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Endometriosis among Women Exposed to Polybrominated Biphenyls

Caroline S. Hoffman, MSPH¹, Chanley M. Small, PhD², Heidi Michels Blanck, PhD³, Paige Tolbert, PhD^{2,4}, Carol Rubin, DVM, MPH⁵, and Michele Marcus, PhD^{2,4}

¹Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

²Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

³Division of Nutrition & Physical Activity, Centers for Disease Control and Prevention, Atlanta, GA, USA

⁴Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

⁵Health Studies Branch, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Purpose—We examined the association between endometriosis and exposure to polybrominated biphenyls (PBBs) and polychlorinated biphenyls (PCBs) among women inadvertently exposed to PBBs in 1973.

Methods—Serum PBB and PCB were measured in the late 1970s. Women self-reported endometriosis at interview in 1997. We constructed Cox models to estimate the relative incidence of endometriosis in relation to PBB and PCB levels.

Results—Seventy-nine of 943 women (9%) reported endometriosis. Compared to women with low PBB exposure (≤ 1 parts per billion [ppb]), women with moderate PBB (1–4 ppb) (hazard ratio [HR] = 0.72; 95% confidence interval [CI], 0.39–1.31) and high PBB (≥ 4 ppb) (HR = 0.90; 95% CI, 0.51–1.59) exposure did not have increased incidence of endometriosis. Increased incidence of endometriosis was suggested among women exposed to moderate PCB (5–8 ppb) (HR = 1.67; 95% CI, 0.91–3.10) and high PCB (≥ 8 ppb) (HR = 1.68; 95% CI, 0.95–2.98) levels compared to low PCB exposure (≤ 5 ppb).

Conclusions—Our study does not support an association between PBB exposure and endometriosis. Findings for serum PCB level are consistent with an emerging body of literature suggesting an association between PCB exposure and endometriosis.

Keywords

cohort; endometriosis; Michigan; polybrominated biphenyls; polychlorinated biphenyls

Corresponding Author: Michele Marcus, Ph.D., Department of Epidemiology, Emory University, 1518 Clifton Rd., Emory University, Atlanta GA 30322, Phone: 404-727-8010, Fax: 404-727-8737, mmarcus@sph.emory.edu.

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Introduction

Polybrominated biphenyls (PBBs) are synthetic chemicals used as flame-retardants. Production of PBBs ceased in the United States after a commercial mixture of PBBs was accidentally introduced into cattle feed in Michigan causing widespread contamination of livestock and human exposure (1). A registry of individuals exposed to PBBs through the incident was organized to assess potential health impacts (2).

PBBs belong to a structurally similar family of polyhalogenated aromatic hydrocarbon chemicals (PHAHs), including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs). PHAHs have been shown to cause endocrine disruption in humans and wildlife (3). Coplanar congeners of these chemicals can elicit biological effects by binding to the aryl hydrocarbon (Ah) receptor, altering the expression of cytochrome P-450 genes and genes involved in cellular growth and differentiation (4,5). Some congeners may act independently of the Ah receptor through disruption of estrogen activity (6).

Endometriosis, defined as the presence of functioning endometrial glands and stroma outside of the uterus (7), affects an estimated 10% of reproductive age women (8). Relatively little is known about the etiology of this disease. The most widely accepted theory of pathogenesis is retrograde menstruation (9), in which viable endometrial cells are transported through the oviducts into the peritoneal cavity where they proliferate and invade surrounding tissue. However, retrograde menstruation may occur in up to 90% of women (10). Additional factors, particularly endocrine and immune function, likely contribute to endometriosis pathogenesis (11).

Because PHAHs can disrupt endocrine and immune function in humans and animals, PHAH exposure may play a role in endometriosis pathogenesis (12). Several studies have found a positive association between endometriosis and dioxin or PCB exposure (13-18), although some of the effects reported are imprecise. One study did not find an association between PCB exposure and endometriosis (19). A recent study in Japan found a non-significant inverse association between total toxic equivalency quotient (TEQ), a measure of overall dioxin-like activity, and endometriosis (20).

The Michigan Female Health Study (21-23) is a follow-up investigation of female members of the Michigan PBB cohort. This analysis investigated the relationship between PBB exposure and endometriosis. The association between PCB exposure and endometriosis was also examined as Michigan residents are exposed to PCBs through diet (*e.g.*, fish consumption).

Materials and Methods

Study population

Actively participating female members of the Michigan PBB cohort who were 18 years of age or older by August 1, 1997 were eligible for participation in the Michigan Female Health study. Of the 1,530 eligible women, 88 (6%) could not be located, nine (0.6%) were deceased, and eight (0.5%) were too ill to participate. 1,185 (83%) women agreed to participate, of whom 1,046 had archived serum PBB measurements. For this analysis, we excluded 18 women with a serum PBB measurement taken after 1981, five women missing information on endometriosis diagnosis status or date of diagnosis, 13 women with incomplete information on menopause, 11 women who reported endometriosis diagnosis before the PBB incident (before July 1, 1973), 22 women over age 55 at the time of the incident and 34 women born after the incident (exposed *in utero*) (24). The final sample size was 943 women. The Institutional Review Boards at Emory

University, the Centers for Disease Control and Prevention, and the Michigan Department of Community Health approved the protocols. Participants gave informed consent.

Exposure assessment

PBBs and PCBs were measured in serum samples collected and analyzed at enrollment into the Michigan PBB cohort or during follow-up (1976-1981). The Michigan Public Health Laboratory measured serum PBB and PCB levels using gas chromatography with electron capture detection (25-27). Quantification of PBB was based upon 2,2',4,4',5,5'-hexabromobiphenyl, which constitutes approximately 61% of Firemaster FF-1® (28). The PBB detection method had a coefficient of variation of 7.1% to 14.0% and recovery ranges of 80% to 90% (depending on concentration) (25). PCB was quantified in serum samples as Aroclor 1254 by a dual determination method introduced in 1977, with a PCB coefficient of variation of 12% to 30% and recovery of 82% (29). Both methods of determination result in virtually identical PBB levels (30). Serum lipids were not measured.

Assessment of outcome and covariates

A telephone interview was conducted in 1997 to obtain information on reproductive health and other covariates of interest. Women were asked if a doctor or healthcare professional had ever told them they had endometriosis. Those women who responded "yes" ($n = 79$; 9%) were asked how old they were when first told they had endometriosis. Additional information was collected on demographics, smoking, reproductive history and healthcare access.

Verification of endometriosis

Consent for medical records release was requested from women who reported endometriosis. Of these women, nine (11%) refused release of their medical records, one (1.4%) later reported she did not seek medical advice for endometriosis, and 12 (15%) could not be contacted. Medical records were not obtained for 11 (19%) consenting women because their medical doctor could not be located or there was no record on file for the women. Medical records were obtained for 46 (58%) women. Thirty-seven (80% of medical records available) had an endometriosis diagnosis by laparoscopic examination noted in the medical record (Figure 1). Self-reported date of diagnosis was ± 2 years of the laparoscopic examination date for all but five women. Compared to women whose endometriosis was not confirmed, women with medical verification were slightly younger and had higher serum PBB levels.

Statistical analysis

We compared the distributions of PBB and PCB levels (mean, median, and standard deviation [SD]) by reported endometriosis status. Serum measurements below the limit of detection (LOD) were set to half the LOD (0.5 parts per billion [ppb] for PBB and 2.5 ppb for PCB) for calculations.

We examined unadjusted associations between endometriosis diagnosis and time-independent covariates using Kaplan-Meier survival curves and unadjusted Cox proportional hazard models. The proportional hazards assumption was assessed by inspection of log-log survival curves and statistical testing of covariate-time product terms ($\alpha = 0.10$). Extended Cox models were used to adjust for time-dependent covariates.

Self-reported endometriosis status was used in the main analysis. A sub-analysis limited to endometriosis cases verified by medical records also was conducted. We calculated time-to-event as the time from exposure in July 1, 1973 until endometriosis diagnosis or censoring. Person-time before a woman reached 13 years of age was excluded as women are not at risk of endometriosis until approximately age 13 years. Women who did not report endometriosis

diagnosis were censored at the time of follow-up interview or their 55th birthday, whichever came first. Endometriosis is primarily a disease of the reproductive years, but a small portion of cases (2% to 4%) occur post-menopause (7,8). Therefore, we chose an arbitrary age to censor women (55 years old) to exclude person-time when women were no longer at risk of diagnosis.

PBB exposure was based on a single serum measurement taken at enrollment (between 1976 and 1981) and categorized into three groups using the distribution of serum levels among endometriosis cases for Cox analyses: less than or equal to the LOD (≤ 1 ppb), above the LOD to the median value among cases with a serum level above the LOD (1–4 ppb), and ≥ 4 ppb. Similarly, PCB exposure was categorized into groups: ≤ 5 ppb (LOD), between 5–8 ppb (the median value among cases with a serum concentration above the LOD) and ≥ 8 ppb. PCB exposure was assigned using the earliest serum PCB measurement available (collected before or during 1981 for 98 percent of women).

We modeled the effects of PBB and PCB exposure controlling for other potential risk factors for endometriosis that may also be associated with PBB or PCB exposure but not believed to be on the causal pathway between exposure and disease. Body mass index (BMI; kg/m^2) was calculated using height and weight measurements collected at enrollment and categorized (< 25 , ≥ 25 to 30, and ≥ 30 kg/m^2). Menopausal status was included as a time-varying indicator variable that changed values if and when a woman reached menopause. Smoking was included as a categorized time-varying covariate (0, 1–15, and > 15 cigarettes per day). Other potential confounders included age at PBB exposure, education level, annual household income, age at menarche, health insurance status, and average number of annual visits to a healthcare professional reported at interview. Oral contraceptive use and hormone replacement therapy use were not included in Cox analysis because information was only available for ever/never use, and these medications may have been prescribed after endometriosis diagnosis. Race was not examined because all women were white.

Effect modification was assessed for exposure-covariate interactions that were biologically plausible from the literature, specifically interaction between PBB and PCB exposure and PBB and age at PBB exposure. Interaction terms were tested for statistical significance using a likelihood ratio (LR) test and retained in the model if the p -value was < 0.10 . The final adjusted model includes covariates that altered the hazard ratios (HR) for PBB or PCB by more than 10% when removed from the model. Analyses were performed using Stata version 9 (College Station, TX).

Results

The mean age at exposure was 22 years (SD = 14.4, median = 18.2) and mean age at interview was 45 years (SD = 14.4, median = 42). Mean serum PBB and PCB levels at enrollment were 17.1 ppb (SD = 99.8, median = 2 ppb, range: 0.5–1,745 ppb) and 6.3 ppb (SD = 5.5, median = 5, range: 2.5–34 ppb), respectively. Eight-nine percent of women reported visiting a health-care provider at least once per year and 92% reported having health insurance.

Seventy-nine women reported diagnosis of endometriosis by a physician during follow-up, with an overall incidence of 4.5 per 1,000 person-years. Fifty percent of affected women reported diagnosis between 25 and 38 years of age (median = 31.6, range: 17–53 years). The median serum PBB level was 2 ppb among both women who reported endometriosis (range: 0.5–22 ppb, 12 women with a PBB level $< \text{LOD}$) and those who did not report endometriosis (range: 0.5–1,745 ppb, 169 women with a PBB level $< \text{LOD}$). The median serum PCB level was 6 ppb (range: 2.5–28 ppb, 24 women with a PCB level $< \text{LOD}$) among women who reported endometriosis and 5 ppb (range: 2.5–78 ppb, 300 women with a PCB level $< \text{LOD}$) among women who did not report endometriosis.

Table 1 presents descriptive statistics by self-reported endometriosis status. Women who reported endometriosis were younger at exposure and had higher PCB levels than women who did not report endometriosis. Post-menopausal women had a significantly lower incidence of endometriosis diagnosis compared to pre-menopausal women.

Unadjusted Cox PH analysis indicated no association between PBB exposure and reported endometriosis diagnosis (Table 1). A higher incidence of endometriosis was found among women with serum PCB levels between 5 and 8 ppb and ≥ 8 ppb (although not statistically significant among the latter group) compared ≤ 5 ppb in unadjusted analysis. The HR estimate for serum PCB between 5 to 8 ppb was somewhat attenuated after adjusting for age at exposure, average household income, and PBB level (Table 2). None of the interaction terms were statistically significant. Similar odds ratio (OR) estimates for PBB and PCB were found when the data were analyzed using logistic regression (results not shown).

When analyses were limited to medically verified cases, a slightly elevated rate of reported endometriosis was found among women with serum PBB levels of 1–4 ppb (HR = 1.58; 95% CI, 0.65–3.83) or ≥ 4 ppb (HR = 1.57; 95% CI, 0.64–3.86) relative to ≤ 1 ppb. The association between serum PCB level and endometriosis was attenuated. The HR estimates for women with serum PCB levels between 5 to 8 ppb and ≥ 8 ppb compared to ≤ 5 ppb were 1.45 (95% CI, 0.62–3.86) and 1.23 (95% CI, 0.52–2.89), respectively. These estimates are unstable and confidence intervals include point estimates from the main analysis using self-reported endometriosis diagnosis.

Discussion

Our results do not support an association between PBB exposure and endometriosis. However, a statistically non-significant increase in self-reported endometriosis associated with PCB exposure was found after adjustment for several potential confounders. This latter finding is consistent with previous studies.

Taken together, epidemiological studies of dioxin and PCB exposure suggest an association with endometriosis, although some studies have not found the association to be statistically significant (13-20). The majority of these studies have been clinic or hospital-based and involve a select group of women seeking treatment for infertility, pelvic pain, or tubal ligation. One population-based cohort study found a non-significant increased risk of endometriosis among women with the high TCDD blood serum levels (relative risk ratio = 2.1) but not a dose response relationship (16).

A strength of our study is the population-based cohort design and access to past serum measurements. PBB exposure occurred at a single, well-defined period of time and serum samples were taken close to the time of exposure. Therefore, measurements in this study likely estimate a participant's peak exposure, which would systematically decrease over time. Nonetheless, it is unclear whether peak exposure or exposure during a specific time period (*e.g.*, a critical period of development) is more important. There also may be a latency period between PBB exposure and disease onset. We repeated our analyses allowing for a 7 and 10-year lag after the PBB exposure incident but found no appreciable differences in results.

Unlike PBB exposure, PCB exposure was most likely ongoing over the follow-up period. Consequently, a single PCB measure would only be representative of a participant's overall exposure if her exposure was reasonably constant over time. We calculated the correlation between multiple serum PCB samples that were available for a subset of participants, stratifying by time between measurements. These measures were moderately correlated ($0.47 < r < 0.73$) and showed no trend by time between measurements. While this finding suggests no systematic

change in PCB exposure over time, it also highlights potentially important variability in PCB serum levels over the follow-up period.

Individual PCB and PBB congener concentrations were not available to derive an estimate for overall “dioxin-like” effect of exposure (4). When we fit models using the sum of serum PBB and PCB concentrations as an estimate of overall exposure to PHAHs, the sum was not associated with endometriosis. An additional potential limitation of our study is the lack of information on serum lipid levels. However, recent work by Schisterman et al. (2005) suggests that failure to adjust for lipid levels is unlikely to bias the total estimated effect of exposure unless serum lipid levels are independently associated with the outcome of interest and serum PHAH and lipid levels have a common (uncontrolled) cause, or adipose PHAH levels (but not serum levels) are causally related to the outcome of interest (31). Both of these scenarios seem unlikely in the case of endometriosis.

Despite high participation (83%), our sample size was limited by the number of eligible women in the Michigan PBB cohort. In addition, results reported here reflect data collected during interviews in 1997. Some women may have subsequently developed endometriosis. The small number of self-reported endometriosis cases ($n = 79$) accrued over follow-up resulted in limited study power.

Our main analysis used self-reported cases of endometriosis because medical verification of endometriosis was available for less than 60% of reported cases. Our referent participants were not confirmed to be free of endometriosis and may have had undiagnosed disease. This is a limitation of our study. Although some women who reported endometriosis may have mistaken their diagnoses with another disease or their diagnoses may have been based solely upon symptoms, 80% of medical records obtained confirmed diagnosis based on laparoscopic examination. Given that all participants lived on or bought produce from a contaminated farm (2) and likely considered themselves exposed, differential reporting of endometriosis is unlikely.

We conducted a small probabilistic sensitivity analysis to quantify potential bias due to non-differential disease misclassification using methods developed by Lash and Fink (32,33). We assumed the specificity of self-reported endometriosis ranged from 0.9-1.0 (mode=0.95) and sensitivity ranged from 0.75-1.0 (modes=0.85, 0.95). Ninety-five percent simulated intervals (accounting for random and systematic error) for the risk ratio (RR) comparing moderate and high to low exposure categories were 0.08-1.45 and 0.19-1.82 for PBB and 0.88-22.6 and 0.82-17.34 for PCB, respectively. While these results follow the general trends found in our main analysis, the wide range of plausible RR values covered by simulation intervals explicitly illustrates that results of this study should be interpreted with caution.

Trends in endometriosis diagnosis over time were accounted for by conducting our survival analysis on the calendar year time scale and adjusting for age at PBB exposure. In addition, we excluded person-time before 13 years and after 55 years of age to account for changes in risk of endometriosis over a woman's lifetime. When we adjusted for age continuously, including a quadratic term, our findings were similar.

Previous studies of endometriosis have found the risk of endometriosis decreases with increasing parity, but it is not clear whether delayed childbearing is a risk factor for endometriosis or reduced parity is an early sign of endometriosis (34). Therefore, we did not include parity status in our main analysis. In a sensitivity analysis, we found parous women had decreased risk of endometriosis relative to nulliparous women (HR = 0.39; 95% CI, 0.20–0.75), but parity was not a confounder of the association between PBB or PCB exposure and endometriosis.

This is the first published study to examine the association between PBB exposure and endometriosis. We found no evidence of an association between PBB and endometriosis but found a statistically non-significant increased risk of endometriosis associated with PCB exposure. Our study has several strengths, including a cohort design, a high participation rate, and a sufficient length of follow-up for endometriosis to develop. Future studies should collect information on congener-specific levels of several PHAHs, as these chemicals may elicit different biological effects. In addition, a noninvasive method for detection of endometriosis is needed for population-based cohort studies such as this one, to help reduce the potential for disease misclassification.

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References

1. Fries GF. The PBB episode in Michigan: an overall appraisal. *Crit Rev in Toxicol* 1985;16(2):105–56. [PubMed: 3002722]
2. Landrigan PJ, Wilcox KR Jr, Silva J Jr, Humphrey HE, Kauffman C, Heath CW Jr. Cohort study of Michigan residents exposed to polybrominated biphenyls: epidemiologic and immunologic findings. *Ann N Y Acad Sci* 1979;320:284–94. [PubMed: 222186]
3. Tolbert, PE. Potential Endocrine Disruptors in the Workplace. In: Harris, RL., editor. *Patty's Industrial Hygiene*. 5. 1. Hoboken: John Wiley & Sons, Inc.; 2000. p. 447-477.
4. Safe S. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit Rev Toxicol* 1990;21(1):51–88. [PubMed: 2124811]
5. Sutter TR, Guzman K, Dold KM, Greenlee WF. Targets for dioxin: genes for plasminogen activator inhibitor-2 and interleukin-1 beta. *Science* 1991;254(5030):415–8. [PubMed: 1925598]
6. Safe SH. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *Crit Rev Toxicol* 1994;24(2):87–149. [PubMed: 8037844]
7. Olive DL, Schwartz LB. Endometriosis. *N Engl J Med* 1993;328(24):1759–69. [PubMed: 8110213]
8. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;24(2):235–58. [PubMed: 9163765]
9. Sampson JA. The development of the implantation theory for the origin of peritoneal endometriosis. *Am J Obstet Gynecol* 1940;40:549–57.
10. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 1984;64(2):151–4. [PubMed: 6234483]
11. Gazvani R, Templeton A. New considerations for the pathogenesis of endometriosis. *Int J Gynaecol Obstet* 2002;76(2):117–26. [PubMed: 11818105]
12. Rier S, Foster WG. Environmental dioxins and endometriosis. *Toxicol Sci* 2002;70(2):161–70. [PubMed: 12441361]
13. Gerhard I, Runnebaum B. The limits of hormone substitution in pollutant exposure and fertility disorders [in German]. *Zentralbl Gynakol* 1992;114(12):593–602. [PubMed: 1285483]
14. Mayani A, Barel S, Soback S, Almagor M. Dioxin concentrations in women with endometriosis. *Hum Reprod* 1997;12(2):373–5. [PubMed: 9070728]
15. Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertil Steril* 2005;84(2):305–12. [PubMed: 16084869]
16. Eskenazi B, Mocarelli P, Warner M, Samuels S, Vercellini P, Olive D, et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. *Environ Health Perspect* 2002;110(7):629–34. [PubMed: 12117638]

17. Louis GM, Weiner JM, Whitcomb BW, Sperrazza R, Schisterman EF, Lobbelt DT, et al. Environmental PCB exposure and risk of endometriosis. *Hum Reprod* 2005;20(1):279–85. [PubMed: 15513976]
18. Pauwels A, Schepens PJ, D'Hooghe T, Delbeke L, Dhont M, Brouwer A, et al. The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: a case-control study of infertile women. *Hum Reprod* 2001;16(10):2050–5. [PubMed: 11574490]
19. Lebel G, Dodin S, Ayotte P, Marcoux S, Ferron LA, Dewailly E. Organochlorine exposure and the risk of endometriosis. *Fertil Steril* 1998;69(2):221–8. [PubMed: 9496332]
20. Tsukino H, Hanaoka T, Sasaki H, Motoyama H, Hiroshima M, Tanaka T, et al. Associations between serum levels of selected organochlorine compounds and endometriosis in infertile Japanese women. *Environ Res* 2005;99(1):118–25. [PubMed: 15927178]
21. Kaiser R, Marcus M, Blanck HM, Naughton M, Zhang RH, Henderson AK, et al. Polybrominated Biphenyl Exposure and Benign Breast Disease in a Cohort of US Women. *Ann Epidemiol* 2003;13(1):16–23. [PubMed: 12547481]
22. Blanck HM, Marcus M, Hertzberg VS, Tolbert PE, Rubin C, Henderson AK, et al. Determinants of polybrominated biphenyl serum decay among women in the Michigan PBB cohort. *Environ Health Perspect* 2000;108(2):147–52. [PubMed: 10656855]
23. Thomas AR, Marcus M, Zhang RH, Blanck HM, Tolbert PE, Hertzberg V, et al. Breast-feeding among women exposed to polybrominated biphenyls in Michigan. *Environ Health Perspect* 2001;109(11):1133–7. [PubMed: 11712998]
24. Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, Hertzberg VS, et al. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology* 2000;11(6):641–7. [PubMed: 11055623]
25. Burse VW, Needham LL, Liddle JA, Bayse DD, Price HA. Interlaboratory comparison for results of analyses for polybrominated biphenyls in human serum. *J Anal Toxicol* 1980;4(1):22–6. [PubMed: 6098783]
26. Kuwahara SS, Calera F, Perry ES. Distribution of polybrominated biphenyls (PBB) among fractions derived from contaminated human plasma. *Transfusion* 1980;20(2):229–34. [PubMed: 6245485]
27. Needham LL, Burse VW, Price HA. Temperature-programmed gas chromatographic determination of polychlorinated and polybrominated biphenyls in serum. *J Assoc Off Anal Chem* 1981;64(5):1131–7. [PubMed: 6270054]
28. Hass JR, McConnell EE, Harvan DJ. Chemical and toxicologic evaluation of firemaster BP-6. *J Agric Food Chem* 1978;26(1):94–9. [PubMed: 202620]
29. Burse VW, Korver MP, Needham LL, Lapeza CR Jr, Boozer EL, Head SL, et al. Gas chromatographic determination of polychlorinated biphenyls (as Aroclor 1254) in serum: collaborative study. *J Assoc Off Anal Chem* 1989;72(4):649–59. [PubMed: 2547752]
30. Kreiss K, Roberts C, Humphrey HE. Serial PBB levels, PCB levels, and clinical chemistries in Michigan's PBB cohort. *Arch Environ Health* 1982;37(3):141–7. [PubMed: 6284069]
31. Schisterman EF, Whitcomb BW, Louis GM, Louis TA. Lipid adjustment in the analysis of environmental contaminants and human health risks. *Environ Health Perspect* 2005;113(7):853–7. [PubMed: 16002372]
32. Lash, TL.; Fink, AK. Boston University Sensitivity Analysis Tools. [Epidemiologic Methods Research webpage] [cited August 21, 2006]; Available from: http://www.bu.edu/dbin/sph/departments/epidemiology/epidemiologic_methods_research.php
33. Lash TL, Fink AK. Semi-automated sensitivity analysis to assess systematic errors in observational data. *Epidemiology* 2003;14(4):451–8. [PubMed: 12843771]
34. Holt, VL.; Jenkins, J. Endometriosis. In: Goldman, M.; Hatch, M., editors. *Women and Health*. San Diego, California: Academic Press; 2000. p. 226-39.

List of Abbreviations

BMI

body mass index

CI	confidence interval
kg	kilogram
HR	hazard ratio
MDCH	Michigan Department of Community Health
m²	meters-squared
LOD	limit of detection
OR	odds ratio
ppb	parts per billion
PBB	polybrominated biphenyls
PCB	polychlorinated biphenyl
PHAH	polyhalogenated aromatic hydrocarbon
TEQ	toxic equivalency quotient

Figure 1.

Flow chart of medical verification of reported endometriosis, Michigan Female Health Study. Participants were unintentionally exposed to PBBs in 1973 and interviewed in 1997. Consent for medical record release was requested from women who reported endometriosis diagnosis by a physician after July 1, 1973 ($n = 79$). Records were requested for 57 women and successfully obtained and reviewed for 46 women; 37 of the records reviewed had sufficient information to verify endometriosis diagnosis.

Table 1
Characteristics of participants stratified by endometriosis status, Michigan Female Health Study^a

Characteristic	Reported endometriosis, n (%) Yes n = 79	No n = 864	Person-years ^b	HR	95% CI
Age at exposure (years) ^c					
≤ 12	28 (35.4)	287 (33.2)	5,678	1	reference
13-24	32 (40.5)	237 (27.4)	6,174	1.07	0.64-1.79
≥ 25	19 (24.1)	340 (39.4)	5,616	0.73	0.41-1.31
Average household income					
< \$19,999	11 (15.1)	140 (17.7)	2,321	1	reference
\$20,000 to \$49,999	35 (47.9)	432 (54.5)	8,985	0.79	0.40-1.55
≥ \$50,000	27 (37.0)	220 (27.8)	4,904	1.11	0.55-2.23
Unknown	6	72			
Education level					
≤ High school graduate	30 (38.0)	408 (47.2)	7,860	1	reference
Some college	25 (31.6)	252 (29.2)	5,342	1.20	0.71-2.05
College graduate	24 (30.4)	204 (23.6)	4,267	1.46	0.85-2.50
BMI at enrollment (kg/m ²)					
< 25	37 (71.2)	363 (61.8)	7,971	1	reference
25-29.9	13 (25.0)	140 (23.9)	2,583	1.11	0.59-2.08
≥ 30	2 (3.8)	84 (14.3)	1,504	0.29	0.07-1.21
Missing	27	277			
Annual number of health-care provider visits					
< 1	2 (2.5)	112 (13.0)	2,316	1	reference
≥ 1	77 (97.5)	749 (87.0)	15,100	6.03	1.48-24.54
Missing	0	3			
Health insurance					
No	2 (2.5)	69 (8.0)	1,445	1	reference
Yes	77 (97.5)	794 (92.0)	16,014	3.56	0.87-14.48
Missing	0	1			
Smoking status (cigarettes/day) ^d					
None	51 (65.4)	597 (69.3)	13,771	1	reference
1-15	13 (16.7)	150 (17.4)	1,727	1.02	0.49-2.14
> 15	14 (17.9)	114 (13.2)	1,882	1.17	0.60-2.28
Missing	1	3			
Menopause status at interview ^e					
Pre-menopausal	47 (59.5)	508 (58.8)	14,934	1	reference
Post-menopausal	32 (40.5)	356 (41.2)	2,534	0.22	0.07-0.70
Age at menarche (year)					
< 12	16 (20.8)	172 (20.0)	3,552	1	reference
12 or 13	37 (48.1)	488 (56.6)	9,785	0.84	0.47-1.51
≥ 14	24 (31.2)	202 (23.4)	4,055	1.32	0.70-2.48
History of oral contraceptive use					
Never	72 (91.1)	629 (72.8)	—	—	—
Ever	7 (8.9)	235 (27.2)	—	—	—
History of hormone replacement therapy					
Never	32 (40.5)	246 (28.5)	—	—	—
Ever	47 (59.5)	618 (71.5)	—	—	—
Parity at interview ^e					
Nulliparous	18 (22.8)	126 (14.6)	7,014	1	reference
Parous	61 (77.2)	738 (85.4)	10,455	0.48	0.31-0.78
Serum PBB level at enrollment					
≤ 1 ppb	30 (38.0)	305 (35.3)	6,240	1	reference
(1-4) ppb	21 (26.6)	270 (31.3)	5,468	0.79	0.45-1.39
> 4 ppb	28 (35.4)	289 (33.4)	5,760	1.01	0.60-1.69

Characteristic	Reported endometriosis, <i>n</i> (%)		Person-years ^b	HR	95% CI
	Yes <i>n</i> = 79	No <i>n</i> = 864			
Serum PCB level at enrollment					
≤ 5 ppb	32 (43.2)	436 (54.3)	9,118	1	reference
(5–8) ppb	21 (28.4)	146 (18.2)	3,039	2.00	1.16–3.48
> 8 ppb	21 (28.4)	221 (27.5)	4,114	1.49	0.86–2.58
Missing	5	61			

Abbreviations: body mass index (BMI), 95% confidence interval (95% CI), hazard ratio (HR), kilogram (kg), meters-squared (m²), parts per billion (ppb), polybrominated biphenyls (PBB), polychlorinated biphenyls (PCB).

^aParticipants unintentionally exposed to PBBs in 1973 and interviewed in 1997.

^bTotal person-years contributed to covariate category; calculated by summing follow-up time (years) allocated to each covariate category over all participants.

^cAge on July 1, 1973.

^dFrequencies and proportions are calculated based on the average number of cigarettes smoked per day while actively smoking. Smoking was treated as a time-dependent variable in Cox model

^eTreated as a time-dependent variable in Cox model; person-years reported in table correspond to time-dependent coding of variable.

Table 2Adjusted Cox analysis of reported endometriosis, Michigan Female Health Study^a

Characteristic	HR ^b	95% CI
Serum PBB level at enrollment		
≤ 1 ppb	1	Reference
(1–4) ppb	0.72	0.39–1.31
> 4 ppb	0.90	0.51–1.59
Serum PCB level at enrollment		
≤ 5 ppb	1	Reference
(5–8) ppb	1.67	0.91–3.10
> 8 ppb	1.68	0.95–2.98
Age at exposure (years) ^c		
≤ 12	1	Reference
13–24	0.72	0.41–1.28
≥ 25	0.59	0.31–1.12
Average household income		
< \$19,999	1	Reference
\$20,000 to \$49,999	0.68	0.34–1.36
≥ \$50,000	0.96	0.47–1.99

Abbreviations: 95% confidence interval (95% CI), hazard ratio (HR), parts per billion (ppb), polybrominated biphenyls (PBB), polychlorinated biphenyls (PCB).

^aParticipants unintentionally exposed to PBBs in 1973 and interviewed in 1997.

^bHazard ratios (HR) adjusted for all other variables in model: age at exposure (age on July 1, 1973), average household income, menopausal status, serum PBB level at enrollment and serum PCB level at enrollment.

^cAge on July 1, 1973.

^dTreated as a time-dependent variable in Cox model.