Published in final edited form as:

Environ Res. 2011 May ; 111(4): 565–572. doi:10.1016/j.envres.2011.01.006.

Uterine Leiomyomata in a Cohort of Great Lakes Sport Fish Consumers

Anissa Lambertino^a, Mary Turyk^a, Henry Anderson^b, Sally Freels^a, and Victoria Persky^a

^aDivision of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, 1603 W Taylor Street, Room 879, (M/C 923), Chicago, IL 60612, USA

^bWisconsin Division of Public Health, Bureau of Environmental Health, 1 W Wilson Street, Room 150, Madison, WI, 53702, USA

Abstract

Diet and endocrine disrupting persistent organic pollutants (POPs) have been associated with gynecologic conditions including uterine leiomyomata (UL), endometriosis, and ovarian cysts. Great Lakes sport fish consumption is a source of exposure to POPs such as *p,p'*-diphenyldichloroethene (DDE) and polychlorinated biphenyls (PCBs). This study was designed to examine retrospectively the effects Great Lakes sport fish consumption on the incidence of UL and to examine the effects of DDE and PCB serum levels on prevalent UL in women participating in the Great Lakes Fish Consumption Study. We hypothesized that associations of exposures with UL would be modified by breastfeeding status. Years of sport fish consumption, demographic, health, and reproductive data were assessed by survey. In a subgroup, serum was collected and tested for DDE and PCB levels. Effects of years of Great Lakes sport fish and sport fish consumption were modeled using time-dependent Cox proportional hazards regression and effects of POP exposures on UL were modeled using multiple logistic regression. Years of sport fish consumption were associated with UL, with an incidence rate ratio of 1.2 (95% CI 1.0-1.3) for each 10-year increment of fish consumption. Summary measures of POP exposures in the overall group were not associated with UL. In the subgroup of women who never breastfed and in whom PCB measurements were available, however, UL was significantly associated with PCBs and groupings of estrogenic, antiestrogenic, and dioxin-like PCBs. These findings support the possibility that PCB exposures from fish consumption may increase the risk of UL and highlight the importance of additional studies exploring biologic pathways by which they could be acting.

Keywords

DDE; fibroids; Great Lakes sport fish; leiomyomata; PCBs

1. Introduction

Uterine leiomyomata (UL), or fibroids, are the most common benign tumor affecting reproductive aged women and are the primary indication for hysterectomy in the United States (Wilcox et al., 1994; Farquhar and Steiner, 2002). UL are hormonally dependent

Corresponding author: Anissa Lambertino, University of Illinois at Chicago School of Public Health, 1603 W Taylor Street, Room 878d, (M/C 923), Chicago, IL 60612, USA, Telephone: 312-413-3496, Fax: 312-996-7726, alambe2@uic.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

tumors that appear after menarche and regress around menopause when steroid hormones decline. Most Caucasian women are generally in their 30s or 40s at the time of clinical diagnosis of UL (Huyck et al., 2008).

The literature for clinically apparent UL give prevalence estimates of 20%-40% in women older than 30 years; however, the true incidence and prevalence of UL is unknown. Baird et al. (2003) screened for leiomyoma tumors in premenopausal women by ultrasonography independent of clinical symptoms and found 21% of Caucasians had previous leiomyoma diagnosis and 43% without previous diagnosis had ultrasound evidence of UL. Which women become clinically diagnosed depends on access to medical care, severity of symptoms, and the presence of unrelated conditions that might result in discovery of UL (Baird et al., 2003).

Increased risk of UL has been related to African-American ethnicity (Baird et al., 2003; Marshall et al., 1997), alcohol consumption (Wise et al., 2004), early menarche (Okolo, 2008), and hypertension (Boynton-Jarrett et al., 2005; Faerstein et al., 2001; Luoto et al., 2001). In addition, some investigations have found a relationship between UL and obesity, although the relationship is complex and may be modified by factors such as parity or other anthropometric characteristics (Faerstein et al., 2001; Takeda et al., 2008; Terry et al., 2007; Wise et al., 2005). Factors that may be protective for UL include increased parity and oral contraceptives, which are also often prescribed to treat menstrual disorders associated with UL (Okolo, 2008). In addition, diabetes was inversely associated with UL in two recent studies (Baird et al., 2009; Wise et al., 2007), although the direction of the diabetes association has not been demonstrated consistently in the literature (Faerstein et al., 2001).

Previous studies of diet have suggested that diets high in meat (Chiaffarino et al., 1999), glycemic index (Radin et al., 2010), and soy (D'Aloisio et al., 2010) and low in fruits, vegetables (Chiaffarino et al., 1999), dairy products (Wise et al., 2010), and total dietary lycopene (Terry et al., 2008) may affect the risk of UL in selected age groups. Diets high in Great Lakes sport fish and sport fish contain exposures for a number of persistent organic pollutants (POPs) including the lipophilic and bioaccumulative chemicals *p,p'*-diphenyldichloroethene (DDE) and polychlorinated biphenyls (PCBs) (Anderson et al., 1998; Hanrahan et al., 1999b). DDE and PCB body burdens increase significantly with age because they are food chain contaminants with long half-lives. POP metabolism in turn is affected by both body fat and changes in body fat (Mullerova et al., 2007; Wolff et al., 2005). Other factors such as parity and breastfeeding duration modify levels of DDE and PCB by transferring body burdens from mother to offspring (Anderson and Wolff, 2000; Hanrahan et al., 1999a).

This report examines data from women in a large cohort of frequent and infrequent Great Lakes sport fish consumers established in 1992 (Anderson et al., 1996; Hanrahan et al., 1999b). We used the cohort study design to examine retrospectively the association of years consuming Great Lakes sport fish and sport fish with incident, clinically apparent, UL obtained by self-report. In addition, we examined the associations of DDE and PCB body burdens with prevalent self-reported UL and examined the hypothesis that associations of exposures with UL are modified by breastfeeding status.

2. Methods

2.1 Subject Recruitment

The Great Lakes Fish Consumption Study was the result of the Great Lakes Water Quality Agreement of 1978 in which the health departments of the Great Lake States formed the Great Lakes Consortium. Organized in the early 1990s, the study was not originally

designed to study UL, but to assess the health risks associated with POP exposures from consumption of contaminated Great Lakes sport fish (Anderson et al., 1996; Hanrahan et al., 1999b). The original cohort of over 4,200 participants included Great Lakes charter boat captains, anglers who fished in inland Wisconsin lakes, their spouses, and a referent group with infrequent consumption of Great Lakes sport fish. Follow-up data was collected on subgroups of the original cohort at several time points. Sport fish consumption, health, and reproductive survey data were collected for 580 women in 2001-3 (n = 22) and 2004-5 (n = 558) and 197 participants provided a blood sample in 2001-5 for POP measurements. Breastfeeding practices were assessed in the initial 1993-5 survey (Hanrahan et al., 1999a). The investigation protocol was approved by Institutional Review Boards at the University of Wisconsin, Madison and University of Illinois at Chicago. All subjects provided informed consent prior to participation.

2.2 Sport Fish Consumption, Health, and Reproductive Assessments

Years of Great Lakes sport fish and sport fish consumption, demographics, diagnosis of medical diseases, and age of diagnosis were assessed by survey. Participants were asked if they had ever eaten Great Lakes sport fish or sport fish and, if so, how many years total have they eaten these fish types in their lifetime. In the health assessment, participants were asked if they were ever told by a doctor that they had benign (non-cancerous) fibroid tumors or fibroids in their uterus and, if so, the year of diagnosis. In addition, reproductive survey data was collected including number of pregnancies, hormonal contraception use, hysterectomy, and the number of births breastfed and weeks breastfed since 1970.

2.3 Biomarker Analyses

Participants were not required to fast before blood collection but were instructed to abstain from eating fish for 72 hours before blood donation. Blood for DDE and PCB congener analysis was collected in red-top vacutainer tubes, allowed to clot for 20 minutes, centrifuged for 15 minutes, transferred to solvent-rinsed glass vials, and stored at -20°C until analysis. The serum was extracted with hexane/ethyl ether, with clean-up and fractionation using Florisil, silica-gel and concentrated sulfuric acid as previously described (Anderson et al., 2008). PCB congeners and DDE were analyzed using high resolution capillary column gas chromatography equipped with an electron capture detector (Burse et al., 1990). Quality control was monitored by the use of method blanks, spiked bovine serum samples, duplicates of bovine serum spikes or sample duplicates, surrogate spikes, and confirmation of the analytes by second column or gas chromatography-mass spectrometry, as appropriate. Total cholesterol and triglycerides were measured by Quest Diagnostics (Auburn Hills, MI and Wood Dale, IL) in samples collected in 2004-2005 and by Meriter Laboratories (Madison, WI) in samples collected in 2001-2003. Total serum lipids were calculated using the formula $\text{total lipid} = [\text{total cholesterol (mg/dL)} \times 2.27] + \text{triglycerides (mg/dL)} + 62.3$.

2.4 Statistical Analyses

For analytical purposes, Great Lakes sport fish included fish caught in Lake Michigan, Lake Superior, Lake Huron, Lake Erie, and Lake Ontario, plus the mouths of rivers feeding into these lakes and parts of the lakes that have separate names (e.g. Green Bay). Sport fish included both the Great Lakes sport fish category and sport fish caught in inland lakes and streams, but were not purchased from a store or restaurant.

Measurements of PCBs and DDE were available for 177 participants in serum collected in 2004-5 and 20 participants with serum collected in 2001-3. Since DDE and PCBs were declining in most participants (Knobeloch et al. 2009), we adjusted the values from 2001-3 to better reflect 2004-5 levels. The median percent decrease in exposure was based on

calculations for participants who had measures at both time points. Missing values for 2004-2005 POP levels were imputed using the formula $\text{POP (ng/g wet weight) 2001-2003} - (\text{median \% change} * \text{POP (ng/g wet weight) 2001-2003})$. Σ Estrogenic PCB levels were not adjusted because median change was negligible.

Congener-specific values for selected PCB congeners (Knobeloch et al., 2009) were summed to yield Σ PCBs (sum of PCB congeners 74, 99, 118, 128, 146, 167, 172, 177, 178, 180, 183, 193, 194, 201, 206, 163/138, 170/190, 203/196, 202/171, 208/195, 187/182, 132/153/105). Variations in action and toxicological properties of individual PCB congeners have guided several investigators to construct antiestrogenic and estrogenic congener groupings (Wolff and Weston, 1997; Cooke et al., 2001). For this paper, groups were constructed using available congeners summed to yield Σ estrogenic PCBs based on Cooke's criteria (sum of PCB congeners 99, 132/153/105) (Cooke et al., 2001), Σ estrogenic PCBs based on Wolff's criteria (sum of PCB congeners 177, 187/182, 201), Σ antiestrogenic PCBs based on Wolff's criteria (sum of PCB congeners 66, 74, 118, 128, 163/138, 167, 170/190) (Wolff and Weston, 1997), and Σ dioxin-like PCBs (sum of PCB congeners 118, 167) (Van den Berg et al., 2006). Because of coelution, dioxin-like PCB 105 was not separated from estrogenic PCB 153 for Σ PCBs and Cooke Σ estrogenic PCBs. According to the National report on Human Exposure to Environmental Chemicals, however, PCB 105 only contributes 6.6% to the 153/105 coelution (CDC, 2010). Antiestrogenic congeners based on Cooke's criteria were not measured in this investigation. We used natural log transformations of DDE, Σ PCBs, Σ estrogenic PCBs, and Σ antiestrogenic PCBs to approximate a normal distribution. Σ Dioxin-like PCBs were dichotomized at the limit of detection (LOD). Prior to summation, congeners below the LOD were imputed as half the LOD.

Bivariate analyses were conducted to determine relationships of potential confounders with 1) self-reported UL status using Chi-square and Student's t tests and 2) Great Lakes sport fish, sport fish, DDE, Σ PCBs, and PCB groupings using Pearson's correlation coefficients and Student's t tests.

2.5 Incident Analysis

For participants with survey data (n=580), a total of 541 remained after excluding 3 participants with missing leiomyoma and hysterectomy information, 2 with year of hysterectomy prior to leiomyoma diagnosis, 1 with missing date of birth, 8 with missing year of hysterectomy, 23 with missing year of leiomyoma diagnosis, 1 with age of leiomyoma diagnosis prior to 15 years, and 1 with age of menopause prior to 15 years. For 72 participants who were ≥ 51 years of age and had missing menopause information, age of menopause was censored at the average age which is 51 years in normal women (Casper, 2009). Similar results were obtained when age of menopause was censored at 61 years (not shown). Each participant contributed person-years of follow-up starting at 15 years of age until age of self-reported leiomyoma diagnosis, hysterectomy, menopause, or the end of follow-up, whichever occurred first. We restricted the analysis because the risk of UL generally increases with age through the reproductive years and UL are rarely diagnosed after menopause (Flake et al., 2003);

We identified 95 incident, clinically apparent leiomyoma cases through a survey that assessed self-reported diagnosis of medical diseases and age of diagnosis. The incidence rates for self-reported UL (incidence/1,000 person-years) were by calculated dividing the number of cases by the number of person-years of follow-up and multiplying by 1,000. Cox proportional hazards regression models with time-dependent covariates were used to evaluate the effect of years of Great Lakes sport fish and sport fish consumption on UL. We obtained incidence rate ratios (IRRs) and 95% confidence intervals (CIs) using SAS PROC

PHREG (version 9.1; SAS Institute Inc., Cary, NC). Variables representing years of fish consumption were divided by 10 to obtain estimates per 10 year increment.

We conducted an a priori evaluation of effect modification by breastfeeding status because breastfeeding may alter the bioaccumulation and metabolism of POP body burdens (Hanrahan et al., 1999a). We used regression models to evaluate effect modification based on the statistical significance of the interaction term (exposure X breastfeeding status) in the regression equation. Models were also stratified by the breastfeeding status to evaluate the heterogeneity of the IRRs in strata. Age and obesity were included in all adjusted models because we considered them to be important potential confounders. Adjustment for BMI evaluated as a continuous variable or as an indicator variable for quartiles did not substantially improve the models. In order to assess confounding, additional covariates were added individually to the adjusted model. Confounding was defined as a change in the exposure odds ratio of more than 10% after the addition of the covariate.

2.6 Prevalent Analysis

Logistic regression analyses were used to evaluate associations of DDE, Σ PCBs, and PCB groupings with UL. Σ PCB and PCB groupings were evaluated as continuous variables and as indicator variables for quartiles 2, 3, and 4 with quartile 1 defined as the reference category to assess dose-response relationships. The ordinal quartile variable was used to test for trend over the categories. We considered serum lipids, age, and obesity for POP exposures to be important confounders and included them in all of the adjusted models. Effect modification and confounding were assessed as described for the incident analysis.

3. Results

The study cohort was comprised of mostly non-Hispanic Caucasian women (99%). We identified a total of 122 out of 577 or 21.1% of participants with self-reported UL. Median age of diagnosis was 43 years (range 18-61 years). Table 1 summarizes cohort characteristics as well as differences between those with and without self-reported UL. The mean age of participants was 53 years (range 31-82 years) and mean body mass index (BMI) was 26.9 kg/m² (range 17.5-54.9 kg/m²). Twenty-two percent of participants were classified as obese (BMI $\geq$ 30) according to categories set by Centers for Disease Control and Prevention (CDC, 2009). UL were more common in obese participants, but the relationship was of borderline significance.

At the time of survey, cohort participants had consumed Great Lakes sport fish and sport fish for an average of 19 and 24 years, respectively. Participants with UL were more likely to be older, have hypertension, and to have consumed Great Lakes sport fish and sport fish for more years than women without self-reported disease. In addition, they were more likely to have had hysterectomy, early menarche, and to have ever used hormonal birth control. Of the POP exposure levels measured in blood samples, Σ PCBs and PCB grouping levels were slightly higher in participants with self-reported UL; however, only for Σ PCBs and Σ estrogenic PCB groupings were differences close to significant. Σ PCBs and PCB congener groupings were strongly correlated, with correlation coefficients from $r = 0.82$ to 0.98 ($p < 0.05$, not shown).

Table 2 presents correlations of exposures with continuous covariates. Age was positively and significantly correlated with Σ PCBs (Pearson's $r = 0.49$, $p < 0.05$), as well as with DDE, and years of Great Lakes sport fish and sport fish consumption (Pearson's $r = 0.25$ - 0.33 , $p < 0.05$). BMI was negatively and significantly correlated with Σ PCBs (Pearson's $r = -0.17$, $p < 0.05$). Both number of births breastfed and weeks breastfed were inversely and significantly or close to significantly correlated with Great Lakes sport fish, sport fish, and

Σ PCBs. Number of pregnancies, however, was not significantly correlated with any of the exposures (Table 2). There were significant and positive correlations of Σ PCB with years of Great Lakes sport fish consumption (Pearson's $r = 0.42$, $p < 0.05$) and sport fish consumption (Pearson's $r = 0.39$, $p < 0.05$) (not shown). Similar correlations were found for both antiestrogenic and estrogenic PCB groupings (Pearson's $r = 0.35$ - 0.45 , $p < 0.05$). DDE was not significantly associated with years of Great Lakes sport fish and sport fish consumption (Pearson's $r = 0.10$ - 0.12 , $p > 0.1$) (not shown).

Table 3 presents associations of exposures with dichotomous covariates. Geometric mean Σ PCBs, but not DDE, was higher in leaner participants ($BMI < 30$). Mean years consuming Great Lakes sport fish and sport fish were significantly higher in participants who consumed alcohol at least once per month or had hypertension. In addition, the mean years of Great Lakes sport fish and sport fish consumption and the geometric mean for Σ PCBs were significantly higher in women who never breastfed.

3.1 Incident Analysis

Participants were retrospectively followed for incident self-reported UL for an average of 30 years. The 39 participants who were excluded from the incident analysis because of missing data were slightly older and had higher average years of Great Lakes sport fish and sport fish consumption when compared with participants who remained in the analysis (not shown).

Table 4 presents the IRRs for UL per 10 year increment in Great Lakes sport fish and sport fish consumption. Great Lakes sport fish and sport fish were associated with incident UL with adjusted IRRs equal to 1.2 (95% CI 1.0-1.4) and 1.2 (95% CI 1.0-1.3), respectively). The relationships remained close to significant or significant after adjustment for age and obesity. Associations were not significant in the subgroup of participants with POP data ($n = 169$) and remained nonsignificant when adjusted for POPs (not shown). Associations were, however, borderline significant for Great Lakes sport fish consumption in the subgroup of participants with breastfeeding survey data ($n = 480$), and remained borderline significant after adjustment for number of births breastfed (not shown).

Interaction terms in the regression equation were not statistically significant and IRR point estimates stratified by breastfeeding status were not heterogeneous. However, there was some evidence of a stronger effect between Great Lakes sport fish consumption and UL in models stratified by obesity status, but the interaction term in the regression model was not significant (not shown). There was no evidence of confounding or effect modification by health or reproductive covariates in the incident analyses (not shown).

3.2 Prevalent Analysis

Measurements of serum POP levels and breastfeeding practices were not available for all participants. The participants who donated blood had significantly higher average years of Great Lakes sport fish and sport fish consumption when compared with participants who did not donate (not shown).

Table 5 presents prevalence odds ratios for associations of UL with Σ PCBs and PCB groupings. DDE was not associated with UL (not shown). The unadjusted associations of Σ estrogenic and Σ dioxin-like PCB groupings with UL were of borderline significance. The interaction term for Σ dioxin-like PCBs and breastfeeding status approached statistical significance. When regression models were stratified by breastfeeding status, the odds of UL with exposure to Σ dioxin-like PCBs in participants who never breastfed was 8.6 (95% CI = 2.0-36.6) and 0.80 (95% CI = 0.23-2.8) in participants who breastfed (Table 5). Similar results were obtained for Σ PCBs, Σ antiestrogenic PCBs, and estrogenic Σ PCBs based on

Cooke's criteria with a slightly weaker association for estrogenic Σ PCBs using Wolff's criteria. There was no evidence of confounding by health or reproductive covariates based on a 10% change in the exposure odds ratio (not shown). Because older participants had experienced longer durations of exposure and also higher PCB contamination levels in the past, a sensitivity analysis was conducted for age using the following categories: 40 to 60 years (n=148), 50 to 70 years (n=133), and 50+ years (n=135). Odds ratios remained elevated for those who never breastfed with associations significant for Σ dioxin-like PCBs in all 3 age groups and for Σ PCBs in the 50+ age group.

In addition to using POP exposures as continuous variables, we noted an increased odds for UL with Σ PCBs and PCB groupings in the second, third, and fourth quartile compared to the first (Table 6). Although trends were not significant for adjusted models, trends across quartiles were borderline significant in unadjusted models.

4. Discussion

This study found associations of self-reported UL incidence with years of Great Lakes sport fish and sport fish that approached significance. In prevalence analyses, associations of Σ PCBs and PCB groupings with self-reported UL were close to significant, but these associations were somewhat attenuated after adjustment for serum lipids, age, and obesity. However, stratified models indicated Σ PCBs, Σ estrogenic PCBs using Cooke's criteria, Σ antiestrogenic PCBs, and Σ dioxin-like PCBs associations with UL were stronger and significant in those participants who never breastfed and the interaction term for Σ dioxin-like PCBs and breastfeeding status approached statistical significance. DDE, considered to be antiandrogenic, was not associated with UL in any of the analyses.

The results of this investigation are consistent with previous epidemiologic studies which suggest that demographic, health, and reproductive factors are associated with UL (Boynton-Jarrett et al., 2005; D'Aloisio et al., 2010; Terry et al., 2007; Wise et al., 2004). In the current investigation, self-reported leiomyoma diagnosis was higher with age, hypertension, and early menarche. Our findings are also consistent with previous studies that do not support a relationship of breastfeeding with UL (Lumbiganon et al., 1996; Samadi et al., 1996), but do suggest breastfeeding is inversely related with PCB body burdens (Hanrahan et al., 1999a; Schantz et al., 1994). However, we relied on a pregnancy variable that included miscarriages or tubal pregnancies for which little or no protective effect on leiomyoma development has been shown (Chen et al., 2001; Sato et al., 2000).

The results of the present investigation are inconsistent with a case-control study of Italian women which reported less frequent consumption of fish in those with UL (Chiaffarino et al., 1999). Potential explanations for these divergent results include higher contaminant levels, especially PCBs or other unmeasured contaminants, in our cohort that was assembled based on consumption of sport fish from contaminated waters. In the general population, fish consumption may be an indicator of healthy dietary habits, and any effects on leiomyoma development may be offset by the improved health outcomes brought about by omega-3 fatty acids found in fish (Calder and Yaqoob, 2009) or diets high in fruits and vegetables (Chiaffarino et al., 1999). No evidence, to our knowledge, is found in previous literature to support fish consumption as a risk factor for UL.

There is substantial biochemical evidence to support estrogen as a major promoter of leiomyoma development (Rein, 2000). UL may also be sensitive to the influences of environmental factors, such as POPs, that can act as exogenous hormones through their ability to bind and activate the estrogen receptor (Hunter et al., 2000). Our failure to find a protective effect with Σ antiestrogenic PCBs and dioxin-like mono-ortho PCB congeners is

inconsistent with laboratory animal and epidemiological studies that investigated the related compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD has been shown to induce antiestrogenic responses in rat uterine cells (Safe et al., 1998) and an epidemiologic investigation found TCDD acts as an antiestrogen, with higher levels inversely related to UL in women participating in the Seveso Women's Health Study (Eskenazi et al., 2007). However, the strong correlations among PCB groupings in our participants make it difficult to identify particular congeners responsible for the noted associations and we have probably underestimated Σ dioxin-like exposure with an imprecise measure that included only two mono-ortho PCB congeners, and no measurements of dioxins and furans.

In stratified analyses based on breastfeeding status, the effect of Σ PCBs, Cooke's Σ estrogenic PCBs, Σ antiestrogenic PCBs, and Σ dioxin-like PCBs on leiomyoma prevalence was stronger and statistically significant in participants who never breastfed; the association was somewhat stronger but not significant in women who never breastfed using Σ estrogenic PCBs proposed by Wolff. Both Cooke and Wolff groupings are incomplete because they were based on the limited congeners measured in this study. Since POP body burdens can be decreased by lactation (Wolff et al., 2005), long-term PCB exposures may be more precisely estimated from current blood samples in women who have not breastfed compared with those who have lactated.

Strengths of this investigation are the measurement of multiple exposures and the retrospective analysis of incident self-reported UL with years consuming Great Lakes sport fish and sport fish. The present investigation has a number of limitations. First, our study was not originally designed to be a leiomyoma study; thus several important risk factors were not obtained, including number of full-term births. Second, the assessment of UL by self-report, and not ultrasound, will result in many undiagnosed cases and therefore, we may have considerable misclassification of disease status. Third, our measures of years of sport fish consumption were based on retrospective recall and we assumed that years of consumption were continuous across time, although this is likely to be true only for participants who never consume sport fish. Furthermore, variations in the number of fish meals annually are not captured in the variables. Finally, the small size of the subgroup with POP exposure measurements limits the power and the ability to draw conclusions about the role of POPs as mediators in the relationship between years of sport fish consumption and UL. It is also possible that PCBs are a marker of general fish contamination, and that unmeasured exposures or concomitant exposures to other POPs are responsible for increased risk of UL.

5. Conclusions

The current investigation found some evidence for incident associations of Great Lake sport fish and sport fish consumption with self-reported UL, which have not been previously noted in the literature. In a subgroup of participants with POP measurements who never breastfed, stronger associations of Σ PCBs, Σ estrogenic PCBs, Σ antiestrogenic PCBs, and Σ dioxin-like PCBs were found with self-reported UL, suggesting effect modification by breastfeeding status for Σ dioxin-like PCBs. Future studies should explore the biologic pathways by which diets high in environmental contaminants affect estrogen-dependent UL.

Human subjects research review

This study was conducted in accordance with national and institutional guidelines for the protection of human subjects. Prior to initiation of this study protocol, it was reviewed and approved by both the University of Illinois-Chicago Internal Review Board and

University of Wisconsin-Madison Medical School Human Subjects Committee. Informed consent was obtained from each subject prior to participation.

Acknowledgments

Funding sources

This research was supported by the Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, Grant Number H75/ATH598322, the U.S. Environmental Protection Agency, Grant Number RD-83025401-1, and the National Institute of Environmental Health Sciences, Grant Number R21ES017121. Although the research described in this article has been funded by the U.S. Environmental Protection Agency, it has not been subjected to the Agency's required peer and policy review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Environmental Health Sciences or the National Institutes of Health.

References

- Anderson H, Falk C, Fiore B, Hanrahan L, Humphrey HE, Kanarek M, Long T, Mortensen K, Shelley T, Sonzogni B, Steele G, Tilden J. Consortium for the Health Assessment of Great Lakes Sport Fish Consumption. *Toxicol. Ind. Health*. 1996; 12:369–373. [PubMed: 8843554]
- Anderson HA, Falk C, Hanrahan L, Olson J, Burse VW, Needham L, Paschal D, Patterson D Jr. Hill RH Jr. The Great Lakes Consortium. Profiles of Great Lakes critical pollutants: a sentinel analysis of human blood and urine. *Environ. Health Perspect*. 1998; 106:279–289. [PubMed: 9560354]
- Anderson HA, Wolff MS. Environmental contaminants in human milk. *J. Expo. Anal. Environ. Epidemiol*. 2000; 10:755–760. [PubMed: 11138667]
- Anderson HA, Imm P, Knobloch L, Turyk M, Mathew J, Buelow C, Persky V. Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish. *Chemosphere*. 2008; 73:187–194. [PubMed: 18599108]
- Baird DD, Dunson DB. Why is parity protective for uterine fibroids? *Epidemiology*. 2003; 14:247–250. [PubMed: 12606893]
- Baird DD, Travlos G, Wilson R, Dunson DB, Hill MC, D'Aloisio AA, London SJ, Schectman JM. Uterine leiomyomata in relation to insulin-like growth factor-I, insulin, and diabetes. *Epidemiology*. 2009; 20:604–610. [PubMed: 19305350]
- Boynton-Jarrett R, Rich-Edwards J, Malspeis S, Missmer SA, Wright R. A prospective study of hypertension and risk of uterine leiomyomata. *Am. J. Epidemiol*. 2005; 161:628–638. [PubMed: 15781952]
- Burse VW, Head SL, Korver MP, McClure PC, Donahue JF, Needham LL. Determination of selected organochlorine pesticides and polychlorinated biphenyls in human serum. *J. Anal. Toxicol*. 1990; 14:137–142. [PubMed: 1695698]
- Calder PC, Yaqoob P. Omega-3 polyunsaturated fatty acids and human health outcomes. *Biofactors*. 2009; 35:266–272. [PubMed: 19391122]
- Casper, RF. Clinical manifestations and diagnosis of menopause. 2009. Online at: <<http://www.uptodate.com/patients/content/topic.do?topicKey=~QDQ.i0ktzNrZtfD>>
- CDC. About BMI for adults. 2009. Online at <http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html>
- CDC. National Report on Human Exposure to Environmental Chemicals. 2010. Online at <http://www.cdc.gov/exposurereport/data_tables/LBX105_DataTables.html>
- Chen CR, Buck GM, Courey NG, Perez KM, Wactawski-Wende J. Risk factors for uterine fibroids among women undergoing tubal sterilization. *Am. J. Epidemiol*. 2001; 153:20–26. [PubMed: 11159141]
- Chiaffarino F, Parazzini F, La Vecchia C, Chatenoud L, Di Cintio E, Marsico S. Diet and uterine myomas. *Obstet. Gynecol*. 1999; 94:395–398. [PubMed: 10472866]

- Cooke, PS.; Sato, T.; Buchanan, DL. Disruption of steroid hormone signaling by PCBs. In: Robertson, LW.; Hansen, LG., editors. PCBs: Recent advances in environmental toxicology and health effects. The University Press of Kentucky; Lexington: 2001. p. 257-263.
- D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study. *Environ. Health Perspect.* 2010; 118:375–381. [PubMed: 20194067]
- Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am. J. Obstet. Gynecol.* 2003; 188:100–107. [PubMed: 12548202]
- Eskenazi B, Warner M, Samuels S, Young J, Gerthoux PM, Needham L, Patterson D, Olive D, Gavoni N, Vercellini P, Mocarelli P. Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. *Am. J. Epidemiol.* 2007; 166:79–87. [PubMed: 17443023]
- Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. *Am. J. Epidemiol.* 2001; 153:11–19. [PubMed: 11159140]
- Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. *Obstet. Gynecol.* 2002; 99:229–234. [PubMed: 11814502]
- Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. *Environ. Health Perspect.* 2003; 111:1037–54. [PubMed: 12826476]
- Hanrahan LP, Anderson HA, Falk C, Olson J, Consortium, T.G.L. Reproductive predictors of serum PCB and DDE levels among frequent Great Lakes sport fish consumers: the role of gender, births, and breastfeeding. *Eur. J. Oncol.* 1999a; 4:585–593.
- Hanrahan LP, Falk C, Anderson HA, Draheim L, Kanarek MS, Olson J, The Great Lakes Consortium. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers-a first look. *Environ. Res.* 1999b; 80:S26–S37. [PubMed: 10092417]
- Hunter DS, Hodges LC, Eagon PK, Vonier PM, Fuchs-Young R, Bergerson JS, Walker CL. Influence of exogenous estrogen receptor ligands on uterine leiomyoma: evidence from an in vitro/in vivo animal model for uterine fibroids. *Environ. Health Perspect.* 2000; 108(Suppl 5):829–834. [PubMed: 11035990]
- Huyck KL, Panhuysen CI, Cuenco KT, Zhang J, Goldhammer H, Jones ES, Somasundaram P, Lynch AM, Harlow BL, Lee H, Stewart EA, Morton CC. The impact of race as a risk factor for symptom severity and age at diagnosis of uterine leiomyomata among affected sisters. *Am. J. Obstet. Gynecol.* 2008; 198:168 e1–e9. [PubMed: 18226615]
- Knobeloch L, Turyk M, Imm P, Schrank C, Anderson H. Temporal changes in PCB and DDE levels among a cohort of frequent and infrequent consumers of Great Lakes sportfish. *Environ. Res.* 2009; 109:66–72. [PubMed: 18950754]
- Lumbiganon P, Rungpa S, Phandhu-fung S, Laopaiboon M, Vudhikamraksa N, Werawatakul Y. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. *Br. J. Obstet. Gynaecol.* 1996; 103:909–914. [PubMed: 8813312]
- Luoto R, Rutanen EM, Auvinen A. Fibroids and hypertension. A cross-sectional study of women undergoing hysterectomy. *J. Reprod. Med.* 2001; 46:359–364. [PubMed: 11354837]
- Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet. Gynecol.* 1997; 90:967–973. [PubMed: 9397113]
- Mullerova D, Kopecky J. White adipose tissue: storage and effector site for environmental pollutants. *Physiol. Res.* 2007; 56:375–381. [PubMed: 16925464]
- Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. *Best Pract. Res. Clin. Obstet. Gynaecol.* 2008; 22:571–588. [PubMed: 18534913]
- Radin RG, Palmer JR, Rosenberg L, Kumanyika SK, Wise LA. Dietary glycemic index and load in relation to risk of uterine leiomyomata in the Black Women's Health Study. *Am. J. Clin. Nutr.* 2010; 91:1281–1288. [PubMed: 20200259]
- Rein MS. Advances in uterine leiomyoma research: the progesterone hypothesis. *Environ. Health Perspect.* 2000; 108(Suppl 5):791–793. [PubMed: 11035984]

- Safe S, Wang F, Porter W, Duan R, McDougal A. Ah receptor agonists as endocrine disruptors: antiestrogenic activity and mechanisms. *Toxicol. Lett.* 1998; 102-103:343–347. [PubMed: 10022276]
- Samadi AR, Lee NC, Flanders WD, Boring JR 3rd, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. *Am. J. Public Health.* 1996; 86:858–862. [PubMed: 8659663]
- Sato F, Miyake H, Nishi M, Kudo R. Fertility and uterine size among Asian women undergoing hysterectomy for leiomyomas. *Int. J. Fertil. Womens Med.* 2000; 45:34–37. [PubMed: 10721742]
- Schantz SL, Jacobson JL, Humphrey HE, Jacobson SW, Welch R, Gasior D. Determinants of polychlorinated biphenyls (PCBs) in the sera of mothers and children from Michigan farms with PCB-contaminated silos. *Arch. Environ. Health.* 1994; 49:452–458. [PubMed: 7818287]
- Takeda T, Sakata M, Isobe A, Miyake A, Nishimoto F, Ota Y, Kamiura S, Kimura T. Relationship between metabolic syndrome and uterine leiomyomas: a case-control study. *Gynecol. Obstet. Invest.* 2008; 66:14–17. [PubMed: 18230910]
- Terry KL, De Vivo I, Hankinson SE, Spiegelman D, Wise LA, Missmer SA. Anthropometric characteristics and risk of uterine leiomyoma. *Epidemiology.* 2007; 18:758–763. [PubMed: 17917603]
- Terry KL, Missmer SA, Hankinson SE, Willett WC, De Vivo I. Lycopene and other carotenoid intake in relation to risk of uterine leiomyomata. *Am. J. Obstet. Gynecol.* 2008; 198:37 e1–e8. [PubMed: 17981250]
- Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicol. Sci.* 2006; 93:223–241. [PubMed: 16829543]
- Wilcox LS, Koonin LM, Pokras R, Strauss LT, Xia Z, Peterson HB. Hysterectomy in the United States, 1988–1990. *Obstet. Gynecol.* 1994; 83:549–555. [PubMed: 8134065]
- Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, Rosenberg L. Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. *Hum. Reprod.* 2004; 19:1746–1754. [PubMed: 15218005]
- Wise LA, Palmer JR, Stewart EA, Rosenberg L. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. *Obstet. Gynecol.* 2005; 105:563–568. [PubMed: 15738025]
- Wise LA, Palmer JR, Stewart EA, Rosenberg L. Polycystic ovary syndrome and risk of uterine leiomyomata. *Fertil. Steril.* 2007; 87:1108–1115. [PubMed: 17241625]
- Wise LA, Radin RG, Palmer JR, Kumanyika SK, Rosenberg L. A prospective study of dairy intake and risk of uterine leiomyomata. *Am. J. Epidemiol.* 2010; 171:221–232. [PubMed: 19955473]
- Wolff MS, Britton JA, Teitelbaum SL, Eng S, Deych E, Ireland K, Liu Z, Neugut AI, Santella RM, Gammon MD. Improving organochlorine biomarker models for cancer research. *Cancer Epidemiol. Biomarkers Prev.* 2005; 14:2224–2236. [PubMed: 16172236]
- Wolff MS, Weston A. Breast cancer risk and environmental exposures. *Environ. Health Perspect.* 1997; 105(Suppl 4):891–896. [PubMed: 9255576]

Table 1

Characteristics of the cohort by self-reported uterine leiomyoma status.

Characteristic	N	Total Cohort	Range	Leiomyoma status	
				Yes ^a	No
<u>Demographic</u>					
Age (years), mean	579	53	31-82	54.7**	52.7
<u>Health</u>					
BMI (kg/m ²), mean	574	26.9	17.5-54.9	27.5	26.8
Alcohol (≥ 1 drink/month), %	533	67.9		66.4	68.6
Cigarette smoking, %	568	14.1		10.0	15.3
Diabetes, %	577	6.8		7.4	6.6
Hypertension, %	556	27.0		34.8**	24.9
Obese (BMI ≥ 30), %	574	21.6		27.1*	19.8
<u>Reproductive</u>					
Number of births breastfed, mean	513	1	0-8	0.96	0.95
Number of pregnancies, mean	568	3	0-10	3.2*	2.8
Number of weeks breastfed, mean	512	27	0-740	27.5	27.1
Breastfed (≥ 1 birth), %	513	50.7		50.0	51.1
Early menarche (< 11 years), %	556	7.4		11.6**	6.2
Hormonal birth control (ever), %	567	62.4		72.1**	59.8
Hysterectomy, %	577	26.7		59.0**	18.0
<u>Exposure^{b,c}</u>					
Great Lakes sport fish (years), mean	566	19	0-83	23.4**	18.1
Sport fish (years), mean	572	24	0-83	29.7**	22.6
Ln DDE (ng/g), GM	197	0.84	0.07-17.0	0.76	0.86
Ln ΣPCBs (ng/g), GM	197	2.2	1.2-9.7	2.5*	2.1
Ln Wolff ΣAntiestrogenic PCBs (ng/g), GM	197	0.76	0.40-3.3	0.84	0.74
Ln Cooke ΣEstrogenic PCBs (ng/g), GM	197	0.36	0.12-1.9	0.42*	0.35
Ln Wolff ΣEstrogenic PCBs (ng/g), GM	197	0.21	0.12-1.2	0.25*	0.20

Characteristic	N	Total Cohort	Range	Leiomyoma status	
				Yes ^a	No
ΣDioxin-like PCBs (ng/g) (>LOD), %	197	26.9		37.0	23.8

GM=geometric mean

ΣPCBs=sum of PCBs 66, 74, 99, 118, 128, 146, 167, 172, 177, 178, 180, 183, 193, 194, 201, 206, 163/138, 170/190, 203/196, 202/171, 208/195, 187/182, 132/153/105.

Wolff ΣAntiestrogenic PCBs=sum of PCBs 66, 74, 118, 128, 163/138, 167, 170/190.

Cooke ΣEstrogenic PCBs=sum of PCBs 99, 132/153/105.

Wolff ΣEstrogenic PCBs=sum of PCBs 177, 187/182, 201.

ΣDioxin-like PCBs=sum of PCBs 118, 167.

**
p < 0.05

* 0.05 ≤ p < 0.1 for Chi square and Student's t tests.

^a 122 out of 577 or 21.1% of participants had self-reported uterine leiomyomata.

^b DDE and PCB measurements were collected in a subgroup of participants in 2001-2005.

^c Antiestrogenic congeners based on Cooke's criteria were not measured in this study.

Table 2Correlations of Great Lakes sport fish, sport fish, DDE, and Σ PCBs with covariates.

Characteristic	n	Great Lakes sport fish	n	Sport fish	n ^a	LnDDE ^b	Ln Σ PCBs ^b
<u>Demographic</u>							
Age (years)	565	0.26**	571	0.33**	197	0.25**	0.49**
<u>Health</u>							
BMI (kg/m ²)	561	0.07	567	0.07	196	-0.08	-0.17**
<u>Reproductive</u>							
Number of births breastfed	500	-0.15**	506	-0.17**	183	-0.10	-0.27**
Number of pregnancies	555	-0.01	561	0.01	191	0.06	-0.01
Number of weeks breastfed	499	-0.11*	505	-0.11*	182	-0.09	-0.26**

^a n for DDE and Σ PCB are equal.^b Results were similar using Spearman's correlation coefficients.***
p < 0.05*
0.05 ≤ p < 0.1 for Pearson's correlation coefficients.

Table 3

Associations of Great Lakes sport fish, sport fish, DDE, and ΣPCBs with covariates.

Characteristic	Category	n	Great Lakes sport fish Mean years	n	Sport fish Mean years	^a n	Ln DDE GM (ng/g)	Ln ΣPCBs GM (ng/g)
<u>Health</u>								
Alcohol (≥ 1 drink/month)	-	165	16.2	167	19.9	57	0.93	2.1
	+	354	21.2**	358	26.3**	127	0.77	2.3
Hypertension	-	399	17.5	403	21.6	124	1.1	2.1
	+	148	24.0**	148	29.6**	53	1.2	2.3
Obese (BMI ≥ 30)	-	440	19.1	446	23.7	150	0.90	2.3**
	+	121	20.2	121	24.7	46	0.67	1.9
<u>Reproductive</u>								
Breastfed (≥ 1 birth)	-	250	20.2**	250	24.9**	72	0.83	2.5**
	+	250	16.2	256	20.3	111	0.74	2.0

GM=Geometric mean

^a n for DDE and ΣPCB are equal.**
p < 0.05* 0.05 $\leq$ p < 0.1 for Student's t tests.

Table 4
Associations of incident self-reported uterine leiomyomata with Great Lakes sport fish consumption.

Exposure	Covariates	Strata	n	Cases	Person-years of follow-up	Incidence/1000 person-years	IRR ^a	95% CI
Great Lakes sport fish	None	All	541	95	16,352	5.8	1.2	1.0-1.4
	Age, obesity	All	535	95	16,143	5.9	1.2	0.99-1.3
	Age, obesity	Never breastfed	233	42	6,930	6.1	1.1	0.91-1.4
		Breastfed	246	44	7,562	5.8	1.1	0.91-1.4
Sport fish	None	All	541	95	16,352	5.8	1.2	1.0-1.3
	Age, obesity	All	535	95	16,143	5.9	1.2	1.0-1.3
	Age, obesity	Never breastfed	233	42	6,930	6.1	1.1	0.93-1.4
		Breastfed	246	44	7,562	5.8	1.1	0.88-1.3

IRR=incident rate ratio for uterine leiomyomata per 10 year increment in fish consumption

^aPerson-years of follow-up started at 15 years of age until age of self-reported leiomyoma diagnosis, hysterectomy, menopause, or the end of follow-up, whichever occurred first.

Table 5

Prevalence odds ratio of uterine leiomyomata in association with SPCBs and PCB groupings.

Exposure	Covariates	Strata	n	Cases	OR ^a	95% CI	Interaction	
							P value ^b	P value ^b
Ln ΣPCBs (ng/g)	None	All	197	46	1.7	0.90-3.3		
	Lipids, age, obesity	All	190	43	1.6	0.72-3.5	0.96	
	Lipids, age, obesity	Never breastfed	68	17	4.1	1.1-16.0		
		Breastfed	109	22	1.3	0.38-4.6		
Ln Wolff ΣAntiestrogenic PCBs ^c (ng/g)	None	All	197	46	1.6	0.87-3.1		
	Lipids, age, obesity	All	190	43	1.5	0.70-3.1	0.61	
	Lipids, age, obesity	Never breastfed	68	17	4.2	1.2-15.4		
		Breastfed	109	22	1.1	0.32-3.7		
Ln Cooke ΣEstrogenic PCBs (ng/g)	None	All	197	46	1.6	0.94-2.6		
	Lipids, age, obesity	All	190	43	1.5	0.79-2.7	0.76	
	Lipids, age, obesity	Never breastfed	68	17	3.8	1.2-12.2		
		Breastfed	109	22	1.3	0.53-3.2		
Ln Wolff ΣEstrogenic PCBs (ng/g)	None	All	197	46	1.6	0.93-2.6		
	Lipids, age, obesity	All	190	43	1.5	0.81-2.8	0.55	
	Lipids, age, obesity	Never breastfed	68	17	2.2	0.79-6.0		
		Breastfed	109	22	1.6	0.61-4.1		
ΣDioxin-like PCBs (ng/g)	None	All	197	46	1.9	0.92-3.8		
	Lipids, age, obesity	All	190	43	1.9	0.88-4.0	0.06	
	Lipids, age, obesity	Never breastfed	68	17	8.6	2.0-36.6		
		Breastfed	109	22	0.80	0.23-2.8		

^a OR=odds ratio per ng/g increment, except for Σdioxin-like PCBs which is the odds ratio comparing above to below the limit of detection.

^b Model with the exposure, breastfeeding status, lipids, age, obese, and the interaction term (exposure*breastfeeding status) in the regression equation.

^c Antiestrogenic congeners based on Cooke's criteria were not measured in this study.

Table 6

Prevalence odds ratio of uterine leiomyomata in association with Σ PCBs and PCB groupings: dose-response models.

Exposure	Adjusted ^a	n	Measure	Exposure Range	OR	95% CI	P-value for trend
Ln Σ PCBs (ng/g)	-	49	Quartile 1	1.2-1.5			0.05
		49	Quartile 2 β	1.5-1.9	3.5	1.2-10.7	
		50	Quartile 3 β	1.9-3.1	3.1	1.0-9.5	
		49	Quartile 4 β	3.1-9.7	3.5	1.2-10.7	
	+	49	Quartile 1	1.2-1.5			0.13
		49	Quartile 2 β	1.5-1.9	4.1	1.2-14.1	
		50	Quartile 3 β	1.9-3.1	3.7	1.0-13.3	
		49	Quartile 4 β	3.1-9.7	3.9	0.98-15.2	
Ln Wolff Σ Antiestrogenic PCBs ^c (ng/g)	-	52	Quartile 1	0.40-0.53			0.06
		46	Quartile 2 β	0.53-0.66	1.5	0.55-4.3	
		50	Quartile 3 β	0.66-1.1	1.9	0.72-5.2	
		49	Quartile 4 β	1.1-3.3	2.4	0.92-6.4	
	+	52	Quartile 1	0.40-0.53			0.15
		46	Quartile 2 β	0.53-0.66	1.5	0.50-4.6	
		50	Quartile 3 β	0.66-1.1	2.0	0.70-5.9	
		49	Quartile 4 β	1.1-3.3	2.2	0.71-7.2	
Ln Cooke Σ Estrogenic PCBs (ng/g)	-	47	Quartile 1	0.13-0.24			0.07
		53	Quartile 2 β	0.24-0.35	4.2	1.3-13.9	
		48	Quartile 3 β	0.35-0.55	4.9	1.5-16.1	
		49	Quartile 4 β	0.56-1.9	3.5	1.0-11.7	
	+	47	Quartile 1	0.13-0.24			0.21
		53	Quartile 2 β	0.24-0.35	3.7	1.0-13.0	
		48	Quartile 3 β	0.35-0.55	4.5	1.3-16.2	
		49	Quartile 4 β	0.56-1.9	3.0	0.78-11.4	

^a Adjusted for lipids, age, and obesity.