1.47 (0.57-3.77)	1.28 (0.40-4.04)
PCB 138					
<LOD to 50%	9	1070	1.00	1.00	1.00
≥ 50%	18	891	2.96 (1.45-6.06)[b]	3.12 (1.32-87.40)b	3.05 (1.21-7.69)b
PCB 153					
<LOD to 50%	11	1080	1.00	1.00	1.00
≥ 50%	16	882	2.17 (1.04-4.53)b	2.18 (0.86-5.53)	2.46 (0.90-6.67)
PCB 18					
<LOD to 50%	14	1149	1.00	1.00	1.00
≥ 50%	13	806	1.75 (0.95-3.23)	1.61 (074-3.50)	1.58 (0.70-3.56)

Table 6: Estimated ORs (95% CIs) of cervical cancer by concentration of lipid adjusted PCBs, among women ≥ 20 years of age, NHANES 1999-2004. [1]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g). [2]Adjusted for age and race/ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 24/1754 in 074; 23/1753 in 099; 24/1755 in 118; 24/1756 in 138 and 153; 24/1749 in 180. Significance [a]p<0.0001, [b]p<0.05.

Estimated ORs and 95% confidence intervals for the risk of having ovarian cancer and the six individual PCB congeners are shown in Table 7. In unadjusted models, PCBs were significantly associated with ovarian cancer risk for subjects in the second group (≥ 50th percentile) when compared to the reference group (<LOD to 50th percentile) for PCB congeners 74 and 118 (Table 7). After adjusting for age, race/ethnicity, BMI, lactation, and age at menarche, PCB 74 and 118 remained significantly associated with ovarian cancer [ORs of 6.47 (95% CI:1.23-34.1) and 6.68 (95% CI:1.39-32.3) respectively] (Table 7).

Analyte[1]	No Cases	Noncases	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)

PCB 074					
<LOD to 50%	2	1048	1.00	1.00	1.00
≥ 50%	9	912	5.88 (1.67-207)b	7.31 (1.62-32.9)b	6.47 (1.23-34.1)b
PCB 099					
<LOD to 50%	3	11721	1.00	1.00	1.00
≥ 50%	8	787	3.67 (0.65-20.9)	4.15 (0.55-31.3)	3.69 (0.43-31.7)
PCB 118					
<LOD to 50%	2	1000	1.00	1.00	1.00
≥ 50%	9	960	5.81 (1.66-20.4)b	7.17 (1.64-31.3)b	6.68 (1.39-32.3)b
PCB 138					
<LOD to 50%	4	1070	1.00	1.00	1.00
≥ 50%	7	891	1.22 (0.24-6.28)	1.23 (0.15-9.81)	0.97 (0.12-7.63)
PCB 153					
<LOD to 50%	3	1080	1.00	1.00	1.00
≥ 50%	8	882	2.12 (0.49-9.13)	2.36 (0.46-12.0)	2.05 (0.50-8.41)
PCB 18					
<LOD to 50%	3	1149	1.00	1.00	1.00
≥ 50%	8	806	2.49 (0.58-10.7)	2.88 (0.53-15.6)	2.55 (0.66-9.85)

Table 7: Estimated ORs (95% CIs) of ovarian cancer by concentration of lipid adjusted PCBs, among women ≥ 20 years of age, NHANES 1999-2004. [1]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g). [2]Adjusted for age and race/ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 10/1754in 074; 10/1753 in 099; 10/1755 in 118; 10/1756 in 138 and 153; 10/1749 in 180. Significance [a]p<0.0001, [b]p<0.05.

Estimated ORs and 95% confidence intervals for the risk of having uterine cancer and the six individual PCB congeners are shown in Table 8. In unadjusted models, PCBs were significantly associated with uterine cancer risk for subjects in the second group (≥ 50th percentile) when compared to the reference group (<LOD to 50th percentile) for PCB congeners 138 and 153 (Table 8). After adjusting for age, race/ethnicity, BMI, lactation, and age at menarche, PCB 138 remained significantly associated with ovarian cancer [OR of 5.83 (95% CI: 1.63-20.9)] (Table 7).

Analyte[1]	No Cases	Noncases	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
PCB 074					
<LOD to 50%	8	1048	1.00	1.00	1.00
≥ 50%	18	912	2.13 (0.63-7.15)	1.41 (0.36-5.55)	1.55 (0.34-7.06)
PCB 099					
<LOD to 50%	13	11721	1.00	1.00	1.00
≥ 50%	12	787	1.55 (0.46-5.27)	1.19 (0.28-4.97)	1.43 (0.34-6.06)
PCB 118					
<LOD to 50%	10	1000	1.00	1.00	1.00
≥ 50%	16	960	1.60 (0.55-4.63)	1.07 (0.24-4.76)	1.52 (0.39-5.92)
PCB 138					

<LOD to 50%	7	1070	1.00	1.00	1.00
≥ 50%	19	891	4.84 (1.68-13.9)b	4.29 (1.21-15.2)b	5.83 (1.63-20.9)b
PCB 153					
<LOD to 50%	8	1080	1.00	1.00	1.00
≥ 50%	18	882	3.71 (1.39-9.89)b	3.14 (0.89-11.0)	4.07 (1.19-14.0)
PCB 18					
<LOD to 50%	8	1149	1.00	1.00	1.00
≥ 50%	18	806	2.64 (0.79-8.87)	2.00 (0.60-6.61)	1.70 (0.53-5.45)

Table 8: Estimated ORs (95% CIs) of uterine cancer by concentration of lipid adjusted PCBs, among women ≥ 20 years of age, NHANES 1999-2004. [1]Lipid adjusted and log transformed polychlorinated biphenyls (ng/g). [2]Adjusted for age and race/ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 24/1754 in 074; 24/1753in 099; 25/1755 in 118; 25/1756 in 138 and 153; 25/1749 in 180. Significance [a]p<0.0001, [b]p<0.05.

Estimated ORs and 95% confidence intervals for the risk of having gynecologic cancers and dioxin-like and non-dioxin-like PCBs are shown in Table 9. In the unadjusted models, dioxin-like and non-dioxin-like PCBs were significantly associated with breast cancer, ovarian cancer and uterine cancer. In the age and race/ethnicity adjusted models, dioxin-like PCBs were significantly associated with ovarian cancer (OR of 1.95, 95% CI: 1.25-3.05). Non-dioxin-like PCBs were significantly associated cervical cancer (OR of 1.29, 95% CI: 1.18-1.40), ovarian cancer (OR of 1.32, 95% CI: 1.02-1.69), and uterine cancer (OR of 1.11, 95% CI: 1.01-1.22). After adjusting for age, race/ethnicity, BMI, and age at menarche dioxin-like PCBs remained significantly associated with ovarian cancer risk (OR of 2.02, 95% CI: 1.06-3.85) and non-dioxin-like PCBs remained significantly associated with uterine cancer risk (OR of 1.12, 95% CI: 1.03-1.23) (Table 9). We further analyzed gynecologic cancer risk of dioxin-like and non-dioxin-like PCBs using the following two groups: <LOD to 50th percentile (reference group) and ≥ 50th percentile. In subjects with PCB levels ≥ 50th percentile, breast cancer, ovarian cancer, and uterine cancer were associated with dioxin-like and non-dioxin-like PCBs in the unadjusted models. Non-dioxin-like PCBs were significantly associated with cervical cancer risk and ovarian cancer risk in the age and race/ethnicity adjusted models [ORs of 2.59, 95% CI: 1.04-6.42 and 6.62, 95% CI: 1.50-29.2], respectively. Dioxin-like PCBs were associated with the risk of ovarian cancer in the age and race/ethnicity adjusted models [OR of 6.32 (95% CI: 1.44-27.7). In the final adjusted models (age, race/ethnicity, BMI, age at menarche) the risk of ovarian cancer remained significant in dioxin-like PCBs [OR of 5.71 (95% CI: 1.12-29.2)] and non-dioxin-like PCBs [OR of 5.99 (95% CI: 1.20-29.9) and the risk of uterine cancer remained significant in non-dioxin-PCBs [OR of 4.85 (95% CI: 1.32-17.8) (Table 9).

	Cases/Noncases	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2a,b] (95% CI)
Breast Cancer				
Dioxin-like PCBs3	43/1953	1.50 (1.27-1.78)[a]	1.50 (1.27-1.77)[a]	1.08 (0.80-1.45)
Dioxin-like PCBs_503,5				
<LOD to 50%	4/985	1.00	1.00	1.00
≥ 50%	39/968	5.23 (2.25-12.2)[a]	1.55 (0.49-4.90)	1.90 (0.33-10.8)
Non- Dioxin-like PCBs4	43/1941	1.28 (1.18-1.38)[a]	1.14 (1.00-1.29)[b]	1.12 (0.98-1.28)
Non-Dioxin-like PCBs_504,5				
<LOD to 50%	2/997	1.00	1.00	1.00
≥ 50%	41/944	12.7 (2.58-62.2)[b]	5.40 (0.87-33.5)	4.27 (0.68-26.8)
Cervical Cancer				
Dioxin-like PCBs3	27/1954	1.15(0.91-1.45)	1.13 (0.82-1.56)	1.10 (0.78-1.55)
Dioxin-like PCBs_503,5				
<LOD to 50%	12/985	1.00	1.00	1.00
≥ 50%	15/968	1.13 (0.50-2.58)	1.04 (0.90-1.20)	0.80 (0.27-2.38)

Non- Dioxin-like PCBs4	26/1941	1.05 (0.94-1.16)	1.29 (1.18-1.40)[a]	1.02 (0.87-1.19)
Non-Dioxin-like PCBs_504,5	9/997	1.00	1.00	1.00
<LOD to 50%	17/944	2.38 (1.14-4.94)[b]	2.59 (1.04-6.42)[b]	2.51 (0.94-6.68)
≥ 50%				
Ovarian Cancer				
Dioxin-like PCBs3	11/1954	1.61 (1.19-2.17)[a]	1.95 (1.25-3.05)[b]	2.02 (1.06-3.85)[b]
Dioxin-like PCBs_503,5				
<LOD to 50%	2/985	1.00	1.00	1.00
≥ 50%	9/968	5.26 (1.51-18.4)[b]	6.32 (1.44-27.7)[b]	5.71 (1.12-29.2)[b]
Non- Dioxin-like PCBs4	11/1941	1.24 (1.01-1.53)[b]	1.32 (1.02-1.69)[b]	1.30 (0.98-1.72)
Non-Dioxin-like PCBs_504,5				
<LOD to 50%	2/997	1.00	1.00	1.00
≥ 50%	9/994	5.51 (1.56-19.5)[b]	6.62 (1.50-29.2)[b]	5.99 (1.20-29.9)[b]
Uterine Cancer				
Dioxin-like PCBs3	26/1954	1.16 (0.88-1.52)	1.02 (0.76-1.37)	1.10 (0.83-1.46)
Dioxin-like PCBs_503,5				
<LOD to 50%	10/985	1.00	1.00	1.00
≥ 50%	16/968	1.14 (1.04-1.25)[b]	0.87 (0.18-4.21)	1.24 (0.29-5.28)
Non- Dioxin-like PCBs4	25/1941	1.28 (1.18-1.38)[b]	1.11 (1.01-1.22)[b]	1.12 (1.03-1.23)[b]
Non-Dioxin-like PCBs_504				
<LOD to 50%	7/997	1.00	1.00	1.00
≥ 50%	18/944	4.14 (1.44-11.3)[b]	3.53 (0.96-13.1)	4.85 (1.32-17.8)[b]

Table 9: Estimated ORs (95% CIs) of having a gynecological cancer by concentrations of Dioxin-like and non-Dioxin-like PCBs among women ≥ 20 years of age, NHANES 1999-2004. [1]Adjusted for age and race/ethnicity. [2]Adjusted for age, race/ethnicity, BMI, age at menarche. [a]Cases/Noncases in dioxin-like PCBs : 40/1749 for breast cancer, 24/1749 for cervical cancer, 10/1749 for ovarian cancer, 25/1749 for uterine cancer. [b]Cases/Noncases in non-dioxin-like PCBs: 40/1737 for breast cancer, 23/1737 for cervical cancer, 10/1737 for ovarian cancer, 24/1737 for uterine cancer. [3]Dioxin-like PCBs: Sum of lipid adjusted and log transformed PCB Congeners (074 + 118). [4]Non-Dioxin-like PCBs: Sum of lipid adjusted and log transformed PCB Congeners (099 + 138 + 153 + 180). [5]Serum PCB Levels < 50th percentile *vs* ≥ 50th percentile. Significance [a]$p<0.0001$, [b]$p<0.05$.

Estimated ORs and 95% CIs for the risk of having cervical, ovarian, or uterine cancer and the eight phthalate metabolites, the sum of DEHP, and total phthalates are shown in Tables 10-12. We analyzed the phthalate levels in the following groups: <LOD to 50th percentile (reference group) and ≥ 50th percentile. Results are presented for two logistic regression models: age and race adjusted; and age, race/ethnicity, BMI, and age at menarche adjusted. Results were not presented for unadjusted models age because the derived ORs and 95% CIs did not differ from the models presented. A significant association between cervical cancer and phthalates was not found in any of the models (Table 10).

Metabolite[1]	No. Cases	Non cases	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
MBP				
<LOD to 50%	10	1045	1.00	1.00
≥ 50%	18	1678	0.70 (0.25-1.97)	0.64 (0.22-1.85)
MEP				
<LOD to 50%	14	1106	1.00	1.00
≥ 50%	14	1616	0.91 (0.39-2.14)	0.80 (0.33-1.97)
MEHP				
<LOD to 50%	12	1339	1.00	1.00
≥ 50%	16	1376	0.95 (0.46-1.96)	0.91 (0.44-1.88)

MBzP				
<LOD to 50%	10	1205	1.00	1.00
≥ 50%	18	1517	1.07(0.51-2.22)	1.04 (0.49-2.21)
MCCP				
<LOD to 50%	16	1396	1.00	1.00
≥ 50%	12	1326	0.73 (0.38-1.38)	0.77 (0.41-1.47)
MEHHP				
<LOD to 50%	10	1280	1.00	100
≥ 50%	18	1443	1.10 (0.39-3.11)	1.00 (0.36-2.77)
MEOHP				
<LOD to 50%	11	1267	1.00	1.00
≥ 50%	17	1456	0.77 (0.31-1.87)	0.68 (0.28-1.65)
MIB				
<LOD to 50%	14	1260	1.00	1.00
≥ 50%	14	1457	0.81 (0.35-1.87)	0.85 (0.35-2.03)
DEHP				
<LOD to 50%	12	1301	1.00	1.00
≥ 50%	16	1422	0.79 (0.33-1.92)	0.73 (0.30-1.76)
Total				
<LOD to 50%	12	1423	1.00	1.00
≥ 50%	16	1300	0.98 (0.44-2.17)	0.81 (0.38-1.74)

Table 10: Estimated ORs (95% CIs) of cervical cancer by concentration of creatinine corrected urinary phthalate metabolite, among women ≥ 20 years of age NHANES 2003-2010. [1] Log transformed and creatinine adjusted urinary phthalates (ng/mg). [2]Adjusted for age and race/ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 26/2410 in MBP, MEHHP, MEOHP, MIB, DEHP; 26/2409 in MEP, MBzP, MCCP; 26/2403 in MEHP. Significance [a]p<0.0001, [b]p<0.05.

Estimated ORs and 95% CIs for the risk of ovarian cancer and uterine cancer by concentration of the eight phthalate metabolites, the sum of DEHP, and total phthalates are shown in Tables 11 and 12. In the age and race adjusted model, MEHHP showed a weak association with ovarian cancer [OR of 3.63 (95% CI: 1.00-13.2) p=.0497], however this association remained significant after adjusting for age, race/ethnicity, BMI, and age at menarche (Table 11). None of the phthalates were significantly associated with the risk of uterine cancer (Table 12).

Metabolite[1]	No. Cases	Noncases	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
MBP				
<LOD to 50%	6	1045	1.00	1.00
≥ 50%	14	1678	1.96 (0.61-6.31)	1.48 (0.42-5.19)
MEP				
<LOD to 50%	11	1106	1.00	1.00
≥ 50%	9	1616	0.43 (0.17-1.12)	0.38 (0.11-1.30)
MEHP				
<LOD to 50%	7	1339	1.00	1.00
≥ 50%	13	1376	2.56 (0.92-7.10)	1.91 (0.61-5.94)
MBzP				
<LOD to 50%	10	1205	1.00	1.00
≥ 50%	10	1517	1.65 (0.56-4.83)	1.59 (0.50-5.11)
MCCP				
<LOD to 50%	12	1396	1.00	1.00
≥ 50%	8	1326	1.13 (0.35-3.60)	1.24 (0.36-4.25)
MEHHP				
<LOD to 50%	4	1280	1.00	1.00
≥ 50%	16	1443	3.63 (1.00-13.2)b	2.73 (0.67-11.1)
MEOHP				
<LOD to 50%	4	1267	1.00	1.00
≥ 50%	16	1456	3.58(0.98-13.1)	2.67 (0.678-10.6)
MIB				
<LOD to 50%	11	1260	1.00	1.00
≥ 50%	9	1457	0.57 (0.16-1.99)	0.61 (0.13-2.83)
DEHP				
<LOD to 50%	6	1301	1.00	1.00
≥ 50%	14	1422	2.88 (0.95-8.76)	2.29 (0.64-8.23)
Total				
<LOD to 50%	9	1423	1.00	1.00
≥ 50%	11	1300	1.21 (0.46-3.17)	1.38 (0.46-4.17)

Table 11: Estimated ORs (95% CIs) of ovarian cancer by concentration of creatinine corrected urinary phthalate metabolite among women ≥ 20 years of age, NHANES 2003-2010. [1]Log transformed and creatinine adjusted urinary phthalates (ng/mg). [2]Adjusted for age and race/

ethnicity. [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 17/2410 in MBP, MEHHP, MEOHP, MIB, DEHP; 17/2409 in MEP, MBzP, MCCP; 17/2403 in MEHP. Significance [a]p<0.0001, [b]p<0.05.

Metabolite[1]	No. Cases	Non cases	Adjusted OR[2] (95% CI)	Adjusted OR[3] (95% CI)
MBP				
<LOD to 50%	10	1045	1.00	1.00
≥ 50%	17	1678	1.17 (0.36-3.78)	1.11 (0.33-3.68)
MEP				
<LOD to 50%	12	1106	1.00	1.00
≥ 50%	15	1616	1.02 (0.47-2.20)	0.99 (0.46-2.12)
MEHP				
<LOD to 50%	21	1339	1.00	1.00
≥ 50%	6	1376	0.34 (0.11-1.03)	0.34 (0.11-1.09)
MBzP				
<LOD to 50%	16	1205	1.00	1.00
≥ 50%	11	1517	0.59 (0.23-1.48)	0.55 (0.21-1.43)
MCCP				
<LOD to 50%	14	1396	1.00	1.00
≥ 50%	13	1326	0.88 (0.32-2.45)	0.85 (0.31-2.32)
MEHHP				
<LOD to 50%	10	1280	1.00	1.00
≥ 50%	17	1443	1.55 (0.65-3.70)	1.43 (0.61-3.34)
MEOHP				
<LOD to 50%	11	1267	1.00	1.00
≥ 50%	16	1450	1.02 (0.46-2.23)	0.95 (0.45-2.02)
MIB				
<LOD to 50%	12	1260	1.00	1.00
≥ 50%	15	2337	1.20 (0.45-3.17)	1.21 (0.45-3.20)
DEHP				
<LOD to 50%	15	1301	1.00	1.00
≥ 50%	12	1422	0.92 (0.40-2.12)	0.87 (0.39-1.93)
Total				
<LOD to 50%	13	1423	1.00	1.00
≥ 50%	14	1300	0.98(0.34-2.84)	0.92 (0.30-2.79)

Table 12: Estimated ORs (95% CIs) of uterine cancer by concentration of creatinine corrected urinary phthalate metabolite among women ≥ 20 years of age, NHANES 2003-2010. [1]Log transformed and creatinine adjusted urinary phthalates (ng/mg).[2]Adjusted for age and race/ethnicity [3]Adjusted for age, race/ethnicity, BMI, age at menarche; Cases/Noncases: 27/2410 in MBP, MEHHP, MEOHP, MIB, DEHP; 27/2409 in MEP, MBzP, MCCP; 27/2403 in MEHP Significance [a]p<0.0001, [b]p<0.05.

Estimated ORs and 95% confidence intervals for the risk of having cervical, ovarian, or uterine cancers by concentration of BPA are shown in Table 13. The following two groups were used to estimate gynecologic cancer risk: <LOD to 50th percentile (reference group) and ≥ 50th percentile. Results are presented for three logistic regression models: unadjusted; age and race/ethnicity adjusted; and age, race/ethnicity, BMI, and age at menarche adjusted. None of the models showed a significant association between BPA and cervical cancer, ovarian cancer, or uterine cancer (Table 13).

	No. Cases	No. Noncases	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Cervical Cancer					
<LOD to 50%	6	985	1.00	1.00	1.00
≥ 50%	9	1082	1.34 (0.37-4.81)	1.39 (0.39-4.91)	1.33 (0.42-4.18)
Ovarian Cancer					
<LOD to 50%	6	985	1.00	1.00	1.00
≥ 50%	10	1082	1.57 (0.43-5.76)	1.64 (0.43-6.25)	1.41 (0.30-6.70)
Uterine Cancer					
<LOD to 50%	13	985	1.00	1.00	1.00
≥ 50%	9	1082	0.58 (0.27-1.28)	0.65 (0.30-1.41)	0.57 (0.25-1.29)

Table 13: Estimated ORs (95% CIs) of a gynecological cancer by concentration of creatinine adjusted urinary BPA among women ≥ 20 years of age, NHANES 2005-2010. Log –transformed and creatinine adjusted BPA measurements (ng/mg); NHANES 2005-2010. [1]Adjusted for age and race/ethnicity. [2]Adjusted for age, race/ethnicity, BMI, age at menarche; Noncases=1821. Significance [a]p<0.0001, [b]p<0.05.

Discussion

In this cross-sectional study of women 20-85 years of age, we separately evaluated 6 individual PCB congeners, the sum of dioxin-like PCBs, the sum of non-dioxin-like PCBs, eight phthalate metabolites, the sum of DEHP, the sum of total phthalates, and BPA in association with gynecological cancers (cervical, ovarian, and uterine)

in women. One of the major findings emerged from this study pointed out a possible association between chronic exposure to xenooestrogen - polychlorinated biphenyls and increased risk of developing ovarian and uterine cancers. Higher PCB levels were detected in the women diagnosed with ovarian cancer and cervical cancer compared to women never diagnosed with cancer. PCBs showed the most significant associations with all three cancers. After adjusting for all confounding variables, women with ovarian cancer had significant associations with PCB 74 and 118, and therefore the dioxin-like PCBs. Dioxin-like PCBs were significantly associated with ovarian cancer and non-dioxin-like PCBs were significantly associated with ovarian and uterine cancers, after adjusting for age, race, BMI, and age at menarche. In our study, exposure to PCB 138 showed the strongest associations to significantly increase the risk of cervical and uterine cancers. Epidemiological studies on the association of PCBs with cervical, ovarian, and uterine cancers are lacking, but results of this study are consistent with our findings in breast cancer studies that also reported higher PCB levels in breast cancer cases compared to controls [8]. Our findings are also in agreement with another study that showed increased levels of PCB 28; PCB 52; PCB 101; PCB 138; PCB 153 and PCB 180 in abdominal adipose tissue in cases of endometrial stromal sarcomas - rare uterine tumors [31]. While these results do not provide any evidence of causal associations, it is noteworthy that NHANES samples show higher body burdens of estrogenic PCB congeners in women with ovarian and uterine cancer compared to women never diagnosed with cancer. We and others have shown that many genes that respond to estrogen play important role to control the development and progression of cervical, ovarian and uterine cancers [3,4]. We have recently reported that all three EDDs–PCBs, phthalates, and BPA influence five common genes—CYP19A1, EGFR, ESR2, FOS, and IGF1 in breast cancer as well as in endometriosis [4]. These genes are environmentally and estrogen responsive and altered in human breast and uterine tumors, endometriosis lesions, and participate in carcinogenesis pathways. These findings suggest that PCB-induced dysregulation of estrogen signaling pathway may contribute to the increased risk of gynecological cancers (cervical, ovarian, and uterine) in women.

Epidemiological studies on the association with phthalates and BPA with cervical, ovarian, and uterine cancers are lacking or limited. In this study MEHP levels was found to be higher in women never diagnosed with cancer. Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was weakly associated (p=0.0497) with ovarian cancer risk in the model adjusted for age and race but did not remain significantly associated when the additional variables of BMI and age at menarche were added. Higher levels of BPA were found in the urine samples of women with cervical cancer only.

There are a number of limitations in our study. The most important is its cross-sectional design with self-reported data that may over report and does not allow causal inferences. Self-reported data increases the risk of misclassification bias of cases and controls with the possibility of undiagnosed or incorrectly reported cancer cases. In the PCB data analysis, we had relatively small sample sizes for cervical cancer (n=27), ovarian cancer (n=11), and uterine cancer (n=26), resulting in decreased statistical power within subgroup analyses. Missing data on confounding reproductive variables such as parity and lactation is another limitation to this study. Furthermore, observed associations can be potentially confounded by the lack of information on family history of hormonal cancers. Nonetheless, this cross-sectional study design has strengths that include a large sample survey size, availability of biological measurements of environmental contaminants, and oversampling of minority populations. We conclude that higher serum PCB concentrations in cervical, ovarian and uterine cancers subjects may be as a result of past exposures to higher environmental PCB concentrations and chronic exposure to xenooestrogen - PCBs may increase the risk of developing cervical, ovarian and uterine cancers. In addition, this study also presents a design to analyze individual as well as the additive, synergistic, or antagonistic combined effects of EEDs within a class or across classes. Our findings, coupled with the lack of available epidemiological evidence concerning EEDs exposures and cervical, ovarian, and uterine cancers warrants the need for future prospective studies to determine the potential role of environmental exposures to PCBs, phthalates, and BPA in the development of gynecologic cancers. Additional research is also needed to consider cumulative exposures of EEDs and their effects on the development of gynecological cancers.

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