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Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma

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Abstract

Bisphenol A, benzophenone-type UV filters, and phthalates are chemicals in high production and use including in a range of personal care products. Exposure of humans to these chemicals has been shown to affect endocrine function. Although short-lived, widespread exposure may lead to continual opportunity for these chemicals to elicit health effects in humans. The association of these chemicals with incident uterine leiomyoma, an estrogen sensitive disease, is not known. Urinary concentrations of bisphenol A (BPA), five benzophenone-type UV filters (2-hydroxy-4-methoxybenzophenone (2OH-4MeO-BP), 2,4-dihydroxybenzophenone (2,4OH-BP), 2,2′-dihydroxybenzophenone (2,2′OH-4MeO-BP), 2,2′4,4′-tetrahydroxybenzophenone (2,2′4,4′OH-BP), and 4-hydroxybenzophenone (4OH-BP), and 14 phthalate monoesters were quantified in 495 women who later underwent laparoscopy/laparotomy at 14 clinical sites for the diagnosis of fibroids. Significantly higher geometric mean creatinine-corrected concentrations of BPA, 2,4OH-BP, and 2OH-4MeO-BP were observed in women with than without fibroids [BPA: 2.09 μg/g vs. 1.46 μg/g p=0.004; 2,4OH-BP:11.10 μg/g vs. 6.71 μg/g p=0.01; 2OH-4MeO-BP: 11.31 μg/g vs.

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Human Subjects

Human subjects approval was obtained (Committee for Human Research, University of California, San Francisco; Institutional Review Board, University of Utah; Intermountain Healthcare Office of Research, Utah; and the National Institutes of Health Institutional Review Board Reliance).

6.10 μg/g p=0.01]. Mono-methyl phthalate levels were significantly lower in women with than without fibroids (1.78 μg/g vs. 2.40 μg/g). However, none of the exposures were associated with a significant odds ratio even when adjusting for relevant covariates. There was a lack of an association between select nonpersistent chemicals and the odds of a fibroid diagnosis.

Keywords

benzophenone; bisphenol A; fibroid; phthalate; ultraviolet filter

1. Introduction

Emerging evidence suggests that short-lived chemicals, particularly select phthalates and UV filters may be associated with endometriosis (Cobellis et al., 2003; Reddy et al., 2006; Weuve et al., 2010; Kunisue et al., 2012; Buck Louis et al., 2013). Many such studies have relied upon a single spot urine sample that may not reflect the timing of disease onset and/or progression. Nearly ubiquitous occurrence of high volume production, short-lived chemicals might mean continual human exposure, despite their short-lived nature (Barr et al., 2003; Silva et al., 2004). In contrast, limited study exists on environmental chemicals and uterine leiomyoma (fibroids), an estrogen sensitive tumor of the myometrium (Hodges et al., 2000), despite it being the most common indication for gynecologic surgery with an elusive etiology. Fibroids are responsible for significant gynecologic morbidity including reproductive dysfunction and pelvic pain (Stewart, 2001). Further, in the US, fibroids cost between $6 to $34 billion per year, due to direct medical expenses and lost productivity (Cardozo et al., 2012). Lifetime uterine fibroid prevalence is 70–80% (Baird et al., 2003). However, few risk factors for fibroids are known, apart from African American ethnicity and age (Laughlin et al., 2010). Phthalates and diethylstilbestrol have been associated with fibroids (Newbold et al. 2007; Weuve et al. 2010). Because fibroids are estrogen sensitive, endocrine-disrupting chemicals may play a role in their development.

Exposure to nonpersistent chemicals from personal care products and diet is widespread. In particular, high volume production chemicals such as BPA, phthalates, and benzophenone-type UV filters have been detected in pregnant women, infants, and adults (Wolff et al., 2008; Guo et al., 2011; Woodruff et al., 2011; Zhang et al., 2011). BPA is a phenolic chemical used in polycarbonate plastics and in epoxy resin coatings of can linings (Burridge, 2003). BPA is purported to have estrogenic activity, stimulating estrogen production at the estrogen receptor, which may consequently modify gonadotropin hormones (Quesada et al., 2002; Alonso-Magdalena et al., 2011). Phthalates are found in cosmetics, and other common consumer products (Guo and Kannan, 2013; Blount et al., 2000), seem to exhibit antiandrogenic effects and may reduce estrogen production (Okubo et al., 2003). Exposure to the UV filter 2-hydroxy-4-methoxybenzophenone (2OH-4MeO-BP or BP-3) comes from dermal exposure to sunscreen products (Benson, 2000; Liao and Kannan, 2014) and this compound exhibits estrogenic activity (Schlumpf et al., 2001; Kunz and Fent, 2006). Toxicologic evidence suggests possible reproductive and developmental toxicity of BP-3 (Honma et al., 2002; Krause et al., 2012; Kay et al., 2013). The endocrine altering properties

of this group of nonpersistent chemicals suggests a role in the etiology of estrogen-sensitive disease.

To date, three studies have assessed select phthalates and fibroids with equivocal results. While informative, these studies have relied on small clinical samples with 36 cases or less (Luisi et al., 2006; Huang et al., 2010) or self-reported fibroids (Weuve et al., 2010). Data from the Third National Health and Nutrition Examination Survey (NHANES) suggested that mono(2-ethylhexyl) phthalate was inversely associated with uterine leiomyoma, while monobutyl phthalate levels were positively associated with self-reported uterine leiomyoma (Weuve et al., 2010). A major limitation was reliance upon self-report of uterine fibroids, which is problematic because many women with fibroids are not aware of their diagnosis (Myers et al., 2012). A case-control study reported that monoethylhexyl phthalate (MEHP) levels were higher in fibroid cases as compared with controls (Huang et al., 2010). A small case-control study limited to Caucasian women found lower serum levels of di-2-ethylhexyl phthalate (DEHP) in fibroid cases but this was a sample without incident disease presentation (Luisi et al., 2006). Hair relaxer use, a possible proxy for phthalate exposure, was associated with risk of uterine leiomyoma in a cohort comprising black women (Wise et al., 2012), although this study relied on proxy exposure and self-reported outcome.

Despite the paucity of evidence directly for fibroids, there is a growing body of literature in support of an association between nonpersistent chemicals and gynecologic conditions including pubertal timing and phthalates (Colon et al., 2000). An evolving body of evidence provides an indication that other gynecologic diseases may be associated with nonpersistent chemicals. In particular, BPA was associated with endometriosis (Itoh et al., 2007; Cobellis et al., 2009) and polycystic ovary syndrome (PCOS) (Kandaraki et al., 2011); while androgen exposure in utero has been shown to induce ovarian and adrenal hormonal disturbances in female monkeys (Eisner et al. 2002). However, other studies found that BPA was not associated with endometriosis (Buck Louis et al., 2013) or PCOS (Li et al., 2011).

Providing further support for a role of nonpersistent chemicals in the development of uterine fibroids, experimental studies have identified disturbances of the hypothalamic-pituitary gonadotropin axis following exposure to BPA (Patisaul et al., 2006; Fernandez et al., 2009; Navarro et al., 2009; Mahoney and Padmanabhan, 2010), UV filters (Schlecht et al., 2006; Klammer et al., 2007; Kerdivel et al., 2013), and phthalates (Sekiguchi et al., 2006; Svechnikova et al., 2007). We are unaware of any studies focusing on BPA, a potent estrogen, or UV filters, particularly those with estrogenic properties, and fibroids. In response to this data gap, we assessed BPA, 14 phthalate metabolites, and 5 UV filters in relation to a fibroids diagnosis.

2. Methods

2.1. Study population

We utilized the Endometriosis, Natural history, Diagnosis, and Outcomes (ENDO) Study, given that all women underwent either a diagnostic and/or therapeutic laparoscopy or laparotomy allowing for the detection of uterine fibroids. Specifically, women were recruited from one of 14 participating clinical centers in the Salt Lake City, Utah (n=431) or

San Francisco, California (n=63) area between 2007 and 2009. Complete details on the study design and methods are provided elsewhere (Louis et al. 2011). Eligibility criteria included women aged 18–44, currently menstruating, without history of laparoscopy-confirmed endometriosis diagnosis, no breastfeeding for ≥6 months, no use of injectable hormones for the past 2 years, and no history of cancer (other than nonmelanoma skin cancer). Study participants were compensated for their time and provided informed consent prior to data collection. Human subjects approval was obtained (Committee for Human Research, University of California, San Francisco; Institutional Review Board, University of Utah; Intermountain Healthcare Office of Research, Utah; and the National Institutes of Health Institutional Review Board Reliance).

2.2. Data Collection

Women completed computer-assisted personal interview questionnaires, which were administered on laptop computers prior to surgery. Anthropometric measurements, including height and weight for the determination of body mass index (BMI), were completed by trained study staff using a portable stadiometer and electronic scales (Lohman et al., 1988). Women provided nonfasting urine specimens upon enrollment. Serum cotinine was measured with high-performance liquid chromatography/tandem MS utilizing an isotope dilution method and external standard calibration plots (Bernert et al., 2009). Serum cotinine was categorized as nonsmoking (0–9.99 ng/ml) and passive/active smoking (10.00–595.31 ng/ml) using established cut-points (Wall et al., 1988).

2.2. Assessment of exposure

Three classes of nonpersistent chemicals were measured in spot urine – BPA, phthalates and UV-filters. High-performance liquid chromatography coupled with API 2000 electrospray triple-quadrupole mass spectrometry (HPLC-MS/MS) was used to quantify total BPA (Zhang et al., 2011). The limit of quantitation was 0.1 ng/mL, which was determined with the minimum point on the calibration standard and a nominal sample volume of 0.5 ml. Next, 14 phthalate monoesters were measured in 0.5 ml urine after enzymatic deconjugation followed by solid phase extraction (Guo et al., 2011). These included: mono-benzyl phthalate (MBzP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-cyclohexyl phthalate (MCHP), mono-ethyl phthalate (MEP), mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-isononyl phthalate (MiNP), mono-(carboxynonyl) phthalate (MCNP), mono-methyl phthalate (MMP), mono-(3-carboxypropyl) phthalate (MCPP), and mono-*n*-octyl phthalate (MOP). The limit of quantitation ranged between 0.1–0.5 ng/mL. Continual quality assurance and control processes were implemented in each batch and included a method blank, a spiked blank, a pair of matrix-spiked sample duplicates. Procedural blanks (water that passed through the entire analytical procedure) had trace levels of mBP, miBP, and mEHP so sample concentrations for these compounds were subtracted from blank values, which led to some negative values. The calibration standard regression coefficient (injected at concentrations between 0.05 ng/ml – 20 ng/ml) was >0.9999. Lastly, 5 benzophenone-type ultraviolet (UV) filter metabolites were measured: 2-hydroxy-4-methoxybenzophenone (2OH-4MeO-BP), 2,4-dihydroxybenzophenone (2,4OH-BP), 2,2′-dihydroxybenzophenone

(2,2′OH-4MeO-BP), 2,2′4,4′-tetrahydroxybenzophenone (2,2′4,4′OH-BP), and 4-hydroxybenzophenone (4OH-BP). UV filters were analyzed per a previously reported procedure (Kunisue et al., 2010). In sum, frozen urine samples were thawed and 500 μL aliquots were spiked with internal and deconjugation standards, mixed, buffer was added and the sample was incubated then centrifuged. The benzophenone derivative portion was prepared for LC-MS/MS analysis using an API 2000 electrospray triple quadrupole mass spectrometer (ESI-MS/MS; Applied Biosystems, Foster City, CA). The limits of detection (LOD) were 0.082 ng/mL for 2,4OH-BP and 4OH-BP, 0.13 ng/mL for 2,2′OH-4MeO-BP, and 0.28 ng/mL for 2OH-4MeO-BP and 2,2′4,4′OH-BP. Coefficients of variation between analyses ranged from 0.53 to 5.9%.

2.3. Assessment of outcome

Uterine leiomyoma denoted a postoperative surgical diagnosis of fibroids. This information was obtained from standardized operative report completed by the laparoscopic surgeon immediately following surgery.

2.4. Statistical analysis

Descriptive analyses included the inspection of data for completeness and by population characteristics in relation to fibroid status. Geometric mean chemical concentrations and accompanying 95% confidence intervals were compared by fibroid status after adjusting for creatinine; negative and zero chemical values (BPA=16.0%; mBP=0.4%; miBP=3.0%; mBzP=0.2%; mEHP=19.0%) were excluded in calculating the geometric means. Women with and without fibroids were compared by various characteristics with significance determined by P-value <0.05 using the Chi-square statistics or nonparametric Wilcoxon rank sum test for categorical and continuous, respectively. The Wilcoxon test compared Geometric mean urinary concentrations and accompanying 95% confidence intervals (CIs) for all chemicals were compared by fibroid status using the Wilcoxon test for assessing significance. In the regression analysis, all machine observed concentrations were utilized regardless of LOD to minimize bias (Guo et al., 2010). Logistic regression was used to estimate the odds of fibroids along with 95% CIs. Separate models were run for each chemical generating both unadjusted and adjusted odds ratios (OR) and corresponding 95% confidence interval (CI). Chemicals were log (x+1) transformed and rescaled by their standard deviations before analysis to aid the interpretation of point and interval estimates. Potential confounders were considered based upon *a priori* literature review and were defined as: urinary creatinine (mg/dL), age (years), race (black vs. nonblack), body mass index (<30 vs. ≥30), serum cotinine, and research site (California/Utah). Parity was not included in the model because it may be in the pathway between exposure and fibroids. Lastly, we conducted sensitivity analyses to assess the potential role of a shared etiology for fibroids and endometriosis (Kunisue et al., 2012; Buck Louis et al., 2013). Specifically, we restricted affected women to include only women with fibroids (n=99) and unaffected women to include only women with a post-operative diagnosis of a “normal pelvis” (n=135). This latter group excluded any women with any visualized surgical gynecologic pathology.

3. Results

The incidence of surgically visualized fibroids was 20% (Table 1). Women with fibroids were older and more likely to self-identify as being non-white and report more annual menstrual cycles and pregnancies resulting in loss in comparison to women without fibroids. Women with fibroids differed from unaffected women relative to surgical indication, in that the former group of women were more likely to have fibroids as indications than the latter group of women ($p<0.05$). No differences were observed for age at menarche or BMI and fibroid status.

Table 2 reflects a general pattern of higher concentrations of BPA, phthalates, and UV filters for women with than without fibroids, most were widely detectable, and this trend persisted without creatinine adjustment. However, only four differences achieved significance: 1) BPA [2.09 μg/g; vs. 1.46 μg/g]; 2) 2,4OH-BP [11.10 μg/g vs. 6.71 μg/g]; 3) 2OH-4MeO-BP [11.31 μg/g vs. 6.10]; and 4) mMP [1.78 μg/g vs. 2.40]. 2,2′4,4′-OH-BP and 2,2′OH-4MeO-BP were detected in less than 6% of samples and are not considered further.

No significant associations were observed for any of the compounds under investigation and odds of a fibroid diagnosis in either the unadjusted or adjusted analysis (Table 3). The sole exception was a reduced odds of a fibroids diagnosis associated with mMP (OR=0.75; 95% CI 0.58, 0.98), but this finding was not robust to adjustment for potential confounders. After conducting sensitivity analyses that compared women with uterine fibroids to women with a postoperative diagnosis of a normal pelvis, none of the findings achieved statistical significance (Supplemental Table 1).

4. Discussion

We did not find that BPA, phthalate metabolites, or UV filter metabolites were associated with surgically visualized fibroids in this cohort of women. Although we observed a general pattern of higher urinary concentrations of BPA, phthalates, and UV filters for women with than without fibroids, only BPA and two UV filter metabolites (2,4OH-BP and 2OH-4MeO-BP) achieved statistical significance and none of the associations conferred elevated odds ratios. Despite our diagnoses being surgically visualized and individually quantified concentrations of a spectrum of short-lived chemicals, we did not find evidence of an association with fibroids.

Our findings are not directly comparable with earlier papers, largely given their reliance on self reported fibroids that is likely to underestimate actual disease (Myers et al., 2012) and focus on a single class of non-persistent compounds despite human exposure to various classes. To our knowledge, no data are available on BPA and UV filter in relation to uterine fibroids. As such, our null findings await corroboration.

Four previous studies have evaluated phthalate metabolites and uterine fibroids and were subject to methodological issues, which underscore the novel aspects of the present study. Of the four prior studies, one relied on proxy exposure assessment and self-reported outcome (Wise et al. 2012) and one was limited to an evaluation of mean differences of phthalate levels measured in blood (Luisi et al., 2006). Measurement of phthalates in serum

is problematic as controlled human studies demonstrate that BPA and phthalate metabolite levels are several orders of magnitude lower in blood compared to urine (Koch et al., 2012). In blood, phthalate diesters are quickly hydrolyzed to their monoesters leading to higher phthalate monoesters, which may not accurately reflect internal dose. Therefore, although levels in blood are related to urinary levels, urine is the best matrix to assess phthalate concentrations (Calafat et al., 2013). One small case control study (cases=36; controls=29) found an increased odds for uterine fibroids associated with urinary MEHP but did not fully consider possible confounding factors, perhaps due to the small study size (Huang et al., 2010). This relationship was stronger among those with the glutathione S-transferase M1 null genotype but age was the only potential confounder considered. The present study did not have genotype information available. Finally, in accordance with our findings, a cross-sectional study found that MBP and MEHP were not significantly associated with fibroids (Weuve et al., 2010).

Although human data linking non-persistent chemicals and fibroids is equivocal, animal studies provide compelling evidence that nonpersistent chemicals may influence gynecologic morbidity. We observed that geometric mean BPA levels were higher among women with fibroids compared to those without fibroids, but we did not observe an association between BPA and the odds fibroids diagnosis. Toxicological research has demonstrated that BPA exposure early in pregnancy led to fibroid development in offspring (Newbold et al., 2009). Fibroid development following prenatal exposure to diethylstilbestrol was also observed in CD-1 mice (Newbold et al., 2002). Experimental evidence shows that benzophenone-type UV filters act as endocrine disruptors in fish (Coronado et al., 2008) and juvenile rats (Nakagawa and Tayama, 2001). Select benzophenone-type UV filters were associated with endometriosis in this cohort of women (Kunisue et al., 2012). One small (n=32) study is available with respect to hormonal changes and benzophenones, which included no premenopausal women and found no changes in reproductive hormones (Janjua et al., 2004). This underscores the need for research in this area on premenopausal women to better understand the role of nonpersistent chemicals and gynecologic disease.

Disentangling the origin of uterine fibroids is a particular challenge, as an early life origin to gynecologic disease has been proposed. Early origins to fibroids posits that because uterine gland development is initiated in utero, perturbations in endocrine signaling during fetal development could lead to changes in adult structure and function (Louis et al., 2011). Experimental evidence provides an indication that in utero exposures to chemicals may alter reproductive tract development and function, leading to uterine fibroids (McLachlan et al., 1980). However, characterizing exposure during sensitive windows of development was not feasible in the present study. Further, this relationship has been demonstrated in women exposed to diethylstilbestrol in utero (Baird and Newbold, 2005). In particular, the ovarian dysgenesis hypothesis (Louis et al. 2010) provides some suggestion that exposure to BPA during prenatal development was associated with fibroids (Newbold et al., 2009). In the present study, we were unable to determine prenatal exposures to phthalates, BPA, and UV filter metabolites, which represents a study limitation, though one difficult to overcome with respect to short-lived chemical exposures in epidemiologic studies.

Our work had several strengths. The design of the operative cohort enabled surgical visualization of fibroids. Biomarker measurement in urine represents another strength, as these chemicals are rapidly metabolized, such measurement provides a better estimate of exposure compared to serum or plasma (Koch et al., 2012). In particular, the phthalate DEHP metabolized in serum during storage (Kato et al., 2003).

However, the present study had some limitations, including the brief time between exposure measurement and outcome ascertainment. The natural history of fibroids is complex and fibroids can have notable growth in the six months prior to their detection (Peddada et al., 2008). Thus, chemical levels measured at the time of diagnosis may reflect a relevant period at least for their short-term growth. Fibroids are generally detected upon the onset of symptoms among women in the 4^{th} and 5^{th} decade of life, although some have been diagnosed in adolescence (Stewart, 2001). Nonetheless, the lack of established risk factors for this important female reproductive disease argues for additional research in this area. Further, utilization of multiple biomarkers of exposure within each individual may have been preferable because the exposures are not persistent. However, evidence demonstrates that single measurements may reflect chronic exposure if daily exposure is consistent. In fact, moderately high correlations were found for BPA measurements taken 2 weeks apart (Spearman correlation 0.5), as were levels of diethyl phthalate and benzylbutyl phthalate over several weeks, with intraclass correlation coefficients of 0.48 and 0.53, respectively (Nepomnaschy et al., 2009). No phthalates were observed to vary across the menstrual cycle (Baird et al. 2010). Categories of phthalate levels were reasonably consistent across one-month averages for all metabolites except DEHP (Peck et al. 2010). However, a period of several weeks is too narrow for the onset of fibroids. For DEHP and BPA, population variability was similar between 24-hour urine samples and spot samples in US adults (Christensen et al. 2012). As such, a single spot urine could serve as a proxy of average population exposure, including during the natural history of various diseases (Christensen et al., 2012; Ye et al., 2011). Unfortunately, we were unable to find any data on the inter-individual variability of benzophenones.

Future research that builds upon the notable assumptions underlying this current research and previous work is essential for determining an etiologic role for these short-lived chemicals. In addition to the need for longitudinal designs and measurement of exposures including during sensitive windows of disease onset and/or progression, future research could include a methodologic component to empirically delineate the variability inherent in these biomarkers (Townsend et al 2013; Braun et al 2012). Such research is critical for affirming the assumption that such biomarker variability generated non-differential measurement error with bias toward the null, though recognizing the possibility that under some conditions bias may be away from the null (Pollack et al. 2013). As such, measurement error may account for our null findings.

Our findings do not support an association between urinary phthalate metabolites, BPA, or UV filters and fibroids in adult women despite geometric mean concentrations of BPA and several phthalates similar to NHANES (2007–2008). However, lower levels of 2OH-4MeO-BP, mEOHP, mEHHP, mECPP, mBP were noted in comparison to NHANES (CDC 2009). Our findings await corroboration from future work. The prevalent nature of fibroids coupled

with its economic and health implications for women underscores the need for continued research focusing on EDCs and fibroids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

2OH-4MeO-BP	2-hydroxy-4-methoxybenzophenone
2,4OH-BP	2,4-dihydroxybenzophenone
2,2′OH-4MeO-BP	2,2′-dihydroxybenzophenone
2,2′4,4′OH-BP	2,2′4,4′-tetrahydroxybenzophenone
4OH-BP	4-hydroxybenzophenone
BMI	body mass index
BPA	bisphenol A
CI	confidence interval
DEHP	di-2-ethylhexyl phthalate
MBzP	mono-benzyl phthalate
MnBP	mono-*n*-butyl phthalate
MiBP	mono-isobutyl phthalate
MCHP	mono-cyclohexyl phthalate
MEP	mono-ethyl phthalate
MEHP	mono-2-ethylhexyl phthalate
MEHHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MECPP	mono-(2-ethyl-5-carboxypentyl) phthalate
MiNP	mono-isononyl phthalate
MCNP	mono-(carboxynonyl) phthalate
MMP	mono-methyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate

MOP	mono-*n*-octyl phthalate
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PCOS	polycystic ovary syndrome

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- We measure bisphenol A, 14 phthalate and ultraviolet filter metabolites in women.
- BPA, 2,4OH-BP, and 2OH-4MeO-BP were higher in women with than without fibroids.
- None of the exposures were associated with odds of uterine fibroids.

Table 1

Population characteristics by fibroids status (n=473)

Characteristic	Fibroids n=99 (20.1%)	No Fibroids n=374 (79.1%)
Self identified race/ethnicity		
Hispanic	15 (15)	48 (13) [b]
White	61 (62)	293 (78)
Black/Asian/Multi/Other	23 (23)	33 (9)
Primary Reason for Surgery		
Tubal ligation	2 (2)	46 (12) [b]
Pelvic pain	22 (24)	184 (49)
Pelvic mass	15 (15)	59 (16)
Infertility	1 (1)	34 (9)
Fibroids	49 (50)	0 (0)
Menstrual irregularities	9 (9)	51 (14)
Serum Cotinine (ng/ml)		
No cigarette smoke exposure (0–9.9)	91 (92)	311 (83) [a]
Cigarette smoke exposure (10.0–595.3)	8 (8)	63 (17)
Parity conditional on gravidity		
Never pregnant	32 (32.7)	123 (33.0) [a]
Pregnant without live birth	17 (17.3)	30 (8.0)
Pregnant with live birth(s)	49 (50.0)	220 (59.0)
Age mean ± SD	37.8 ± 4.9	31.7 ± 6.9 [b]
BMI (kg/m^2) mean ± SD	28.4 ± 7. 8	27.9 ± 8.1
<30	67 (67.7)	245 (66.4)
≥30	32 (32.3)	124 (33.6)
Age at menarche mean ± SD	12.6 ± 1.6	12.9 ± 1.7
Menstrual cycle length mean ± SD	31.8 ± 39.5	28.9 ± 19.9
Number menstrual cycles in past 12 months mean ±SD	11.5 ± 4.2	11.1 ± 7.5 [a]

[a] p<0.05

[b] p<0.005

NOTE: Chi-square and nonparametric Wilcoxon rank sum tests were used to compare categorical and continuous, respectively, characteristics between those with and without fibroids. BMI, body mass index; CI, confidence interval; SD, standard deviation

Table 2

Geometric mean (95% confidence interval) comparison of chemicals by fibroid status (n=473)

Chemicals (μg/g)	Fibroids (n=99) Geometric Mean (95% CI)	No Fibroids (n=374) Geometric Mean (95% CI)	LOQ value (ng/mL)	% above LOQ/L OD	% of negative & zero values
Bisphenol A (BPA)	2.1 (1. 6, 2.8)	1.5 (1.2, 1.7) [b]	0.05	82	16.0
Phthalates					
mMP	1. 8 (1.35, 2.4)	2.4 (2.1, 2.7) [a]	1.0	70	0
mEP	108.0 (80.9, 144.2)	108.8 (95.3, 124.2)	0.2	100	0
mCPP	3.3 (2.7, 3.9)	3.1 (2.7, 3.5)	0.2	99	0
mBP	11.8 (9.8, 14.1)	11.3 (10.4, 12.3)	0.2	99	0.4
miBP	7.2 (6.1, 8.5)	7.0 (6.4, 7.6)	0.2	96	3.0
mECPP	25.5 (21.2, 30.7)	24.7 (22.2, 27.4)	0.2	100	0
mCMHP	30.5 (25.0, 37.1)	28.9 (26.1, 32.1)	0.2	100	0
mEHHP	15.8 (12. 7, 19.6)	15.0 (13.2, 17.0)	0.2	100	0
mEOHP	10.7 (8.8, 13.1)	10.4 (9.3, 11.6)	0.2	100	0
mCHP	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.2	5	0
mBzP	7.1 (6.0, 8.6)	7. 6 (6.9, 8.3)	0.2	99	0.2
mEHP	4.7 (3.5, 6.3)	4.3 (3.6, 5.1)	1.0	69	19.9
mOP	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.5	2	0
mNP	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	0.5	8	0
Benzophenone derivatives					
2,4OH-BP	11.1 (7.1, 17.4)	6.7 (5.4, 8.3) [a]	0.08	99	0
4OH-BP	0.2 (0.2, 0.3)	0.3 (0.2, 0.3)	0.08	83	0
2OH-4MeO-BP	11.3 (6.4, 20.1)	6.1 (4.6, 8.0) [a]	0.28	91	0

[a] $p<0.05$

[b] $p<0.005$

NOTE: All chemicals were creatinine (mg/dL) standardized using the following formula: 100 × chemical (ng/ml)/creatinine (mg/dL). Nonparametric Wilcoxon rank sum test was used to compare chemical concentrations between those with and without fibroids.

Table 3

Bisphenol A, phthalates, and benzophenone derivatives and the odds (OR) of a uterine fibroids diagnosis (n=473; fibroids n=99)

Chemicals (*μg/g*)	OR (95% CI)*	aOR (95% CI)**
BPA	1.0 (0. 8, 1.3)	0.9 (0.7, 1.2)
Phthalates		
mMP	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)
mEP	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)
mCPP	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
mBP	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)
miBP	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
mECPP	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)
mCMHP	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
mEHHP	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
mEOHP	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
mCHP	1.1 (0.9, 1.4)	1.2 (0.9, 1.4)
mBzP	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)
mEHP	1.0 (0.8, 1.3)	1.0 (0.8, 1.4)
mOP	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
mNP	1.0 (0.8, 1.3)	0.9 (0.6, 1.3)
Benzophenone derivatives		
2,4OH-BP	1.1 (0.9, 1.4)	1.1 (0.8, 1.5)
4OH-BP	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)
2OH-4MeO-BP	1.2 (0.9, 1.5)	1.1 (0.8, 1.4)

NOTE: All chemicals were log(x+1) transformed then standardized by their standard deviations.

*Includes chemical, research site (California/Utah) and creatinine (mg/dL).

**Includes chemical, research site (California/Utah), creatinine (mg/dL) and adjusted for age (continuous), race (black/nonblack), BMI (<30.0/≥30.0), serum cotinine (smoker/nonsmoker).