Adipose Concentrations of Organochlorine Compounds and Breast Cancer Recurrence in Long Island, New York

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Abstract

Several studies have measured the association between blood or adipose concentrations of organochlorinated compounds (OCs), such as pesticides and polychlorinated biphenyls (PCBs), and breast cancer. The estrogenic effects of OCs might adversely affect breast cancer recurrence. The participants were 224 women with nonmetastatic breast cancer enrolled in a New York-based case-control study. Supercritical fluid extraction followed by gas chromatography was conducted on adipose surgical specimens to determine OC concentrations. The mean follow-up time from surgery was 3.6 years. Thirty women (13.4%) were diagnosed with a recurrence. The concentration of pesticides and PCBs was correlated with baseline age and body mass index, but not with cancer stage. The highest tertile of total PCB concentration was associated with an increased risk of recurrence [relative risk (RR), 2.9; 95% confidence interval (CI), 1.02–8.2 *versus* the lowest tertile]. The risk for the highest tertile of the PCB congener Ballschmiter and Zell 118 was 4.0 (95% CI, 1.3–4.9). There was an increased risk for the middle level of the most abundant pesticide, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (RR, 2.3; 95% CI, 0.9–5.7), and for β-hexachlorocyclohexane, but not for their highest levels. Self-reported home termiticide exposure, alcohol consumption (≥1 drink/day), and race were not associated with prognosis. The RR for current cigarette smoking at diagnosis was 2.1 (95% CI, 0.9–5.1). In contrast to previous data showing no relationship between OC exposure and risk of breast cancer in these women, adipose PCB concentrations were associated with tumor recurrence. Pesticide levels were not related to recurrence.

Introduction

The IARC classifies organochlorinated compounds (OCs) as probable or possible human carcinogens (1). OC compounds include agricultural pesticides such as 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane and the industrial polychlorinated biphenyls (PCBs). Although domestic use was banned in the 1970s, OCs persist ubiquitously in the environment, wildlife, and human adipose tissue.

The estrogenic properties of OCs (2) are thought to increase the risk of breast cancer. Estrogens possibly promote the development of breast cancer by increasing cellular proliferation, and some studies found that women with high circulating blood estrogen levels or with a history of postmenopausal estrogen use had increased breast cancer rates (3). There have been several studies of OC concentrations in blood or adipose tissue and breast cancer risk. In general, positive associations were observed in earlier studies, whereas more recent investigations found no effects or increased risks only in study subgroups (4). Environmental exposures to OCs are also thought to affect the progression of breast cancer. High blood levels of 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (p,p′-DDE) were correlated with more extensive lymph node involvement in one report (5), and elevated blood concentrations of dieldrin but not other OCs were associated with increased breast cancer mortality in a Danish study (6). In the current investigation, we examined whether adipose OC concentrations were associated with the risk of breast cancer recurrence.

Materials and Methods

The women in this study were participants in our hospital-based case-control study of OC concentrations and breast cancer risk in Long Island, New York (7). The case-control study included 359 women who were newly diagnosed at Long Island Jewish Medical Center (New Hyde Park, NY) and North Shore University Hospital (Manhasset, NY) between 1994 and 1996. More than 95% of eligible patients participated. Trained study personnel interviewed the women before surgery using a structured questionnaire that contained items on known and suspected breast cancer risk factors. Three hundred and eight women (86%) agreed to provide breast adipose tissue samples, which were obtained at surgery and immediately frozen. Concentrations of pesticides and PCBs were determined for 232 randomly selected case women by supercritical fluid extraction and gas chromatography with electron capture (8). The pesticides included 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, 1,1-dichloro-2-(ortho-chlorophenyl)-2-(para-chlorophenyl)ethane, p,p′-DDE, trans-nonachlor, oxychlordane, β-hexachlorocyclohexane, and hexachlorobenzene. The PCB congeners included Ballschmiter and Zell (BZ) 74, BZ 99, BZ 118, BZ 138, BZ 146, BZ 153, BZ 156, BZ 167, BZ 170, BZ 172, BZ 178, BZ

180, BZ 183, and BZ 187. The limits of detection were reported previously and ranged from 0.069 (oxychlordane, t-nonachlor) to 0.723 ng/g [BZ 153 and BZ 180 (8)]. Nondetectable concentrations were coded as zero.

The women were followed for up to 5 years after surgery to determine their health status. Medical records were reviewed to determine the date of any subsequent recurrence, tumor stage, histology, hormone receptor status, hormone treatment, chemotherapy, radiation, and other postoperative care. The stage of cancer was determined using the American Joint Committee on Cancer criteria (9). Recurrence was defined as the development of a postoperative tumor in the same breast, regional spread of the primary tumor, or metastatic spread to vital organs. A subsequent primary cancer in the contralateral breast was not defined as a recurrence. The women were mailed a short survey to determine postdiagnosis changes in smoking habits, weight, and other factors. If a participant failed to return the questionnaire, additional requests were made by follow-up telephone calls and home visits. The data analysis was based on 224 women because 8 of the 232 women presented with advanced-stage disease at diagnosis. The follow-up questionnaire was completed by 185 (82.6%) women. Consequently, the sample size for some analyses was 185. All patients signed a consent form that was approved by the Institutional Review Boards of the Institute for Cancer Prevention and the participating medical centers.

Data analysis was conducted using SAS statistical software (Version 8.2; Cary, NC). Descriptive statistics were calculated including frequency tables and means and SDs. Spearman correlation coefficients were calculated to determine the associations between log OC concentrations and age, body mass index (BMI), and stage of disease at diagnosis. The association between weight at baseline and weight at the time of follow-up was determined by the Pearson correlation coefficient. Proportional hazard models were fit to estimate the relative risks (RRs) and corresponding 95% confidence intervals (CIs) of breast cancer recurrence in relation to log-transformed concentrations of OCs. Subjects were grouped into tertiles based on the distribution of log-transformed values (ln +1 to account for values of zero). *P*s were based on two-sided tests. Initial models included terms for the effects of known confounders including age and BMI [weight (kg)/height^2 (m)]. The independent and potential confounding effects of other risk factors at the time of diagnosis were also evaluated including cancer stage, education, smoking (current *versus* not current), and alcohol consumption (≥1 drink/day *versus* <1 drink/day).

Estrogen receptor (ER) assays are usually performed for women with invasive tumors. In the current study, ER assays were performed on 185 women (83%). Adjuvant hormonal therapy is routinely administered to women with ER+ tumors, except where contraindicated or if refused. However, it is also administered routinely as treatment for ductal carcinoma *in situ* and to younger women. The majority of women who are ER– are not treated with adjuvant estrogen therapy. Consequently, statistical adjustment was also made for adjuvant hormone therapy (treatment *versus* no treatment).

All terms were modeled as categorical variables except for BMI, which was treated as a continuous variable. Tests for trends were conducted by modeling OC concentrations as continuous variables. Departures from the proportional hazard model assumption were tested by inclusion of a time-dependent interaction term.

Results

Table 1 shows the age and tumor characteristics of the 224 women. Seventy-four subjects (33.0%) were <50 years old, 23 (10.3%) were black, and 3 (1.3%) were Asian. The most common histological type was ductal carcinoma (72.3%). About 65% of subjects had early-stage disease, and 35% had stage II or III disease. There were 30 (13.4%) recurrences during the follow-up period.

Table 2 shows the mean and SD of the OC concentrations by recurrence status, with nondetects treated as zero values. The pesticide residue and PCB congener with the highest mean concentration were p,p′-DDE and BZ 153, respectively. The mean total pesticide and PCB concentrations were both about 10% higher in blacks than in whites.

The Spearman correlation coefficients between age at diagnosis and total pesticide and PCB concentrations were both about 0.54 (Table 3). For BMI, the *r* was 0.35 for total pesticide concentrations and 0.14 for total PCB concentrations. Cancer stage was not correlated with OC levels. The Pearson correlation between BMI at the time of diagnosis and that reported on the follow-up questionnaire was 0.90. For subjects who experienced a recurrence, the *r* was 0.92 (*n* = 23).

The mean length of time between the date of surgery and the date of the follow-up (or date of recurrence) was 3.6 years. Proportional hazard model results are shown in Tables 4 and 5. After adjustment for age, stage, and other factors, the RR for the middle tertile of the most abundant pesticide, p,p′-DDE, was 2.5 (95% CI, 1.0–6.4; Table 4). The RR for the middle tertile of hexachlorobenzene was 3.0 (95% CI, 1.1–8.4). An increased risk was not found for the upper tertile of total pesticide concentrations. Trend tests for all pesticide measurements were not significant. Among PCB congeners, an increased risk was found for the upper tertile of BZ 118 relative to the lowest tertile (RR, 2.9; 95% CI, 1.0–8.5; Table 5). The risk for the upper tertile of total PCB levels was 2.9 (95% CI, 1.02–8.2). Nonsignificant increased risks of ≥2.0 were observed for the upper tertile of the PCB congeners BZ 138, BZ 153, BZ 167, BZ 183, and BZ 187 (Table 5). The trend tests did not reach the level of statistical significance, although the value for BZ 118 was <0.06.

Table 1 Age, race, tumor characteristics, and prognosis of 224 women diagnosed with nonmetastatic breast cancer in New York, 1994–1996

Characteristic	N (%)
Age (yrs)	
<50	74 (33.0)
50	150 (67.0)
Race	
White	198 (88.4)
Black	23 (10.3)
Asian	3 (1.3)
Histology	
Ductal	162 (72.3)
Lobular	29 (13.0)
Mixed	17 (7.6)
Tubular	7 (3.1)
Other	9 (4.0)
Stage	
0	31 (13.8)
1	114 (50.9)
2	69 (30.8)
3	10 (4.5)
3–5 yr prognosis	
No recurrence	194 (86.6)
Recurrence	30 (13.4)

There were no significant differences in individual or total mean pesticide levels by ER status [geometric mean for total pesticides: 645.5 ng/g (ER+ women) *versus* 560.6 ng/g (ER− women)], by progesterone receptor status, or by adjuvant hormonal treatment. Total mean PCB levels also did not vary significantly by ER status [311.5 ng/g (ER+ women) *versus* 272.2 ng/g (ER− women)], progesterone receptor status, or adjuvant hormone therapy. Of the 30 recurrences, only 9 women received tamoxifen or other hormone therapy, and consequently it was not possible to adequately measure the

Table 2 Mean concentrations (mean ± SD) of adipose pesticides and PCB[a] congeners by recurrence status[b]

	No recurrence (N = 194)	Recurrence (N = 30)
OC (ng/g)		
DDT	20.5 ± 33.7	17.5 ± 22.2
DDE	633.9 ± 643.2	507.7 ± 390.9
DDD	23.3 ± 25.6	19.5 ± 9.9
HCB	20.3 ± 11.3	20.7 ± 9.6
β-HCH	45.3 ± 243.1	226.3 ± 20.8
TNC	61.4 ± 43.4	68.9 ± 56.7
OXY	54.9 ± 36.9	62.3 ± 43.2
Total pesticides	859.6 ± 811.3	727.4 ± 488.4
Whites	817.8 ± 733.8	742.4 ± 457.4
Blacks	923.3 ± 589.4	720.7 ± 706.1
Asian	3924.9 ± 2969.2	402.6 (n = 1)
PCB congener		
74	35.5 ± 27.3	44.3 ± 48.1
99	23.7 ± 18.6	26.0 ± 23.4
118	41.3 ± 38.6	48.5 ± 38.4
138	36.4 ± 29.4	28.9 ± 39.8
146	11.3 ± 11.2	8.2 ± 11.8
153	89.2 ± 69.1	96.3 ± 69.1
156	14.2 ± 12.1	15.1 ± 15.2
167	2.5 ± 2.9	2.7 ± 2.6
170	15.5 ± 9.5	13.5 ± 9.0
172	3.9 ± 11.5	2.9 ± 3.6
178	5.1 ± 3.8	5.3 ± 5.6
180	53.4 ± 42.3	57.4 ± 61.9
183	8.5 ± 16.5	7.9 ± 6.1
187	21.0 ± 15.3	21.9 ± 21.7
Total PCB	361.3 ± 235.9	393.4 ± 279.3
Whites	353.9 ± 232.2	369.7 ± 201.1
Blacks	406.7 ± 256.0	529.7 ± 550.8
Asian	594.7 ± 369.2	280.9 (n = 1)

[a] PCB, polychlorinated biphenyl; OC, organochlorinated compound; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; DDE, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene; DDD, 1,1-dichloro-2-(ortho-chlorophenyl)-2-(para-chlorophenyl)ethane; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; TNC, trans-nonachlor; OXY, oxychlordane.
[b] Nondetects treated as zero.

Table 3 Spearman correlation between log total pesticide and PCB[a] concentrations and age, body mass index, and stage of disease

	Log pesticide (ng/g)	Log PCB (ng/g)
Age	0.55	0.54
P	<0.01	<0.01
Body mass index	0.35	0.14
P	<0.01	0.04
Stage	−0.04	−0.03
P	0.52	0.69

[a] PCB, polychlorinated biphenyl.

Table 4 RR[a] of breast cancer recurrence associated with adipose concentrations of organochlorine pesticides[b]

Pesticide log (ng/g)	N (recurrent, not recurrent)	RR	95% CI
HCB			
Lowest tertile	6, 68	1.0	Ref.
Middle tertile	13, 62	3.0	1.1–8.4
Highest tertile	11, 64	2.3	0.7–7.4
β-HCH			
Lowest tertile	6, 68	1.0	Ref.
Middle tertile	11, 64	1.7	0.6–5.1
Highest tertile	13, 62	2.7	0.9–8.3
OXC			
Lowest tertile	9, 65	1.0	Ref.
Middle tertile	10, 65	1.3	0.5–3.1
Highest tertile	11, 64	1.4	0.5–4.0
TNC			
Lowest tertile	8, 66	1.0	Ref.
Middle tertile	13, 62	2.0	0.7–5.3
Highest tertile	9, 66	2.1	0.7–6.8
DDE			
Lowest tertile	8, 66	1.0	Ref.
Middle tertile	16, 59	2.3	0.9–5.7
Highest tertile	6, 69	1.1	0.4–3.5
DDT			
Lowest tertile	9, 65	1.0	Ref.
Middle tertile	13, 62	1.2	0.5–2.9
Highest tertile	8, 67	1.1	0.4–3.0
DDD			
Lowest tertile	5, 69	1.0	Ref.
Middle tertile	15, 60	2.2	0.8–6.1
Highest tertile	10, 65	2.3	0.7–8.0
Total pesticides			
Lowest tertile	7, 67	1.0	Ref.
Middle tertile	17, 58	2.5	1.0–6.4
Highest tertile	6, 69	1.3	0.4–4.0

[a] RR, relative risk; CI, confidence interval; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; OXC, oxychlordane; TNC, trans-nonachlor; DDE, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; DDD, 1,1-dichloro-2-(ortho-chlorophenyl)-2-(para-chlorophenyl)ethane; Ref., referent.
[b] Adjusted for age, body mass index, education, stage of disease, tamoxifen treatment. Tests for trend were not significant.

independent effects of OCs on recurrence stratified by tamoxifen status.

Table 6 shows the risk of recurrence associated with other potential risk factors. Self-reported home termite treatment, either professionally or personally, was unrelated to breast cancer recurrence. There was no difference in risk between black and white/Asian women. Thirty-three women who were cigarette smokers at the time of diagnosis had a nonsignificant increase in risk of recurrence (RR, 2.1; 95% CI, 0.9–5.1). There was no dose-response effect with number of cigarettes smoked per day. In the follow-up survey, 10 of the women who smoked reported quitting after diagnosis, although the date of smoking cessation was not collected. Among women who continued to smoke, four reported a lower amount of smoking. The RR for alcohol consumption (≥1 drink/day) was 0.2 (95% CI, 0.03–1.8). Tamoxifen treatment was associated with a reduced risk of breast cancer recurrence (RR, 0.4; 95% CI, 0.2–0.8).

Discussion

In this study the levels of OCs in breast adipose tissue were not correlated with stage of breast cancer. The highest concentration of the most abundant pesticide p,p′-DDE, was not a sig-

Table 5 RR[a] of breast cancer recurrence associated with adipose concentrations of PCB[b]

PCB congener	N (recurrent, not recurrent)	RR	95% CI
BZ 74			
Lowest tertile	10, 64	1.0	Ref.
Middle tertile	8, 67	1.3	0.5–3.6
Highest tertile	12, 63	1.7	0.6–4.9
BZ 99			
Lowest tertile	9, 65	1.0	Ref.
Middle tertile	11, 64	1.1	0.4–2.7
Highest tertile	10, 65	1.7	0.6–4.4
BZ 118			
Lowest tertile	6, 68	1.0	Ref.
Middle tertile	11, 64	2.9	1.0–8.5
Highest tertile	13, 62	4.0	1.32–4.9
BZ 138			
Lowest tertile	9, 65	1.0	Ref.
Middle tertile	7, 68	1.1	0.4–3.2
Highest tertile	14, 61	2.3	0.8–6.2
BZ 146			
Lowest tertile	11, 63	1.0	Ref.
Middle tertile	9, 66	0.8	0.3–2.1
Highest tertile	10, 65	1.6	0.5–5.5
BZ 153			
Lowest tertile	10, 64	1.0	Ref.
Middle tertile	7, 68	0.7	0.2–1.9
Highest tertile	13, 62	2.6	1.0–7.1
BZ 156			
Lowest tertile	11, 63	1.0	Ref.
Middle tertile	7, 68	0.7	0.3–1.9
Highest tertile	12, 63	1.7	0.6–4.8
BZ 167			
Lowest tertile	8, 67	1.0	Ref.
Middle tertile	9, 65	1.3	0.5–3.7
Highest tertile	13, 62	3.1	1.0–9.3
BZ 170			
Lowest tertile	12, 62	1.0	Ref.
Middle tertile	8, 67	0.9	0.4–2.5
Highest tertile	10, 65	1.5	0.6–4.2
BZ 172			
Lowest tertile	13, 61	1.0	Ref.
Middle tertile	7, 68	0.8	0.3–2.2
Highest tertile	10, 65	1.1	0.5–2.9
BZ 178			
Lowest tertile	12, 62	1.0	Ref.
Middle tertile	10, 65	0.7	0.3–1.8
Highest tertile	8, 67	1.1	0.3–3.3
BZ 180			
Lowest tertile	11, 63	1.0	Ref.
Middle tertile	11, 64	1.1	0.4–2.9
Highest tertile	8, 67	1.3	0.4–3.8
BZ 183			
Lowest tertile	8, 67	1.0	Ref.
Middle tertile	10, 64	1.8	0.7–5.0
Highest tertile	12, 63	2.4	0.9–6.4
BZ 187			
Lowest tertile	10, 64	1.0	Ref.
Middle tertile	11, 64	0.9	0.4–2.4
Highest tertile	9, 66	2.3	0.7–7.1
Total PCB			
Lowest tertile	9, 65	1.0	Ref.
Middle tertile	8, 67	0.9	0.3–2.6
Highest tertile	13, 62	2.9	1.02–8.2

[a] RR, relative risk; PCB, polychlorinated biphenyl; CI, confidence interval; Ref., referent.
[b] Adjusted for age, body mass index, education, stage of disease, adjuvant tamoxifen therapy. Tests for trend were not significant.

nificant 3–5 year predictor of breast cancer recurrence. Intermediate levels of some pesticides were associated with an increased risk relative to the lowest levels, but the associations were clearly not dose dependent. In contrast, the risk of recurrence was significantly elevated for the highest total PCB concentrations and for BZ 118. Increased risks of ≥ 2.0 were also observed for the highest levels of several other PCB congeners, although a dose-dependent effect was not found.

There were relatively few events in this study, and the positive findings could have been due to bias. It was noted that patients with stage 3 or stage 4 disease were significantly more likely to experience a recurrence, providing some assurance that the study findings were consistent with well-documented clinical observations. Some data suggest that chemotherapy alters serum OC levels (10), but all samples were collected before chemotherapy treatment. There might have been confounding from changes in risk factor profiles after the diagnosis. For example, obesity adversely affects breast cancer survival. In our data, there was a very high correlation between weight at the time of surgery and at the time of follow-up. Unmeasured confounders might have affected the risk estimates. However, here too we did not observe substantial differences in risk estimates between models with varying numbers of independent variables. There are an insufficient number of studies to determine whether our results are consistent with the literature. In a Danish cohort of 195 breast cancer patients, the RR of subsequent mortality was unrelated to both blood pesticide and PCB concentrations but positively related to dieldrin levels (6).

Some data show or suggest a carcinogenic effect of specific PCB congeners. Several PCB congeners are tumor promoters in experimental systems, including BZ 118 and BZ 153, which enhance foci growth in rat liver (11, 12). Mixtures of TCDD, BZ 118, BZ 153, and other PCB congeners cause liver enlargement and increased activity of hepatic CYP1A1/2 and CYP2B1/2 in rats (13). BZ 153, BZ 180, and BZ 138 were reported to interfere with sexual hormone-regulated processes in 17β-estradiol induced MCF-7 cells, and this was interpreted as evidence of endocrine disruptive potential (14). BZ 153 has been shown to alter the secretion of estradiol, progesterone, and testosterone in porcine ovarian cells (15) and luteal cells (16). BZ 153 also exhibited estrogenic properties similar to those of estradiol with respect to increasing serum thyroxine and reducing follicle-stimulating hormone isoforms in male rats com-

Table 6 RR[a] of breast cancer recurrence associated with baseline risk factors: reported home pesticide treatment, smoking, alcohol consumption, and tamoxifen therapy[b]

Characteristic	No. exposed	RR	95% CI
Reference group		1.0	
Professional home termite control	89	0.9	0.4–1.9
Reference group		1.0	
Personal home termite control	167	0.9	0.3–2.1
Reference group		1.0	
Black race	23	1.4	0.5–3.9
Reference group		1.0	
Current cigarette smoker	33	2.1	0.9–5.1
Reference group		1.0	
Alcohol (GE 1 drink/day)	22	0.3	0.04–2.3
Reference group		1.0	
Tamoxifen treatment	115	0.4	0.2–0.8

[a] RR, relative risk; CI, confidence interval.
[b] Adjusted for age and body mass index.

pared to controls (17). However, BZ 138, BZ 153, and BZ 180 did not form DNA adducts or provide evidence of oxidative stress-induced damage (18). The authors of the Danish survival study suggested that some OCs might increase the aggressiveness of the tumor or affect the growth of malignant cells that remain after treatment. Some data indicate that higher levels of PCBs are associated with estrogen-negative tumors, which have a faster rate of progression. However, the literature in this area is ambiguous and based on cancer stage (19), and our data set was too small to examine the risk separately by receptor status. Nonestrogenic mechanisms by which PCBs might increase tumor aggressiveness include the induction of cytochrome P450 1A1 (CYP1A1) gene. An increased risk for breast cancer was reported for women with the highest blood levels of PCBs who also possessed CYP1A1 variants (20, 21).

Our finding that smoking affects recurrence suggests that smoking cessation might be an important means to reduce further morbidity from breast cancer. Alcohol consumption was not a factor as has been reported elsewhere (22), although some data suggest that recurrence risk increases with weekly or more frequent consumption (23).

In summary, these results suggest that relatively high PCBs concentrations were related to increased rate of breast cancer recurrence, although this contrasts with our previous data showing no effect of OCs on breast cancer risk in these women. Like the many case-control studies of organochlorine exposure and breast cancer risk, more studies are needed to confirm or refute these results.

Acknowledgments

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