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

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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',6'-heptachlorobiphenyl), 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 OCCs3 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; p,p’-DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; BMI, body mass index; BZ, Ballenschmiter and Zell; HCB, hexachlorobenzene; \( \beta \)-HCH, \( \beta \)-hexachlorocyclohexane; PCB, polychlorinated biphenyl; OR, odds ratio; CI, confidence interval; LOD, limits of detection; PB, phenobarbital; ER, estrogen receptor.

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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. This 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 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 CO₂. The extraction with CO₂ 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 CO₂ 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...
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 \( g \)-chlordane and Aldrin, justifying the usage of these two compounds as a recovery and gas chromatography standard, respectively. Only assays with recoveries of \( g \)-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% (\( \beta \)-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 \( p,p' \)-DDT, 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 \( o,o' \)-DDD (\( p,p' \)-DDE is the major breakdown product of \( p,p' \)-DDT), oxychlordane and trans-nonachlor (products of chlordane), \( \beta \)-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 \( \chi^2 \) 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 Ps 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.

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.
thrown out. For all pesticides except DDT (93.2%), and four of the PCB congeners, there were no 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 analytic makes on average relative to total pesticides or to total PCBs. p,p'-DDT 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 (Ps 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 breast cancer risk and body burden of p,p'-DDT, 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 total pregnancies. All analyses 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'-DDT, 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, 0.32–2.33), 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'-DDT 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'-DDT, 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
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, \( \beta \)-HCH and BZ 167, did differ significantly \((P < 0.05)\), with the mean level of \( \beta \)-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>
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<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases (n = 232)</strong></td>
<td><strong>% of total OCPs</strong></td>
</tr>
<tr>
<td>25%</td>
<td>50%</td>
</tr>
</tbody>
</table>
| HCB | 12.4 | 17.8 | 26.0 | 2.4 | 10.6 | 16.3 | 21.8 | 2.5 | 0.5 | 10.0 | 19.8 | 39.4 | 5.1 | 8.7 | 15.8 | 29.2 | 4.4 | 0.4 | 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).

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<table>
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<th>Table 3</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>n</td>
</tr>
<tr>
<td>Reference age (yr)</td>
<td>323</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>323</td>
</tr>
<tr>
<td>BMI</td>
<td>323</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>323</td>
</tr>
<tr>
<td>No. of full-term pregnancies</td>
<td>323</td>
</tr>
<tr>
<td>Age at first full-term pregnancy (yr)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>255</td>
</tr>
<tr>
<td>Breastfed (mo)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>255</td>
</tr>
</tbody>
</table>

<sup>a</sup>OCP, sum of seven organochlorine pesticide species; PCB, sum of 14 congeners; see text for details.

<sup>b</sup> \( P < 0.01 \).

<sup>c</sup> Parous women only.

<sup>d</sup> Postmenopausal women only.

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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’-DDT 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 organochlorines 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-penetration 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 4 ORs for breast cancer in Long Island, New York, 1994–1996, in relation to adipose DDE, total OCPs, and total PCBs

<table>
<thead>
<tr>
<th>Concentration in adipose tissue (ng/g)</th>
<th>Cases (n = 232)</th>
<th>Controls (n = 323)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤121.92</td>
<td>60</td>
<td>108</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>121.93–618.81</td>
<td>86</td>
<td>108</td>
<td>1.14</td>
<td>0.71–1.81</td>
</tr>
<tr>
<td>&gt;618.81</td>
<td>86</td>
<td>107</td>
<td>0.74</td>
<td>0.44–1.25</td>
</tr>
<tr>
<td>P-trend</td>
<td></td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>OCPb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤340.13</td>
<td>54</td>
<td>108</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>340.14–878.14</td>
<td>98</td>
<td>108</td>
<td>1.29</td>
<td>0.80–2.08</td>
</tr>
<tr>
<td>&gt;878.14</td>
<td>80</td>
<td>107</td>
<td>0.66</td>
<td>0.38–1.17</td>
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<td>P-trend</td>
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<td>0.1</td>
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<td>PCBb</td>
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<td></td>
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<td></td>
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<tr>
<td>≤181.81</td>
<td>55</td>
<td>108</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>181.82–332.24</td>
<td>74</td>
<td>108</td>
<td>1.06</td>
<td>0.67–1.69</td>
</tr>
<tr>
<td>&gt;332.24</td>
<td>103</td>
<td>107</td>
<td>1.01</td>
<td>0.60–1.69</td>
</tr>
<tr>
<td>P-trend</td>
<td></td>
<td></td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age and BMI (continuous), hospital (two hospitals, indicator), race (white versus non-white, indicator).
* 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 in other studies, it should be kept in mind that at least 8 of the 15 human CYP enzymes thus far characterized are polymorphic. 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). 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 antioestrogenic effects have been attributed to various PCBs based upon standard uuterotronic 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 Swedish case-control study (49). This congener was not in-cluded in the panel investigated by Aronson (19) nor in the Swedish case-control study (49). 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 <5% of the total PCB concentration),

<table>
<thead>
<tr>
<th>Concentration in adipose tissue (ng/g)</th>
<th>ER+</th>
<th>ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n = 129)</td>
<td>Controls (n = 323)</td>
</tr>
<tr>
<td>DDE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤212.92</td>
<td>30</td>
<td>108</td>
</tr>
<tr>
<td>212.93–618.81</td>
<td>42</td>
<td>108</td>
</tr>
<tr>
<td>&gt;618.81</td>
<td>57</td>
<td>107</td>
</tr>
<tr>
<td>P-trend</td>
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</tr>
<tr>
<td>OCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤340.13</td>
<td>27</td>
<td>108</td>
</tr>
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<td>340.14–878.14</td>
<td>48</td>
<td>108</td>
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<tr>
<td>&gt;878.14</td>
<td>54</td>
<td>107</td>
</tr>
<tr>
<td>P-trend</td>
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<td></td>
</tr>
<tr>
<td>PCB</td>
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<td></td>
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<tr>
<td>≤181.81</td>
<td>23</td>
<td>108</td>
</tr>
<tr>
<td>181.81–332.24</td>
<td>40</td>
<td>108</td>
</tr>
<tr>
<td>&gt;332.24</td>
<td>66</td>
<td>107</td>
</tr>
<tr>
<td>P-trend</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

Cancer Epidemiology, Biomarkers & Prevention
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 room 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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References

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

Steven D. Stellman, Mirjana V. Djordjevic, Julie A. Britton, et al.


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