Breast Adipose Tissue Concentrations of Polychlorinated Biphenyls and Other Organochlorines and Breast Cancer Risk[1]

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Abstract

Numerous studies have examined the relationship between organochlorines and breast cancer, but the results are not consistent. In most studies, organochlorines were measured in serum, but levels in breast adipose tissue are higher and represent cumulative internal exposure at the target site for breast cancer. Therefore, a hospital-based case-control study was conducted in Ontario, Canada to evaluate the association between breast cancer risk and breast adipose tissue concentrations of several organochlorines. Women scheduled for excision biopsy of the breast were enrolled and completed a questionnaire. The biopsy tissue of 217 cases and 213 benign controls frequency matched by study site and age in 5-year groups was analyzed for 14 polychlorinated biphenyl (PCB) congeners, total PCBs, and 10 other organochlorines, including p,p′-1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene. Multiple logistic regression was used to assess the magnitude of risk. While adjusting for age, menopausal status, and other factors, odds ratios (ORs) were above 1.0 for almost all organochlorines except five pesticide residues. The ORs were above two in the highest concentration categories of PCB congeners 105 and 118, and the ORs for these PCBs increased linearly across categories (*P*s for trend ≤0.01). Differences by menopausal status are noted especially for PCBs 105 and 118, with risks higher among premenopausal women, and for PCBs 170 and 180, with risks higher among postmenopausal women. Clear associations with breast cancer risk were demonstrated in this study for some PCBs measured in breast adipose tissue.

Introduction

Organochlorines, a class of 15,000 chlorine-containing organic chemicals, including DDT[3] and 209 PCB congeners, have been widely used in the past in industrial applications and as pesticides. Some are resistant to degradation and are very lipid soluble and therefore, have persisted in the environment and have biomagnified up the food chain to humans (1). The general population is exposed to organochlorines through many commonly eaten foods but also through water, ambient and indoor air, dust, and soil (2, 3). As a result, several organochlorines are now detectable in most human serum, adipose tissue, and breast milk.

Studies in animals have lead to a consensus that DDT, its metabolite DDE, and other related pesticides and chemicals are known animal and suspected human carcinogens (4, 5). PCBs have produced liver cancer in rats and are classified as probable human carcinogens (4, 6). Organochlorines have been studied with respect to breast cancer due to the potential to act as direct carcinogens or as indirect carcinogens by mimicking the action of estrogen, interfering with intercellular communication, inducing cytochrome p450 enzymes in humans, and disrupting immune function (7–10). Because known risk factors for breast cancer do not account for all cases, it is reasonable to investigate as potential risk factors chemicals that persist in the environment, accumulate in humans, and for which a plausible biological mechanism of action exists.

Nineteen epidemiological studies have been published examining breast cancer risk in relation to organochlorines (11–31). In some, compared with controls, women with breast cancer had higher levels of some chlorinated compounds, including total PCBs, some PCB congeners, DDE, and the pesticides, β-HCH, HCB, and dieldrin (11, 13, 20, 22–25, 28). In others, compared with controls, cases had lower concentrations or similar levels of DDE (11, 12, 14–16, 18, 19, 26, 27, 31), β-HCH (11, 29), and HCB (30). Some researchers also have found increased risks associated with some PCBs, DDE, and the pesticide, Mirex, in subgroups defined by estrogen receptor status of cases, lactation status, or CYP1A1 polymorphisms (17, 21, 32). Considered together, the relationship between the

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[3] The abbreviations used are: DDT, 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane; DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene; BBD, benign breast disease; BMI, body mass index; CI, confidence interval; GM, geometric mean; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; OR, odds ratio; PCB, polychlorinated biphenyl; HRT, hormone replacement therapy.

organochlorines investigated and breast cancer risk is not consistent (for review, see Refs. 33 and 34).

In most studies, organochlorines were measured in serum (11–20), whereas only small studies and one recent larger study have measured these chemicals in breast adipose tissue (21–26, 28–31). In humans, adipose tissue levels are 200-1000 times higher than levels in serum (35–38). Therefore, even small samples of adipose tissue have organochlorine compounds in the detectable range and are more suitable for congener-specific analyses (39). Congener-specific analyses are important because individual congeners have been shown to have different biological activity (40). Finally, organochlorines measured in breast adipose tissue provide a good measure of cumulative internal exposure at the target site for breast cancer, accounting for all routes and sources of exposure (41, 42). To evaluate the association between breast cancer risk and breast adipose tissue concentrations of several persistent organochlorines, a hospital-based case-control study was conducted in the province of Ontario, Canada between July 1995 and June 1997.

Materials and Methods

Subjects. Women under the age of 80 were enrolled by their surgeons at Women's College Hospital in Toronto and Kingston General Hospital in Kingston when they were being scheduled for excision biopsy of suspected breast cancer. Women were excluded if they had a previous diagnosis of any cancer except nonmelanoma skin cancer, had breast implants, were participating in a Tamoxifen trial, or were too ill. Of the 824 eligible women, 735 (89%) agreed to participate and signed informed consent. Following biopsy, pathology records were reviewed. Cases were subjects diagnosed with *in situ* or invasive breast cancer. Controls were subjects with biopsies negative for malignancy, but most were diagnosed with some form of BBD.

A questionnaire providing information about known and suspected risk factors for breast cancer was completed by 663 women (80.5% of those eligible) by telephone interview or by mail. Seventy-two women who had originally agreed to participate were unreachable after at least eight attempts made at different times of the day and different days, had phone numbers that were not in service and were not listed in the telephone directory, or found they were too anxious about their biopsy to complete the questionnaire. Because no information was obtained from these women, it is unknown if they were different from the women who completed a questionnaire except that more were from Toronto (90%), a large metropolitan area. Answers to the questionnaire were recorded by a trained interviewer (91%) or the questionnaires were received by mail (9%); most (60%) were received before the subject's biopsy date. The majority of questionnaires were received before participants knew their diagnosis.

The questionnaire included demographics, menopausal status, weight at age 25 and two years prior to interview, height, reproductive history variables, use of exogenous hormones, physical activity and diet variables, and family history of breast cancer. Subjects who reported that their menstrual periods had stopped permanently were classified as postmenopausal except those who had a hysterectomy in the absence of bilateral oophorectomy and were under the mean age of menopause of the subjects having a natural menopause (49 years); these six subjects were classified as premenopausal. Those who reported that a first or second degree relative had breast cancer were classified as having a family history of breast cancer. Ethnicity was coded to Statistics Canada groupings used for the census of the population (43), where British referred to those with British, Scottish, Irish, or Welsh ancestry and Canadian referred to those with native or aboriginal ancestry. The rest of the ethnic groups were collapsed together into one category.

The food frequency section of the questionnaire, which was used to record the consumption of 67 foods two years before the interview, was used to create indices of intake of nutrients and foods within the major groups. The food frequency questionnaire was based on that developed by Jain *et al.* (44) for a similar population (*i.e.,* Ontario women undergoing mammography), but it was modified to take into account foods, especially those high in animal fat, that contribute significantly to organochlorine exposure (2). A standard table of nutritive contents based on the Canadian Nutrient File was used to assign nutrient values to the food on the questionnaire (45).

Organochlorines were determined in all cases for whom enough tissue was available ($n = 217$) as well as in a subset of controls frequency matched by age in 5-year groups and study site ($n = 213$). Those with organochlorine concentrations analyzed differed from those without this analysis in a few respects. Among the cases, the 50 women without enough breast tissue to analyze were younger (by a mean of about 4 years), had a lower BMI, and a higher proportion were premenopausal and from Toronto. Among the controls, the 183 not analyzed for organochlorines were much younger than those analyzed because this group was frequency matched by age to cases. The controls not analyzed also had a lower BMI, and a lower proportion were from Toronto, were ever pregnant, were of British ethnicity, and had a negative family history of breast cancer.

Tissue Analysis. Approximately 0.2–1 g of benign tissue taken during the breast biopsy was frozen in a glass vial at −70°C. Samples, labeled only with identification numbers to conceal case-control status, were shipped to Le Center de Toxicologie du Québec on ice and kept at −20°C. Levels of 14 PCB congeners (International Union of Pure and Applied Chemists nos. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187) and total PCBs were determined. Total PCBs was calculated as the sum of PCBs 138 and 153 multiplied by 5.2 to approximate a level of the commercial PCB mixture, Aroclor 1260. This approximates the measurement of total PCBs using older analytic techniques. Levels of 10 organochlorinated pesticides were also determined (p,p′-DDT, p,p′-DDE, *cis*-nonachlor, *trans*-nonachlor, oxychlordane, HCB, Mirex, and β-HCH, α-chlordane, and γ-chlordane).

Samples were analyzed in batches of 5–10, each batch containing samples from both cases and controls randomly selected from the pool of subjects to be analyzed. Laboratory personnel were blind to case-control status. A polar extract of lipids was obtained. The sample was cleaned on Florosil columns, concentrated, and analyzed on a Hewlett Packard 5890 series II gas chromatograph with dual capillary columns and dual Ni-63 electron capture detectors. Peaks were identified by their relative retention times obtained from the two columns and quantified (46–48). The percentage of lipids in each sample was determined in a portion of the extracted samples, and the concentrations of the organochlorines were expressed in micrograms per kilogram of lipid. The instrument detection limits were set at three times the average SD of background and were, on a wet weight basis, 3 μg/kg for total PCBs, 0.6 μg/kg for p,p′-DDT and β-HCH, and 0.3 μg/kg for the rest of the organochlorines determined. The detection limits on a lipid basis depend on the sample weight and the percentage of lipids in the sample and therefore, vary by subject.

For each batch, two references were used. A nonextracted verification standard containing PCB congeners and organochlorines at concentrations of 10 μg/kg was run at the beginning of each batch to check the performance of the columns and the sensitivity of the detectors. An extracted verification standard was run to calculate the relative response factors. Le Centre de Toxicologie du Québec is accredited by the Canadian Association for Environmental Analytical Laboratories and participates in many quality assurance/quality control programs, including the Great Lakes Research Program's Quality Assurance/Quality Control Project of the Community Public Health Agency in Michigan and the Environment Canada's Arctic Environment Strategy's Quality Assurance/Quality Control Program.

Statistical Analyses. Because >30% of subjects had undetectable levels of PCBs 28, 52, 101, and 128, α-chlordane, and γ-chlordane, these organochlorines were not considered further. The distributions of organochlorines in adipose tissue were positively skewed and, therefore, were log-transformed to improve normality. The GMs and associated 95% CIs were calculated in cases and controls. Associations among organochlorines were investigated by calculating the Pearson correlation coefficient (r) on log-transformed organochlorine concentrations. Associations between age and the organochlorines were investigated by calculating the Spearman correlation coefficient (r_s).

Exposure to organochlorines was examined in four categories. To form a relatively extreme uppermost exposure category with an adequate number of subjects, the cutpoint for the upper category was at the 85th percentile. The first three categories were formed by dividing the distribution of controls with detectable levels into thirds below the 85th percentile (*i.e.*, cutpoints were at the 28th and 57th percentiles). Subjects with undetectable levels were included in the lowermost category if their detection limit of the organochlorine was below the 28th percentile. The remaining subjects with undetectable levels were excluded because their detection limits were above the cutpoint for the first category, and they could not be reliably placed in either the first or the second category. Eight subjects were excluded from the PCB 105 analysis, one from the PCB 183 analysis, three from the *cis*-nonachlor analysis, and three from the Mirex analysis.

To estimate breast cancer risk associated with exposure to each substance, unconditional logistic regression was used to calculate ORs and associated two-sided 95% CIs (49) using EGRET (Cytel Software, Cambridge, MA). All ORs were adjusted for age (continuous), site (Toronto/Kingston), and menopausal status (pre/post). Of the many covariates measured in the questionnaire, those that were included in a model built by a forward selection procedure and were associated with breast cancer risk at $P < 0.3$ were further tested as confounders. This model included the variables in Table 1 plus use of HRT (never/ever), age at menarche (<12/≥12 years), and duration of oral contraceptive use. To make an even more parsimonious confounder model for each organochlorine, these covariates were then modeled with the organochlorine exposure variable and kept in the confounder model if their deletion caused any organochlorine OR to change >10% from the model saturated with all of the additional covariates. The covariates that were confounders in the analyses of each organochlorine are shown in the "Appendix." Within the subset of 150 cases and 152 controls for whom digitized mammographic density was available, inclusion of this variable did not change ORs associated with the organochlorine variables and so was not included in confounder models.

Table 1 Characteristics of cases and controls with respect to covariates

Covariate	Mean (SD) or *n* (%)	
	Cases	Controls
Age (yr)	57.7 (11.6)[a]	53.9 (10.9)[a]
Site		
Toronto	102 (47.0%)	104 (48.8%)
Kingston	115 (53.0%)	109 (51.2%)
Menopausal status		
Premenopausal	74 (34.1%)	97 (45.5%)
Postmenopausal	143 (65.9%)	116 (54.5%)
Ever pregnant		
No	37 (17.1%)	33 (15.5%)
Yes	180 (82.9%)	180 (84.5%)
Lactation (mo)	5.8 (8.9)	6.0 (12.9)
Age last breast fed		
Never	98 (45.2%)	112 (52.6%)
<30 yr	54 (28.9%)	56 (26.3%)
≥30	65 (30.0%)	45 (21.1%)
Present use of hormone replacement therapy		
No	199 (91.7%)	174 (81.7%)
Yes	18 (8.3%)	39 (18.3%)
Ethnicity		
British	123 (56.9%)	113 (53.6%)
Canadian	24 (11.1%)	14 (6.6%)
Other	69 (31.9%)	84 (39.8%)
Family history		
No	129 (59.4%)	142 (66.7%)
Yes	88 (40.6%)	71 (33.3%)
BMI (kg/m^2)	25.2 (4.4)	25.2 (4.3)
Fat intake (g/day)	39.1 (16.0)	34.8 (19.0)
Alcohol intake (drinks/wk)		
<1	130 (60.5%)	107 (50.7%)
≥1	85 (39.5%)	104 (49.3%)
Present smoking		
No	182 (83.9%)	162 (76.1%)
Yes	35 (16.1%)	51 (23.9%)
Cumulative smoking (pack-yr)	11.3 (16.4)	10.0 (15.7)

[a] Mean age of premenopausal cases was 45.7 (5.5) and that of controls was 45.2 (5.3). Mean age of postmenopausal cases was 63.9 (8.5) and that of controls was 61.2 (8.8).

ORs were calculated for the whole sample and by menopausal status, the latter derived from one model with an interaction term between the organochlorine variable and menopausal status. ORs were calculated by menopausal status to improve comparability to other studies that have included only postmenopausal women (17, 27) and because it is hypothesized that premenopausal and postmenopausal breast cancer are distinct diseases and, therefore, risk factors may be related differently to each (50). To examine the modification of effects by other risk factors, interaction terms between organochlorine variables and the variables in the confounder models were examined. The hypothesis proposed by Moysich and colleagues (17), that breast cancer risk related to Mirex and some PCBs among postmenopausal parous women may differ by lactation, was also tested by including an interaction term between the organochlorine variable and lactation status (never/ever). To examine the effect of using only cases with invasive cancers and controls with nonproliferative BBD, ORs were also calculated among this subgroup while excluding cases with carcinoma *in situ* and controls with hyperplasia with or without atypia or papillomas.

Table 2 GMs of organochlorines with 95% CIs among those with detectable levels by case-control status

Organochlorine	GM (95% CI)	
	Cases	Controls
PCB 99 (μg/kg)	19.5 (17.9–21.2)	17.7 (16.2–19.3)
PCB 105 (μg/kg)	7.1 (6.4–7.8)	6.3 (5.7–7.0)
PCB 118 (μg/kg)	30.3 (27.7–33.2)	24.7 (22.4–27.3)
PCB 138 (μg/kg)	73.8 (68.9–79.1)	66.8 (62.1–71.9)
PCB 153 (μg/kg)	105.2 (98.5–112.3)	98.3 (91.8–105.3)
PCB 156 (μg/kg)	18.6 (17.5–19.9)	17.2 (16.0–18.5)
PCB 170 (μg/kg)	34.3 (32.1–36.6)	32.0 (29.7–34.4)
PCB 180 (μg/kg)	71.9 (67.5–76.5)	65.7 (61.5–70.2)
PCB 183 (μg/kg)	10.3 (9.6–11.1)	9.5 (8.8–10.2)
PCB 187 (μg/kg)	25.7 (23.9–27.7)	24.2 (22.6–26.0)
Aroclor 1260 (mg/kg)	0.94 (0.88–1.00)	0.87 (0.81–0.92)
p,p′-DDE (μg/kg)	693 (615–780)	596 (530–670)
p,p′-DDT (μg/kg)	22.0 (19.6–24.7)	19.3 (17.3–21.6)
cis-nonachlor (μg/kg)	6.0 (5.5–6.5)	6.0 (5.6–6.5)
trans-nonachlor (μg/kg)	40.4 (37.4–43.6)	41.1 (38.7–43.6)
oxychlordane (μg/kg)	30.4 (28.6–32.3)	30.5 (28.8–32.2)
HCB (μg/kg)	32.0 (29.3–34.8)	30.1 (27.8–32.5)
Mirex (μg/kg)	9.0 (8.1–10.0)	9.9 (8.8–11.2)
β-HCH (μg/kg)	43.1 (38.0–48.9)	41.5 (36.1–47.6)

Results

Table 1 provides summary descriptive information on study subjects with respect to covariates that were included in at least one confounder model. Cases are on average 4 years older than controls because not enough controls were in the older age groups to satisfy the frequency matching requirements. Related to this, a higher proportion of cases are postmenopausal. Fewer cases than controls presently use HRT, possibly because use of HRT increases the false-positive rate of mammography (51). More cases than controls have been pregnant, and although more have breast fed, cases breast fed for a shorter time, and more have last breast fed after 30 years of age. More cases are of British or Canadian ethnicity and have a family history of breast cancer in first or second degree relatives. Cases also have higher average dietary fat and BMI than controls, and more cases drink less than one alcoholic beverage per week and presently do not smoke.

The GMs of the organochlorine concentrations measured in breast adipose tissue are seen in Table 2. The more highly chlorinated PCBs, 138, 153, 156, 170, 180, 183, and 187, are very highly correlated with each other ($0.74 \leq r \leq 0.98$), but correlations with the less chlorinated PCBs, 99, 105, and 118, tend to be lower ($0.42 \leq r \leq 0.83$). Correlations between the PCBs and the organochlorinated pesticides, and among the organochlorinated pesticides, also tend to be lower ($0.03 \leq r \leq 0.80$). Cases have higher levels of almost all of the organochlorines measured, but organochlorines bioaccumulate and thus, their levels are associated with age ($0.10 \leq r_s \leq 0.48$; all Ps < 0.05). Therefore, all further analyses are controlled for age.

Risk estimates for the whole sample and by menopausal status for the association between breast cancer and PCBs adjusted for confounders are presented in Table 3, and those for the other organochlorines are presented in Table 4. The covariates that are confounders in the analyses of each organochlorine are shown in the "Appendix." For the whole sample, ORs are above 1.0 for almost all organochlorines except *cis*- and *trans*-nonachlor, oxychlordane, HCB, and β-HCH. Breast cancer risk is elevated most notably for PCBs 105 and 118, but risk is not elevated for most other substances. The magnitude of the risk is above two in the highest concentration categories of PCBs 105 and 118, and the ORs for these PCBs increase linearly across categories (Ps for trend ≤ 0.013). Differences by menopausal status are noted for many PCB congeners, with risks higher among postmenopausal women for PCBs 170 and 180 and higher among premenopausal women for PCBs 105 and 118. However, only the interaction term between menopausal status and PCB 170 is significant at the $\alpha = 0.05$ level.

Breast cancer risk associated with Mirex, but not other organochlorines, among postmenopausal parous women differs by lactation (P for interaction $= 0.050$; Table 5). Increases are clear among those who have never lactated, with the OR in the uppermost category above 4 (P for trend $= 0.08$). Risks among those who had lactated are reduced in the upper categories of Mirex.

Additional analyses investigating possible interactions between organochlorines and covariates in each of the confounder models indicate that estimated dietary fat and present HRT interact with some organochlorines. To explore this interaction with fat, intake was categorized by the median among controls (33.1 g/day). Differences in the association between organochlorines and breast cancer risk by dietary fat are not consistent across the organochlorines or across the levels of each organochlorine, but the ORs for PCBs 105 and 118 are higher among those with higher levels of fat intake (>33.1 g/day; data not shown).

Too few subjects presently use HRT to do a subgroup analysis. When present users are excluded, ORs are generally similar to those for the whole sample with some exceptions. ORs are increased in the upper categories for PCB 105 (third category: 2.6; 95% CI, 1.3–4.9; fourth category: 4.3; 95% CI, 1.9–9.8) and PCB 118 (third category: 2.1; 95% CI, 1.1–4.3; fourth category: 2.6; 95% CI, 1.2–5.8). The OR in the fourth category of p,p′-DDE is also increased (OR = 2.0; 95% CI, 1.0–4.2).

Dietary fat can be conceptualized as a confounder, independently related to the body burden of organochlorines and possibly to breast cancer risk. However, because dietary fat is a major source of persistent organochlorines, it could instead be hypothesized as part of the causal pathway between organochlorines and breast cancer. If so, it should not be included in confounder models. Reanalysis excluding fat from confounder models in which it had been included reveals no changes in ORs large enough to change conclusions from the results in Tables 3 and 4 (data not shown).

Results from additional analyses conducted to understand the effect of including only cases with invasive cancer and controls with nonproliferative BBD show that exclusion of the 27 carcinoma *in situ* cases consistently leads to very slightly reduced ORs compared to the whole sample. Excluding the 80 controls with proliferative BBD consistently results in slightly higher ORs for the uppermost category of chemical concentration and conclusions identical to those made for the whole sample. When excluding both *in situ* cases and proliferative BBD controls, most ORs increase slightly compared to those for the whole sample, and PCBs 105 and 118 remain associated with increased risk at the highest categories of concentration.

Discussion

This study demonstrates increased breast cancer risk associated with the breast adipose tissue concentrations of some specific PCB congeners, but inconsistent or null results for the other compounds that were measured. Among the total sample, PCBs 105 and 118 were associated consistently with breast cancer risk. Among premenopausal women, the risk estimates for PCBs 105 and 118 were even higher. Among postmenopausal women, risk estimates for PCBs 170 and 180 were elevated but

Table 3 Frequencies of breast cancer cases and controls by tissue concentration of PCBs and menopausal status and ORs with 95% CIs

Tissue concentration	Whole sample OR[a] (95% CI)	Premenopausal			Postmenopausal		
		n_{cases}	$n_{controls}$	OR[a] (95% CI)	n_{cases}	$n_{controls}$	OR[a] (95% CI)
PCB 99							
≤11 μg/kg	1.00	23	31	1.00	16	20	1.00
12–18	1.41 (0.77–2.60)	21	37	0.95 (0.42–2.16)	40	25	2.20 (0.87–5.52)
19–29	1.40 (0.75–2.62)	19	15		42	42	
≥30	1.92 (0.95–3.86)	9	11	1.63 (0.71–3.72)	43	27	1.70 (0.74–3.91)
PCB 105							
≤4.1 μg/kg	1.00	25	46	1.00	29	24	1.00
4.2–6.1	1.16 (0.62–2.14)	12	24	1.29 (0.52–3.20)	25	31	0.89 (0.38–2.06)
6.2–12	2.03 (1.12–3.68)	23	13		49	38	
≥13	3.17 (1.51–6.68)	7	6	3.91 (1.73–8.86)	37	21	1.49 (0.70–3.16)
PCB 118							
≤16 μg/kg	1.00	24	38	1.00	19	20	1.00
17–27	1.25 (0.68–2.29)	19	35	1.04 (0.46–2.35)	30	25	1.39 (0.57–3.41)
28–49	1.88 (1.00–3.55)	20	13		50	44	
≥50	2.31 (1.11–4.78)	8	7	2.85 (1.24–6.52)	41	25	1.58 (0.70–3.58)
PCB 138							
≤50 μg/kg	1.00	27	38	1.00	19	22	1.00
51–71	1.38 (0.79–2.42)	24	31	1.19 (0.56–2.54)	38	28	1.65 (0.71–3.83)
72–112	1.55 (0.86–2.80)	14	16		52	41	
≥113	1.56 (0.80–3.06)	8	10	1.52 (0.69–3.35)	32	23	1.69 (0.79–3.60)
PCB 153							
≤75 μg/kg	1.00	29	36	1.00	16	21	1.00
76–105	1.28 (0.71–2.30)	20	30	0.88 (0.40–1.93)	47	30	2.01 (0.84–4.79)
106–167	1.32 (0.72–2.40)	18	17		49	42	
≥168	1.04 (0.51–2.11)	6	12	1.06 (0.48–2.34)	29	21	1.61 (0.72–3.63)
PCB 156							
≤12 μg/kg	1.00	23	36	1.00	17	20	1.00
13–18	1.99 (1.12–3.53)	28	28	1.90 (0.87–4.13)	48	31	2.09 (0.90–4.86)
19–28	1.38 (0.76–2.49)	15	17		49	44	
≥29	1.35 (0.68–2.69)	7	14	1.35 (0.61–2.98)	27	19	1.41 (0.65–3.06)
PCB 170							
≤23 μg/kg	1.00	24	29	1.00	16	25	1.00
24–34	1.60 (0.92–2.78)	24	35	0.83 (0.39–1.78)	51	27	3.27 (1.44–7.44)
35–53	1.09 (0.61–1.96)	16	17		48	45	
≥54	1.15 (0.60–2.22)	9	15	0.89 (0.41–1.91)	28	19	1.63 (0.77–3.45)
PCB 180							
≤51 μg/kg	1.00	24	32	1.00	17	25	1.00
52–71	1.56 (0.90–2.70)	26	31	1.07 (0.51–2.27)	46	31	2.43 (1.09–5.43)
72–105	1.21 (0.68–2.14)	17	22		47	38	
≥106	1.27 (0.66–2.46)	6	11	0.89 (0.42–1.91)	33	22	1.77 (0.85–3.69)
PCB 183							
≤7.0 μg/kg	1.00	28	36	1.00	25	24	1.00
7.1–10	0.97 (0.55–1.71)	19	29	0.99 (0.44–2.22)	30	28	0.94 (0.42–2.10)
11–16	1.23 (0.71–2.14)	18	18		57	41	
≥17	1.27 (0.66–2.45)	8	11	1.37 (0.63–2.96)	29	21	1.16 (0.58–2.33)
PCB 187							
≤16 μg/kg	1.00	27	29	1.00	21	18	1.00
17–25	0.77 (0.44–1.36)	21	31	0.75 (0.35–1.64)	35	36	0.82 (0.36–1.85)
26–39	0.84 (0.48–1.48)	15	22		49	41	
≥40	1.26 (0.66–2.40)	11	14	0.86 (0.41–1.83)	37	20	1.08 (0.52–2.28)
Aroclor 1260							
≤0.67 mg/kg	1.00	31	38	1.00	19	21	1.00
0.68–0.92	1.13 (0.64–1.98)	19	29	0.86 (0.40–1.87)	42	31	1.52 (0.66–3.49)
0.93–1.4	1.41 (0.79–2.52)	18	17		48	37	
≥1.5	1.15 (0.58–2.25)	5	11	1.24 (0.58–2.66)	32	25	1.53 (0.71–3.30)

[a] Adjusted for age, study site, menopausal status, and confounders listed in the "Appendix."

did not follow a clear linear trend across categories. The only increased risk found for p,p′-DDE was among a subgroup excluding present HRT users. Among postmenopausal women who were parous but had never lactated, increased risk was apparent for Mirex.

Only a handful of studies can be directly compared with this study because they have used breast adipose tissue to quantify organochlorine levels (21–26, 28–31). Of the studies that examined the PCB congeners for which an association was found with breast cancer in this study, one found a higher risk for PCB 118 (23) and another found that PCB 118 was lower among estrogen receptor-negative cases compared with controls but no difference with PCB 105 (21). Also in agreement with this study, many have found a lack of a convincing

Table 4 Frequencies of breast cancer cases and controls by tissue concentrations of organochlorinated pesticides and menopausal status and ORs with 95% CIs

Tissue concentration	Whole sample OR[a] (95% CI)	Premenopausal			Postmenopausal		
		n_{cases}	$n_{controls}$	OR[a] (95% CI)	n_{cases}	$n_{controls}$	OR[a] (95% CI)
p,p′-DDE							
≤368 μg/kg	1.00	31	41	1.00	24	19	1.00
369–727	0.96 (0.55–1.68)	20	31	0.75 (0.34–1.62)	39	30	1.15 (0.50–2.63)
728–1389	0.92 (0.51–1.67)	10	17		44	42	
≥1390	1.62 (0.84–3.11)	13	8	1.52 (0.70–3.33)	36	25	1.05 (0.50–2.19)
p,p′-DDT							
≤12 μg/kg	1.00	26	31	1.00	32	27	1.00
13–20	0.82 (0.47–1.43)	19	36	0.54 (0.24–1.21)	37	26	1.20 (0.55–2.63)
21–37	0.93 (0.53–1.61)	20	18		40	41	
≥38	1.18 (0.61–2.29)	9	12	1.09 (0.49–2.40)	34	22	1.05 (0.53–2.06)
cis-nonachlor							
≤4.3 μg/kg	1.00	37	40	1.00	34	22	1.00
4.4–6.5	0.81 (0.47–1.39)	17	21	0.74 (0.33–1.70)	47	36	0.81 (0.39–1.68)
6.6–10	0.48 (0.27–0.86)	11	23		33	37	
≥11	0.80 (0.41–1.53)	8	11	0.67 (0.31–1.44)	29	21	0.54 (0.27–1.08)
trans-nonachlor							
≤31 μg/kg	1.00	33	38	1.00	25	18	1.00
32–43	0.93 (0.54–1.60)	24	33	0.93 (0.45–1.93)	39	31	0.93 (0.41–2.08)
44–64	0.69 (0.39–1.23)	13	18		46	41	
≥65	0.78 (0.40–1.53)	4	8	0.73 (0.33–1.63)	33	26	0.72 (0.34–1.49)
Oxychlordane							
≤24 μg/kg	1.00	38	40	1.00	23	16	1.00
25–32	0.68 (0.40–1.17)	16	33	0.46 (0.21–0.97)	44	29	1.00 (0.44–2.26)
33–46	0.61 (0.35–1.07)	16	16		44	46	
≥47	0.59 (0.31–1.16)	4	8	0.78 (0.37–1.67)	32	25	0.66 (0.31–1.40)
HCB							
≤21 μg/kg	1.00	31	42	1.00	24	16	1.00
22–31	0.97 (0.56–1.69)	27	32	1.27 (0.62–2.60)	31	29	0.62 (0.25–1.49)
32–51	0.75 (0.42–1.36)	9	18		52	43	
≥52	1.15 (0.57–2.34)	7	5	1.03 (0.45–2.37)	36	28	0.62 (0.28–1.40)
Mirex							
≤5.8 μg/kg	1.00	24	32	1.00	37	31	1.00
5.9–9.7	1.22 (0.71–2.09)	20	35	0.94 (0.42–2.10)	41	25	1.53 (0.73–3.20)
9.8–24	1.35 (0.79–2.30)	21	17		48	40	
≥25	1.18 (0.59–2.38)	8	12	1.72 (0.78–3.76)	17	19	1.13 (0.60–2.13)
β-HCH							
≤24 μg/kg	1.00	34	39	1.00	24	18	1.00
25–38	0.73 (0.42–1.29)	17	30	0.59 (0.27–1.30)	38	31	0.86 (0.37–1.99)
39–79	1.02 (0.57–1.83)	14	16		60	46	
≥80	0.69 (0.34–1.40)	9	12	1.01 (0.46–2.18)	21	21	0.89 (0.41–1.93)

[a] Adjusted for age, study site, menopausal status, and confounders listed in the "Appendix."

Table 5 ORs with 95% CIs for the association between tissue concentration of Mirex by lactation status among postmenopausal parous women

Mirex tissue concentration	All postmenopausal parous women OR[a] (95% CI)	Never lactators			Lactators		
		n_{cases}	$n_{controls}$	OR[a] (95% CI)	n_{cases}	$n_{controls}$	OR[a] (95% CI)
≤5.8 μg/kg	1.00	15	7	1.00	12	21	1.00
5.9–9.7	1.95 (0.86–4.44)	11	10	2.64 (0.65–10.8)	11	27	1.54 (0.53–4.45)
9.8–24	1.13 (0.54–2.39)	15	15	1.91 (0.53–6.88)	20	26	0.87 (0.33–2.31)
≥25	0.97 (0.37–2.50)	10	11	4.23 (1.01–17.8)	8	4	0.27 (0.06–1.15)

[a] Adjusted for age, study site, and confounders listed in the "Appendix" except age last breast fed.

association with total PCBs (21, 24–26), some PCB congeners (21, 23), DDE (22, 24–26, 31), and other organochlorinated pesticides, including HCB, β-HCH, and chlordane residues (21–25, 29, 30). However, some found that cases had higher levels than controls of some organochlorines, including total PCBs (22), DDE (21–23), or β-HCH (25). Adjustment for confounding in some of these studies was limited to only a few variables. One larger study using buttocks adipose tissue to measure DDE concentration in 265 cases and 341 controls found that DDE was associated with a reduced risk of breast cancer (27), a finding not replicated in this study.

The majority of studies investigating the association between organochlorines and breast cancer have used serum or plasma to quantify organochlorine levels and can be compared cautiously with this study. Many of these studies did not conduct congener-specific analyses due to limitations of using serum and older quantification techniques. Three of the studies with congener-specific analyses and with the congeners found

to be associated with breast cancer in this study either did not show the results but noted that no association existed (12, 13) or created indices based on the sum of PCBs in various classes based on the degree of chlorination (17). A fourth study, however, found no increased risk with either PCB 118 or PCB 138 (11). The difference by lactation status in the association between breast cancer risk and Mirex among parous postmenopausal women seen in this study was also found in one other study (17), but not a more recent study (12). Like this study, most other studies found no convincing association with total PCBs (11–15, 17), DDE (11–19), HCB (17), or β-HCH (11, 13). Only in one early nested case-control study measuring total PCBs and DDE were increased risks observed, but this study had a small sample size and did not adjust for serum lipids (20).

One of the main advantages of this study was that breast adipose tissue was chosen over serum in which to measure organochlorines. Because organochlorines theoretically will come to an equilibrium where the concentration is equal throughout the lipids in the body (52), most researchers have measured organochlorines in serum, and some have removed the variation introduced by fluctuating lipid levels in the blood either by using fasting samples or calculating concentrations on a lipid basis. However, more recent studies have shown that the ratio of adipose to serum levels is greater than one, even when adjusted for lipids (36, 53, 54). Not only do measurements made in serum or plasma not represent the concentration in adipose tissue on an absolute level, but they also do not represent concentrations closely on a relative level. Correlations between serum and adipose tissue concentrations in the general population are variable, with most reported correlation coefficients being above 0.8, but sometimes as low as 0.3–0.6, or even negative (36, 53–55). Therefore, measurements in adipose tissue may be more representative of exposure accumulated in breast tissue proximal to the epithelial cells, which give rise to breast tumors, and because this results in less misclassification, measurements in adipose tissue will be more powerful in an epidemiological study. Also, because adipose tissue is largely composed of lipid (>80%), concentrations on a wet weight basis will be much higher than in blood, which has much less lipid (<1%), and even small samples of adipose tissue will have organochlorine compounds in the detectable range and are more suitable for congener-specific analyses (39).

The use of breast adipose tissue in this study has necessitated the use of women who had a negative breast biopsy as controls. The use of this control group strengthened the design of this study by minimizing two important biases. First, cases and controls have come from the same hospital catchment areas and have undergone the same diagnostic tests. Therefore, the control group is drawn from the same population as the cases, and the absence of breast cancer in controls was histologically confirmed. Second, because subjects were enrolled before their biopsy, most of the questionnaire answers were received before the biopsy date and even more were completed before the participants' knowledge of their diagnosis. Therefore, differences in recall on the basis of case-control status were minimized. Because the main exposure, organochlorines, was measured as a biomarker, it cannot be subject to observation bias.

Women with biopsies negative for breast cancer generally have some form of BBD. Some exposures, including hormonal factors, are risk factors for both breast cancer and BBDs (56–58). If organochlorine exposure is positively related to both BBD and breast cancer, the risk estimates in this study would be underestimated. As well, some types of BBDs are thought to be part of the causal chain or risk factors for breast cancer (59) and could contaminate the control group by including subjects with precursor conditions. This was investigated by doing a sensitivity analysis excluding controls with diseases most strongly linked to breast cancer, and as expected, risk estimates associated with organochlorines were increased.

Differences between studies may be due to noncomparable levels of organochlorines in the subjects, although different measurement techniques, including use of different tissue compartments, analytical protocols and quantification techniques, especially of total PCBs, and inappropriate reporting of average levels (*i.e.*, using arithmetic means for positively skewed distributions) make the levels difficult to compare. However, the levels of organochlorines in this study can be compared generally to other studies using adipose tissue. The levels in this study are similar to another Canadian study (21), but DDT, DDE, and the higher PCB congeners seem to be in lower concentration in this study than studies conducted outside Canada (22–25, 27), and β-HCH and HCB seem to be at a higher concentration in this study than the one conducted in Connecticut (29, 30). Although the concentration of these organochlorines is low in this population, the compounds are detected in most of the subjects, and this study provides the opportunity to assess the association between organochlorines and breast cancer at a lower section of the dose-response curve.

Some older studies measured only DDE, DDT, and total PCBs. This study and several other recent studies have used high performance gas chromatography to quantify more organochlorinated pesticides and individual PCB congeners (13, 17, 21, 23, 24). Levels of individual organochlorines are correlated due to their common sources of exposure, particularly in the diet. This is especially true for the PCB congeners because they had been used as mixtures. However, the amounts and proportions of PCB congeners and other organochlorines do vary widely from individual to individual. Thus, the PCB congeners and other organochlorines were treated as separate entities in this study to help identify whether specific organochlorines are associated with breast cancer risk and to suggest groupings of organochlorines that may be relevant.

Examining each PCB congener and organochlorine individually leads to testing numerous associations, where even if true associations did not exist, some measured associations would appear significant by chance. However, the approach taken in the interpretation of this study was to look for patterns in the measured associations and consistency across the categories of compounds, not isolated occurrences of statistical significance. Of note in this study is that the PCBs found to be associated with breast cancer risk, PCBs 105, 118, and 156, are all mono-*ortho* substituted, a quality that makes them have some dioxin-like activity, but at a much lower level than dioxins or coplanar PCBs. However, because they are at higher concentrations than the dioxins or the PCB congeners that have greater dioxin-like activity, they, especially PCB 118, are the major contributors of dioxin-like activity in the body (60).

Even if environmental factors account for only a small percentage of breast cancer cases, given the tremendous number of women newly diagnosed each year, associations with some PCBs of the magnitude demonstrated in this study could translate into a large number of breast cancer cases if the association is truly causal. Further release of these compounds into the environment can be prevented with the careful disposal of existing stores and with public health education to prevent exposure through highly contaminated sources, such as fish in the Great Lakes. However, evidence for causality cannot be drawn on the basis of this study alone.

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Appendix

Table A1 Covariates included in the confounder models[a]

Organochlorine	Covariate										
	Ever pregnant	Lactation	Age last breast fed	Present use of HRT	Ethnicity	Family history	BMI	Fat intake	Alcohol intake	Present smoking	Cumulative smoking
PCB 99		•	•	•	•	•	•	•	•		
PCB 105	•	•	•	•	•	•	•	•	•		•
PCB 118				•	•	•	•	•	•	•	•
PCB 138				•	•	•		•	•		
PCB 153		•	•	•	•			•	•		
PCB 156				•	•	•		•			
PCB 170				•			•				
PCB 180				•			•				
PCB 183	•	•	•		•			•			
PCB 187				•	•						
Aroclor 1260				•	•	•		•	•		
p,p′-DDE				•	•		•	•			
p,p′-DDT			•		•		•	•	•		
cis-nonachlor			•		•			•			
trans-nonachlor					•			•			
oxychlordane									•		
HCB				•	•	•	•				
Mirex			•	•	•	•		•			
β-HCH				•	•	•	•	•	•		

[a] All confounder models included age, study site, and menopausal status plus the covariates indicated for each organochlorine in this table.

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