Breast Cancer Risk in Relation to Adipose Concentrations of Organochlorine Pesticides and Polychlorinated Biphenyls in Long Island, New York[1]

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Abstract

To assess a possible etiological role of organochlorine compounds in breast cancer development on Long Island, a high-risk region of New York State, concentrations of organochlorine pesticides and polychlorinated biphenyls (PCBs) were measured in the adipose tissue of 232 women with breast cancer and 323 hospital controls admitted to surgery for benign breast disease or non-breast-related conditions. Seven pesticide residues and 14 PCB congeners were assayed via a supercritical fluid extraction method followed by gas chromatography with electron capture detection. After adjustment for age and body mass index, which were strongly correlated with organochlorine levels, adipose concentrations of 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene, total pesticides, and total polychlorinated biphenyls (PCBs) did not differ significantly between cases and controls. The relative abundance of individual pesticide species and PCB congeners was similar in cases and controls. Odds ratios adjusted for age, BMI, hospital, and race gave no evidence of a dose-response for 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene, total pesticides, or total PCBs, whether stratified by estrogen receptor status or not. Breast cancer risk among Long Island residents was not elevated compared with residents of the adjacent New York City borough of Queens. We did not confirm a previously reported association between breast cancer risk and levels of PCB congener 118 (2,3′,4,4′,5-pentachlorobiphenyl), nor did we observe an association with the most abundant congener 153 (2,2′,4,4′,5,5′-hexachlorobiphenyl), a strong inducer of phase I enzymes that was reported recently to have estrogenic properties. Only PCB congener 183 (2,2′,3,4,4′,5′,6-heptachlorobiphenyl), which is also an inducer, was significantly associated with risk, with an adjusted odds ratio of 2.0 (95% confidence interval, 1.2–3.4) in women with adipose levels >5.67 ng/g; the biological importance of this observation is unclear without confirmation in additional studies. Although neither the present nor other studies have provided convincing evidence of an association between body burden of 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane and PCBs with cancer of the breast, these compounds are rated as "possible" and "probable" human carcinogens, respectively, by the International Agency for Research on Cancer. Investigations of associations with cancer at other sites should be carried out.

Introduction

Breast cancer is the most common type of cancer diagnosed in women nationally (1), as well as in New York State (2). The many established risk factors do not fully explain its incidence or geographic variation (3, 4). Wide intra- and international variation, as well as changes in rates in successive generations of migrants, suggest that lifestyle and environmental factors affect breast cancer risk (5).

Until the early 1990s, few epidemiological studies of potential environmental risk factors for breast cancer had been carried out. Since then, a great many studies have been reported, with a special emphasis on exposure to "environmental estrogens," so-called because they include chemicals or groups of environmentally persistent chemicals that also exhibit estrogenic activity in model systems (6, 7). These include the broad class of OCCs[3] used as pesticides, such as *p,p′*-DDT and its breakdown products, and the more narrowly defined group of PCBs.

Associations between breast cancer risk and either serum or adipose levels of *p,p′*-DDT or related compounds as well as PCBs have been reported in a number of case-control and cohort studies beginning in 1976. Significant associations between *p,p′*-DDE and/or PCB levels and breast cancer risk have been reported in at least five studies ranging from a very small study in Brazil (8) and a pilot study in Connecticut (9), to larger studies in Quebec (10, 11), New York City (12), and a study in

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[3] The abbreviations used are: OCC, organochlorinated compound; OCP, organochlorinated pesticide; *p,p′*-DDE, 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene; *o,p′*-DDD, 1,1-dichloro-2-(*ortho*-chlorophenyl)-2-(*para*-chlorophenyl)ethane; *p,p′*-DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; BMI, body mass index; BZ, Ballschmiter and Zell; HCB, hexachlorobenzene; β-HCH, β-hexachlorocyclohexane; PCB, polychlorinated biphenyl; OR, odds ratio; CI, confidence interval; LOD, limits of detection; PB, phenobarbital; ER, estrogen receptor.

Upstate New York in which the association was confined to a subgroup of parous women who had not breastfed (13). A nested case-control study by Krieger *et al.* (14) showed no overall elevation in risk, although Savitz (15) suggested a positive interpretation for *p,p′*-DDE based among separate strata of whites and blacks. Most later reports, however, have shown little or no association between exposure to OCCs and breast cancer risk, whether assessed using adipose tissue (16–19) or serum or plasma (20–23). In an otherwise negative study, Demers *et al.* (11) reported a dose-related risk of breast cancer and organochlorine exposure for cancers only for tumors >2 cm in size with lymph node involvement. A summary of study findings published through 1999 was published recently by Helzlsouer *et al.* (21).

There has been particular interest and concern among residents of the Northeastern United States, where breast cancer rates are high. Public concern has been especially strong in New York State's two easternmost counties, Nassau and Suffolk, generally referred to as Long Island (excluding coterminous parts of New York City). Excluding New York City, Nassau and Suffolk ranked first and second, respectively, among New York State counties in the average numbers of new cases of breast cancer diagnosed per year in 1991–1995, with a combined total of 1961 annual cases (2). In the same period, Nassau County's incidence rate ranked second and Suffolk's was tenth among the 62 counties of New York State. Kulldorf *et al.* (24) have shown that an unusually high rate of breast cancer on Long Island qualifies it as one of four clusters in the Northeastern region of the United States. Intense concern among local residents led to Federal legislation under which the National Cancer Institute initiated a group of epidemiological studies known as the Long Island Breast Cancer Study Project, one of whose goals is to examine the possible etiological role of environmental factors among Long Island residents (25, 26). Other risk factors targeted by the legislation were contaminated drinking water, sources of indoor and ambient air pollution, including emissions from aircraft, electromagnetic fields, pesticides and other toxic chemicals, and hazardous and municipal waste.

The present study was carried out in response to the section of the legislative mandate which targets "pesticides and other toxic chemicals" by examining the association of breast cancer risk diagnosed in Long Island women with their body burden of OCCs.

Materials and Methods

Study Participants. A hospital-based case-control study was conducted from October 1994 through October 1996 in the two largest hospitals serving the Long Island population: Long Island Jewish Medical Center (New Hyde Park, NY) and North Shore University Hospital (Manhasset, NY). Both hospitals serve sections of New York City (primarily in the borough and county of Queens) as well as Nassau and Suffolk Counties. No restrictions were placed upon residence of study participants. Patients scheduled for breast biopsies and/or surgery were identified through frequent contacts with breast physicians affiliated at both hospitals and by consulting the lists of patients scheduled for presurgical testing. Cases were women newly diagnosed with malignant breast cancer or carcinoma *in situ*. Controls included patients diagnosed with benign breast diseases and women undergoing non-breast-related surgery in which small amounts of adipose tissue would ordinarily be removed.

All patients signed consent forms that were approved by the Institutional Review Boards of the American Health Foundation and the two hospitals. Patients were met at the presurgical testing units of both hospitals by trained interviewers who administered structured face-to-face interviews about medical history, reproductive and other breast cancer risk factors, diet, smoking, and family history. More than 95% of eligible patients approached by interviewers agreed to participate. Patients were asked to provide a blood sample (usually taken as an "extra" tube during the preadmission blood drawing) and also for permission for us to obtain ~0.5 g of adipose tissue from a subsequent surgical procedure. Diagnoses and classification into case or control groups were based upon review of pathological reports subsequent to the surgical procedures. Thus, in most instances the patients, interviewers, physicians, and the investigators were unaware of the definitive case or control status of the patient until after the questionnaire data and biological samples had been obtained.

A total of 1030 patients (359 cases and 671 controls) were interviewed and contributed either adipose tissue, serum, or both. Adipose tissue samples were obtained from 86% and serum from 94% of all women enrolled in the study. Adipose tissue analyses were completed for 232 cases (199 invasive and 33 carcinoma *in situ*) and 323 controls (250 benign breast and 73 surgical patients); the remaining samples have been stored frozen for future studies. The present analysis is based upon body burden of OCCs using adipose tissue for these 555 subjects. The 73 surgical control women were admitted for procedures involving the gallbladder ($n = 33$), removal of lipomas ($n = 8$), abdominal hernias ($n = 7$), osteoarthritis ($n = 4$), and other disorders unrelated to the breast. The mean levels of DDE, total pesticides, and total PCBs did not differ significantly between controls with benign breast disease and controls with other conditions. Samples were received in separate batches from the two hospitals and analyzed in the order received, with analytical batches alternating between the hospitals. The women whose adipose tissues were analyzed did not differ significantly from the remainder of study subjects with respect to age, menopausal status, education, religion, or family history of breast cancer. In other words, selection from the sample pool did not appear to be biased with respect to important breast cancer risk factors.

Laboratory Methods. Levels of OCP/PCB in adipose tissue were determined using an analytical procedure developed in our laboratory for this study (27). The method is based on supercritical fluid extraction and simultaneous *in situ* removal of the bulk of fat on a partially deactivated neutral alumina sorbent, additional clean-up of supercritical fluid extracts by adsorption column chromatography also on a partially deactivated neutral alumina sorbent to remove the remaining traces of fat, and analysis by capillary gas chromatography with electron capture detection. We previously used this procedure to describe OCP/PCB partitioning between serum and adipose tissue (28).

The assay consists of extraction of a small amount of tissue (0.1–0.3 g) to which γ-chlordane has been added as an internal standard, with supercritical CO_2. The extraction with CO_2 is carried out twice (both in static and dynamic modes). To assure the quantitative recovery of all OCPs/PCBs, including the more polar compounds, an additional extraction step with CO_2 modified with 5% dichloromethane is carried out in both static and dynamic modes as before. Removal of residual traces of lipids from OCP/PCB extracts by adsorption column chromatography is an essential part of the assay because they interfere with gas chromatography-electron capture detection analysis. The 10 g of alumina (activity II–III) in the column

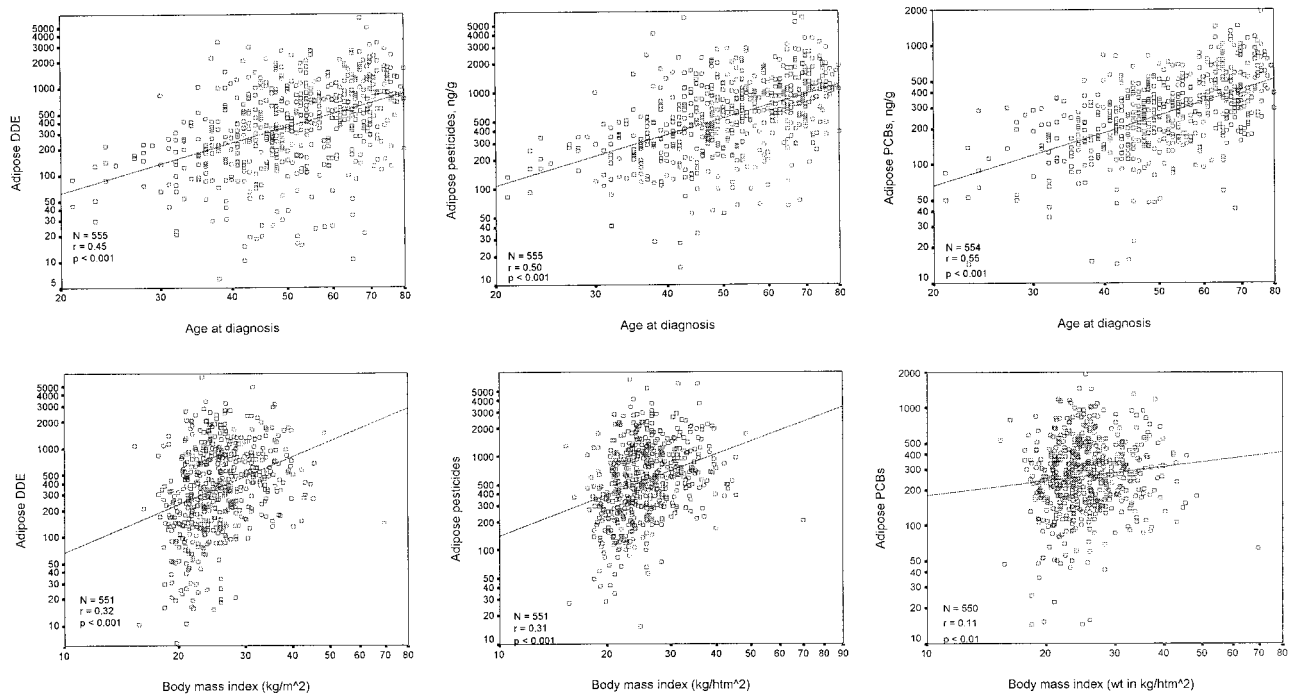

Fig. 1. Scatter plots (log-log scale) of *p,p′*-DDE, total OCPs, and total PCBs *versus* age at diagnosis (*upper panel*) and BMI (*lower panel*) for 555 cases and controls. The regression line is also shown.

provides enough surface to retain all of the lipids, whereas the choice and amount of solvents enable complete elution of all analytes. Aldrin is added to each sample prior to gas chromatographic analysis. We have not observed any background in the areas of elution of γ-chlordane and Aldrin, justifying the usage of these two compounds as a recovery and gas chromatography standard, respectively. Only assays with recoveries of γ-chlordane that exceeded 90% are reported. Our methodology was validated against samples of Certified Reference Material 430 (CRM 430; pork fat containing known concentrations of OCPs) purchased from the European Community Bureau of Reference, Brussels, Belgium. Recoveries of the OCPs ranged from 92.3% for DDE to 115% for HCB, and coefficients of variation ranged between 2.0% (β-HCH) and 6.3% (HCB; Ref. 27). Coefficients of variation for the targeted PCB congeners ranged between 4.2% (BZ 187) and 8.4% (BZ 180), based on a series of five assay replicates using CRM 430 to which known quantities of specific congeners were added. Operational quality control procedures also included daily calibration of instrumentation with a complete mixture of OCC pesticides and the PCB congeners of interest, using Aldrin as an internal standard. We have previously reported our LOD (28), which are based upon the IUPAC and American Chemical Society definition as the smallest concentration that is statistically different from an analytical blank (29).The LOD were 0.231 ng/g for both *p,p′*-DDE and β-HCH, 0.116 ng/g for HCB, and 0.723 ng/g BZ 153 and ranged between 0.07–0.72 ng/g for all other OCCs.

Statistical Analysis. Analytes were considered individually or summed into related groups. Seven OCPs or their products were measured: *p,p′*-DDE, *p,p′*-DDT, and *o,p′*-DDD (*p,p′*-DDE is the major breakdown product of *p,p′*-DDT), oxychlordane and *trans*-nonachlor (products of chlordane), β-HCH, and HCB. Fourteen PCB congeners were measured individually [the IUPAC nomenclature suggested by Ballschmiter and Zell (30) is used]: BZ 74, 99, 118, 138, 146,153, 156, 167, 170, 172, 178, 180, 183, and 187. Total PCBs in this report means the sum of the concentrations of these 14 species. Proportions of women with detectable levels of individual analytes (*i.e.*, levels above the instrumental LOD) were compared between cases and controls via χ^2 with Yates correction.

The $\log_{10}$ of the concentrations of *p,p′*-DDE, total pesticides, and total PCBs exhibited near-normality. Therefore, means of log-transformed adipose concentrations of the target analytes were compared between cases and controls using analysis of covariance, with age at diagnosis and BMI as continuous covariates. Associations among continuous variables were assessed with Spearman correlation coefficients, which are based upon rank orders and therefore provide comparable results with both untransformed and transformed variables. Fig. 1 shows that these concentrations were correlated with both age at diagnosis and BMI (weight/height^2 in kg/m^2). ORs for breast cancer risk were computed via unconditional logistic regression, with adjustment for age at diagnosis and BMI, as well as hospital and race. Exposure variables were grouped by tertiles of their respective distributions among controls. The *P*s for trends in the ORs were obtained by entering an indicator variable with values 0, 1, and 2, representing the tertiles as an ordinal variable in the logistic models.

Results

Characteristics of the 232 cases and 323 controls are shown in Table 1. The controls were younger than cases, reflecting the younger average age at diagnosis for benign breast diseases compared with breast cancer. This led to a greater proportion of cases (59%) being postmenopausal compared with controls

Table 1 Characteristics of cases and controls in the Long Island Study population

	Cases (n = 232)		Controls (n = 323)		P
	n	%	n	%	
Age					
<50	79	34	178	55	
50–59	55	24	66	20	
60–69	54	23	48	15	
70–82	44	19	31	10	<0.001
Education					
≤ High school	90	39	112	35	
≤ College graduate	90	39	135	42	
Postgraduate	52	22	76	24	0.61
Race					
White	205	88	286	89	
Non-white	27	12	37	11	0.95
Residence					
New York City	98	42	129	40	
Nassau	99	43	147	46	
Suffolk	29	13	39	12	
Other	6	3	8	2	0.93
Religion					
Protestant	27	12	34	11	
Catholic	89	38	158	49	
Jewish	97	42	113	35	
Other/none/refused	19	8	18	6	0.09
First-degree family history of breast cancer					
No	191	83	285	89	
Yes	40	17	37	11	0.05
BMI					
≤23.03	67	29	119	37	
23.04–27.01	78	34	105	33	
≥27.02	83	36	99	31	0.16
Menopausal status					
Premenopausal	94	41	181	56	
Postmenopausal	136	59	140	44	<0.001
Age at menopause					
≤49	28	21	52	37	
50	42	31	41	29	
≥51	64	48	46	33	<0.01
Age at first live birth, parous women					
<23	54	26	86	34	
23–26	73	35	84	33	
≥27	84	40	84	33	0.13

(44%) and underscores the necessity for age-adjustment of risk estimates. Controls as a group were similar to cases in education, race, BMI, age at first live birth, and county of residence, with 57% of cases and controls residing in Long Island and all but 2% of the remainder living in New York City. Associations between breast cancer and its well-known risk factors did not differ significantly between Long Island and New York City residents. A significantly greater proportion of cases reported a history of breast cancer in a first-degree relative (17% *versus* 11%; $P = 0.05$) as expected. Late age at menopause was strongly associated with increased breast cancer risk, with an adjusted OR of 2.31 (95% CI, 1.2–4.3) for women who experienced menopause after age 50 relative to those who underwent menopause before age 50.

Measured levels of *p,p′*-DDE were above LOD for all women. Levels of all analytes were above detection limits in >95% of all cases and controls, except for β-HCH (above LOD in 94.1% of controls), *p,p′*-DDT (93.2%), and four of the PCB congeners: BZ 167, 172, 178, and 183, all of which were detected in at least 69% of subjects. For all pesticides except β-HCH, and for the majority of PCB congeners, there were no significant differences between cases and controls in the percentage detected. However, β-HCH exceeded LOD in a significantly higher proportion of cases than controls (98.3% *versus* 94.1%; $P < 0.05$) and for three PCB congeners: BZ 167 (85.7% *versus* 75.5%; $P < 0.001$), BZ 172 (73.2% *versus* 69.3%; $P < 0.001$), and BZ 183 (97.0% *versus* 91.6%; $P < 0.05$).

Table 2 shows the median, 25th, and 75th percentiles of the adipose concentrations of all 21 OCCs and the percentage that each analyte makes on average relative to total pesticides or to total PCBs. *p,p′*-DDE comprised 73.3% of total pesticides in cases and 75.5% in controls. The difference (2.2%) was the largest observed for any of the 21 analytes; the majority of pesticides differed in abundance between cases and controls by <1%. Unadjusted concentration parameters were generally higher for cases than for controls because of the greater average age of cases and the strong correlation between age and OCC levels (Fig. 1). After adjustment for age at diagnosis and BMI, cases and controls did not differ significantly in $\log_{10}$ mean levels of total pesticides or PCBs (*P*s shown in Table 2). Residue levels of the seven individual pesticides and 14 PCB congeners did not differ significantly between cases and controls except for *p,p′*-DDT (geometric mean, 13.6 *versus* 13.4 ng/g; $P = 0.04$) and for 2 of the 14 PCB congeners: BZ 74 (27.6 *versus* 26.8 ng/g; $P < 0.01$) and BZ 183 (5.9 *versus* 4.3 ng/g; $P = 0.02$).

Associations between *p,p′*-DDE, total pesticides, and total PCBs and other risk factors are shown as Spearman correlation coefficients in Table 3. Organochlorine body burden was significantly correlated with age and number of full-term pregnancies. All analytes were negatively correlated with education and age at first full-term pregnancy. BMI was correlated with pesticide levels but not with total PCBs. Adipose measures of body burden were not correlated with either age at menarche or age at menopause. Concentrations of PCBs (but not pesticides) were negatively associated with months of lactation, *i.e.*, women who had lactated for longer periods of time had lower levels.

Associations between breast cancer risk and body burden of *p,p′*-DDE, total pesticides, and total PCBs are shown in Table 4 as adjusted ORs. Adipose OCC levels were represented by tertiles of concentration among controls. The magnitude of the largest OR was 1.27 (95% CI, 0.80–2.02) for the middle tertile of total pesticides. There were no significant ORs or trends. Findings were unchanged when controls were restricted to the 250 women with benign breast disease. Table 5 shows ORs stratified by ER level classified as ER+ and ER−. The OR for the second tertile of total OCPs among ER− women increased to 2.36 (95% CI, 1.14–4.88), but the OR for ER− women in the highest tertile was 0.93 (95% CI, 0.37–2.33), and the trend was not significant. In additional analyses (not shown), there were no significant interaction terms between menopausal status and body burden of exposure to OCCs. Findings were unchanged when restricted to parous women who did not breast feed (data not shown).

Adjusted ORs were also computed for the six pesticide residues besides *p,p′*-DDE and 14 PCB congeners, with each species categorized as low (reference), medium, or high on the basis of its distribution among controls. As was the case with *p,p′*-DDE, none of the six other pesticide species was associated with a significantly increased risk of breast cancer at any concentration above the reference level. For 12 of the 14 measured PCB congeners, there were no significantly elevated risks among women with either medium or high adipose levels. Among women with a medium level of BZ 156 (5.87–13.59

Table 2 Median, 25th, and 75th percentiles of concentrations (ng/g) of individual pesticide residues and PCB congeners in adipose tissue and the percentage each makes of total concentration

	Cases (n = 232)			% of total OCPs	Controls (n = 323)			% of total OCPs	P^a
	25%	50%	75%		25%	50%	75%		
Pesticide residue									
HCB	12.4	17.8	26.0	2.4	10.6	16.3	21.8	2.5	0.5
β-HCH	10.2	19.8	39.4	5.1	8.7	15.8	29.2	4.4	0.4
OXC[b]	28.4	46.4	71.7	6.6	23.8	38.9	64.8	6.2	0.06
TNC	32.0	51.0	81.6	7.3	25.2	39.6	63.8	6.6	0.9
p,p′-DDE	204.9	419.2	803.8	73.3	161.6	374.1	837.5	75.5	0.2
o,p′-DDD	8.3	16.4	27.6	2.8	7.8	13.3	22.0	2.4	0.9
p,p′-DDT	7.5	12.3	21.4	2.5	6.3	12.1	21.9	2.5	0.04
Total OCPs	359.2	628.6	1080.1	100.0	271.8	546.9	1094.5	100.0	0.1
BZ number									
74	15.8	29.6	46.2	9.9	15.1	26.7	45.6	11.1	<0.01
99	11.3	19.3	31.3	6.7	8.2	13.9	25.1	6.5	0.2
118	15.9	30.4	53.9	11.5	13.1	24.0	42.0	11.2	0.9
138	16.0	28.7	47.0	9.9	12.4	21.7	36.1	8.9	0.08
146	5.0	9.2	14.7	3.1	4.2	6.9	11.6	3.0	0.8
153	47.2	76.1	112.4	24.4	39.2	63.1	99.4	24.2	0.6
156	7.0	11.2	17.6	3.9	4.8	9.1	15.6	4.1	0.8
167	0.8	1.7	3.2	0.8	0.2	1.3	2.4	0.8	0.7
170	8.4	13.5	19.5	4.1	6.5	11.2	17.5	4.3	0.8
172	0.0	2.4	4.1	1.4	0.0	1.6	3.7	1.2	0.7
178	2.3	3.9	6.8	1.4	1.5	3.0	5.3	1.5	0.9
180	24.4	42.4	67.2	14.8	19.2	33.7	61.8	15.8	0.9
183	3.4	5.8	9.0	2.3	2.4	4.0	6.7	1.8	0.02
187	10.0	16.2	26.5	5.7	7.5	12.8	21.5	5.5	0.5
Total PCBs	184.9	294.7	458.1	100.0	156.5	257.1	382.4	100.0	0.9

[a] P for comparison of logarithms of case-control means, adjusted for age and BMI.
[b] OXC, oxychlordane; TNC, *trans*-nonachlor.

Table 3 Spearman correlations between breast cancer risk factors and adipose levels of DDE, total OCPs, and total PCBs among 323 controls, Long Island, New York, 1994–1996

Risk factor	n	DDE (ng/g)	Total OCP[a] (ng/g)	Total PCB[a] (ng/g)
Reference age (yr)	323	0.465[b]	0.508[b]	0.524[b]
Education (yr)	323	−0.246[b]	−0.258[b]	−0.180[b]
BMI	323	0.354[b]	0.351[b]	0.105
Age at menarche (yr)	323	0.002	0.013	0.025
No. of full-term pregnancies	323	0.247[b]	0.260[b]	0.198[b]
Age at first full-term pregnancy (yr)[c]	255	−0.209[b]	−0.230[b]	−0.215[b]
Breastfed (mo)[c]	255	−0.097	−0.095	−0.175[b]
Age at menopause (yr)[d]	140	0.085	0.089	0.162

[a] OCP, sum of seven organochlorine pesticide species; PCB, sum of 14 congeners; see text for details.
[b] $P < 0.01$.
[c] Parous women only.
[d] Postmenopausal women only.

ng/g), the OR relative to the reference level (<5.87 ng/g) was 1.9 (95% CI, 1.1–3.0) but fell to 1.5 (95% CI, 0.9–2.5) at the highest body burden (13.60 ng/g), which was not significant. A significant dose-related increase in risk was observed for the heptachlorinated species BZ 183. Relative to women with adipose levels of 3.15 ng/g or less, the OR for levels in the range 3.16–5.66 ng/g was 1.3 (95% CI, 0.8–2.1), and for BZ 183 concentrations of 5.67 ng/g and above, it was 2.0 (95% CI, 1.2–3.4).

Because cases and controls were drawn both from Long Island and neighboring New York City, it was of interest to test whether OCC levels in control patients differed between the two regions. Among controls, the mean adipose levels of *p,p′*-DDE, total pesticides, and PCBs did not differ significantly between residents of Long Island and adjacent Queens County. Levels of two individual analytes, β-HCH and BZ 167, did differ significantly ($P < 0.05$), with the mean level of β-HCH higher among Queens residents than among Long Island residents. There were no significant residence effects for *p,p′*-DDE, total pesticides, or total PCBs. When analyses were restricted to Long Island residents, there were no significant effects attributable to county of residence (*i.e.*, Nassau *versus* Suffolk) for any analyte; however, only 29 cases and 39 controls were Suffolk County residents, so that these tests had limited power to detect intercounty differences in body burden.

Discussion

The present analysis for the Long Island population is consistent with numerous studies in other populations that have shown little association between OCC body burden and breast cancer risk. Strengths of the study include a large number of cases and

Table 4 ORs for breast cancer in Long Island, New York, 1994–1996, in relation to adipose DDE, total OCPs, and total PCBs

Concentration in adipose tissue (ng/g)	Cases (n = 232)	Controls (n = 323)	Adjusted OR[a]	95% CI
DDE				
≤212.92	60	108	1.00	
212.93–618.81	86	108	1.14	0.71–1.81
>618.81	86	107	0.74	0.44–1.25
P-trend			0.3	
OCP[b]				
≤340.13	54	108	1.00	
340.14–878.14	98	108	1.29	0.80–2.08
>878.14	80	107	0.66	0.38–1.17
P-trend			0.1	
PCB[b]				
≤181.81	55	108	1.00	
181.82–332.24	74	108	1.06	0.67–1.69
>332.24	103	107	1.01	0.60–1.69
P-trend			0.9	

[a] Adjusted for age and BMI (continuous), hospital (two hospitals, indicator), race (white *versus* non-white, indicator).
[b] OCP, sum of seven organochlorine pesticide species; PCB, sum of 14 congeners; see text for details.

controls, a low refusal rate for both cases and controls, and collection of all biological samples prior to treatment. The latter point is important because of concern that cancer treatment may affect subsequently measured levels of OCCs (31). Although the two interviewers could not be completely blinded to the suspected diagnoses, all interviews were conducted prior to biopsy or other surgery so that diagnostic confirmation was always made subsequent to the interview.

The control group consisted of 250 patients with benign breast disease and 73 admitted for other surgical procedures not related to conditions of the breast or other gynecological conditions, primarily gallbladder and hernia operations. The ORs calculated using only benign breast or only surgical controls did not differ materially from the ORs using the combined control group. Miller has argued that choosing as controls women with benign breast conditions, apart from the availability of breast adipose tissue, has the advantage that the women in this group have entered the study via a selection mechanism that is nearly identical to that of the cases (32). The drawback is that some forms of benign breast disease (*e.g.*, those with a high proportion of atypia) may themselves be risk factors for breast cancer. If these types are caused by OCCs, the result would be to overmatch controls to cases on exposure. However, review of pathological reports for the controls with benign breast disease showed that fewer than 4% of women with benign breast disease diagnoses had any mention of atypia, so this is not considered a serious concern in this control group. In addition, Zheng *et al.* (18) reported comparable levels for both *p,p′*-DDE and *p,p′*-DDT in adipose tissue of 91 women diagnosed with breast cancer compared with levels in 95 women with proliferative benign breast disease.

Interviewers attempted to frequency-match control patients on age. However, the age distribution of women with benign breast disease was somewhat younger than that of women with breast cancer, so that the goal of frequency matching could not be completely achieved. Therefore, age adjustment was an essential component of all risk calculations. The strong positive correlations of adipose organochlorine levels with age most likely reflects the fact that the older members of the study population have lived a greater proportion of their lives during the era before *p,p′*-DDT and PCBs were banned from commercial use in the United States.

A serious weakness of this study, as with all case-control and prospective studies in which measurement of body burden is made at a single time, is that such a measurement may at best be regarded as a cross-sectional surrogate for a continuum of exposures that may have been experienced earlier in life. Over one's lifetime, body burden may increase because of continued exposure. The higher levels of OCCs measured in older women very likely reflect lengthier exposures that began prior to bans on manufacturing and/or usage, when environmental levels were much higher than at present. On the other hand, in the absence of continued exposure, body stores may be reduced over time as the compounds in question are metabolized and their products excreted, as well as by lactation (33). Our measurements provide no information about metabolic processes that may have been activated by past exposures. Nearly all epidemiological investigations published to date, including prospective studies, share these weaknesses. An additional weakness that has been pointed out in an Institute of Medicine report on health effects of the phenoxy herbicide Agent Orange may be termed the problem of false negatives. A low observed level of a metabolizable OCC may reflect either absence of exposure or the end stage of a higher level that has decayed over time (34). Case-control studies are more strongly affected by this source of false-negative measurements than are prospective studies, but in either type of study measurements made at a single time are inadequate to discriminate between these possibilities.

It was possible to test for an association between breast cancer risk and county of residence because both hospitals serve sections of New York City as well as the two Long Island counties. We found no important differences in OCC-related risk levels between Long Island and the adjacent county of Queens, whose breast cancer incidence ranks in the lower half of New York State counties (2).

The pattern of relative abundance of the individual analytes that belong to larger families of OCCs is often regarded as a "fingerprint" that may potentially convey information about sources of exposure or metabolism. As we have pointed out previously (28), the PCB congener profile (Table 2) is more typical of exposures of environmental origin than occupational. As is typical with case-control studies, few women in the present study were employed in occupations or industries with likely exposure to pesticides or PCBs.

The 1994 report by Dewailly *et al.* (10) of OCC-related increased risk in ER+ women has led many investigators to examine ER status. In the present study, when ER status was ignored the OR in the middle (but not the highest) tertile of total pesticide exposure was slightly elevated (1.27), but neither this nor any of the other ORs was statistically significant; the OR in this stratum (but in no others) became significant when calculations were restricted to ER− women; specifically, the ORs for the highest levels were not elevated. Our data therefore do not support the 1994 finding by Dewailly *et al.* (10).

This study did not attempt to assess either genetic factors by themselves or possible gene-environment interactions. A number of genetic factors such as mutations in the genes *BRCA1* and *BRCA2* are known to affect predisposition to breast cancer (35). Dunning *et al.* (36) recently summarized case-control studies that examined a wide variety of candidate genes for low-penetrance breast cancer susceptibility alleles and concluded that the maximum relative risk related to any of the polymorphisms *BRCA1, COMT, CYP17, CYP1A1, NAT1,* and *NAT2* was 1.5, whereas greater risks for *CYP2D6, GSTT1,* and

Table 5 ORs for breast cancer in Long Island, New York, 1994–1996, in relation to adipose DDE, total OCPs, and total PCBs by ER status[a]

Concentration in adipose tissue (ng/g)	ER+				ER−			
	Cases (n = 129)	Controls (n = 323)	Adjusted OR[b]	95% CI	Cases (n = 64)	Controls (n = 323)	Adjusted OR[b]	95% CI
DDE								
≤212.92	30	108	1.00		15	108	1.00	
212.93–618.81	42	108	1.06	0.58–1.92	31	108	1.63	0.80–3.35
>618.81	57	107	0.83	0.44–1.56	18	107	0.81	0.34–1.93
P-trend			0.5				0.9	
OCP[c]								
≤340.13	27	108	1.00		13	108	1.00	
340.14–878.14	48	108	1.21	0.61–2.06	35	108	2.17	1.03–4.58
>878.14	54	107	0.75	0.38–1.48	16	107	0.80	0.31–2.05
P-trend			0.3				0.8	
PCB[c]								
≤181.81	23	108	1.00		17	108	1.00	
181.82–332.24	40	108	1.20	0.65–2.21	24	108	1.29	0.63–2.65
>332.24	66	107	1.26	0.66–2.41	23	107	1.08	0.48–2.45
P-trend			0.4				0.9	

[a] Thirty-nine cases with either borderline or unknown ER status were excluded from analysis.
[b] Adjusted for age and BMI (continuous), hospital (two hospitals, indicator), race (white *versus* non-white, indicator).
[c] OCP, sum of seven organochlorine pesticide species; PCB, sum of 14 congeners; see text for details.

several others could not be excluded by existing data. Far fewer studies of gene-environment interactions in relation to breast cancer have been conducted, and several have produced conflicting results (37, 38). Ambrosone *et al.* (39) reported that breast cancer risk was unaffected by GSTM1 polymorphisms in women with either high or low dietary consumption of antioxidants. Moysich *et al.* (40) have reported an increased risk in postmenopausal breast cancer among women whose serum PCB levels were above the median and whose *CYP1A1* genotype was either isoleucine:valine or valine:valine, relative to women with serum PCBs below the median and homozygous (Ile:Ile). Although this intriguing result needs to be followed up in other studies, it should be kept in mind that at least 8 of the 15 human CYP enzymes thus far characterized are polymorphic at the phenotypic or genotypic level, and it is quite likely that multiple CYP enzymes are involved in metabolizing human carcinogens (41).

There is emerging interest in identifying possible carcinogenic effects related to body burden of specific PCB congeners in humans. Three adipose tissue studies have reported associations of breast cancer risk with BZ 118 (10, 19, 42), whereas in a serum study (43) positive associations were "suggested" between serum levels of BZ 118 and BZ 138 and breast cancer risk. [In the study by Güttes *et al.* (42), no statistical adjustment for age was made despite the fact that the cases were considerably older than controls.] On the other hand, we found no significant association either with BZ 118 or BZ 138. Additional studies are needed to resolve these differences.

Most toxicological data on PCB congeners have been obtained in experimental studies [recently reviewed by Hansen (44)]. Seven of the congeners included in the present study of breast cancer in Long Island women were also among 18 tested by Connor *et al.* (45) for PB-like activity in induction of rat hepatic microsomal pentoxyresorufin *O*-dealkylase. Connor *et al.* (45) found BZ 187 to belong to the most potent group, with induction activity comparable with PB. A weaker group that included BZ 99, BZ 153, BZ 180, and BZ 183 induced pentoxyresorufin *O*-dealkylase activity at least 50% of the maximal response observed for PB. BZ 118 and BZ 170 were weak inducers. Of these seven congeners, only the concentration of BZ 183 differed significantly between cases and controls in our study (Table 2). Thus, strength as a PB inducer did not predict mammary carcinogenicity in our population, and cases and controls differed little in the adipose concentration of most PB inducers. In fact, we found no association between breast cancer risk and 12 of the 14 measured congeners. A slight elevation was noted for the hexachlorinated congener BZ 156 that was statistically significant for the middle but not for the highest tertile. We noted a consistently elevated OR only for the heptachlorinated congener BZ 183, primarily in postmenopausal women; among such women with tissue concentrations >5.66 ng/g, OR was 3.2 (95% CI, 1.5–7.0). However, the more abundant di-*ortho* congener BZ 153, which makes up nearly one-fourth of total PCBs in humans (28), is a very strong PB-type inducer of cytochrome P-450 enzymes (44). It has also been reported recently to possess estrogenic properties (46). (There are no available reports on the estrogenicity of BZ 183.) The fact that neither the present study nor that of Aronson (19) observed an increased risk for BZ 153 makes it difficult to attach substantial biological significance to our elevated risk estimates for BZ 183 in the absence of replication in other populations or at least supportive mechanistic data.

Both estrogenic and antiestrogenic effects have been attributed to various PCBs based upon standard uterotropic animal models (44). Nesaretnam *et al.* (47) have demonstrated that the non-*ortho* tetrachlorinated biphenyl BZ 77 can act as both an agonist and antagonist of estrogen action, and that this congener can enhance mammary carcinogenesis in the rat (48). Adipose levels of BZ 77 were reportedly associated with a 6-fold risk of breast cancer (OR, 5.8; 95% CI, 0.8–42) in a Swedish case-control study (49). This congener was not included in the panel investigated by Aronson (19) nor in the present study.

The large number of statistical tests that can be carried out in this database may produce a few statistically significant findings that have little or no biological meaning. As noted above, the proportions of cases and controls with nondetectable levels of analytes were significantly different for one pesticide and three PCB congeners, *i.e.*, β-HCH, BZ 167, BZ 178, and BZ 183; yet, the absolute case-control difference for β-HCH was <4% and for the PCBs was only 5–10%. Except for BZ 183 (which comprises <9% of the total PCB concentration),

the analytes that showed differences in detectability were not the same as those that showed significant case-control differences the mean in mean levels. Furthermore, as shown in Table 2, the largest difference in the relative abundance pattern was for *p,p′*-DDE, whose mean did not significantly differ between cases and controls; no other differences exceeded 1.3% (BZ 74), and the majority of analytes differed by <1%. Judging the evidence as a whole, we conclude that the few observed case-control differences in detectability and mean analyte levels are not biologically meaningful.

Although the majority of epidemiological studies, including this one, have not confirmed these chemical compounds or related OCCs as likely causes of breast cancer, the fact that all samples tested to date have shown detectable levels of both pesticides (especially *p,p′*-DDE) and PCBs provides ample reason for concern about other possible health effects of these compounds, including cancers other than the breast. PCBs are classified by IARC as group 2A, "probably carcinogenic to humans," and *p,p′*-DDT is classified as group 2B, "possibly carcinogenic to humans" (50). Those classifications do not rely only upon epidemiological evidence but are based upon a multitude of additional considerations including carcinogenicity in animal bioassays and mechanistic considerations. The Agency for Toxic Substances and Disease Registry concluded in 1996 that "Studies in animals show that PCBs containing 60% chlorine by weight are clearly carcinogenic" (51). Systematic epidemiological studies of possible associations between OCCs and other types of cancer should continue to be undertaken.

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