Dichlorodiphenyldichloroethene, Polychlorinated Biphenyls, and Breast Cancer among African-American and White Women in North Carolina[1]

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Abstract

We examined plasma dichlorodiphenyldichloroethene (DDE) and total polychlorinated biphenyl (PCB) levels in relation to breast cancer in a population-based, case-control study of African-American women (292 cases and 270 controls) and white women (456 cases and 389 controls) in North Carolina. Adjusted odds ratios (ORs) for breast cancer comparing the highest to lowest third of DDE were 1.41 [95% confidence interval (CI), 0.87–2.29] in African-American women and 0.98 (95% CI, 0.67–1.43) in white women. ORs comparing the highest to lowest third of total PCBs were 1.74 (95% CI, 1.00–3.01) in African-American women and 1.03 (95% CI, 0.68–1.56) in white women. Among African-Americans, the OR for total PCBs was highest for obese women (body mass index ≥34.2; OR, 4.92; 95% CI, 1.63–14.83). In contrast, the OR for DDE was highest for the leanest African-American women (body mass index, <25; OR, 3.84; 95% CI, 0.98–15.08). ORs for DDE were not elevated among women who lived or worked on farms or elevated among farming women who reported exposure to pesticides. Our results suggest absence of a strong effect for DDE or total PCBs in breast cancer but lend support for associations among subgroups of women. In our study, factors such as income, parity, breastfeeding, race/ethnicity, and body mass index influenced the relationship of organochlorines and breast cancer. Differing distributions of such factors may explain some of the inconsistencies across previous studies.

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Introduction

The most common organochlorine residues found in humans are *p,p′*-DDE[3] and PCBs (1). DDE is a breakdown product of DDT, an agricultural and antimalarial insecticide introduced in the United States in 1943 and discontinued in 1972. PCBs comprise a series of 209 congeners that were introduced in the United States in the 1930s as lubricants, protective sealants, and industrial solvents. Use of PCBs was discontinued in 1977. DDE and PCBs were detected in the majority of adipose tissue and blood samples taken from participants in the United States Public Health Service surveillance program conducted between 1970 and 1983 (2). Blood samples can be used to estimate body burden of exposure to organochlorine compounds, because equilibrium is reached between peripheral blood and adipose tissue stores (1–3). Lipid adjustment improves the comparability of blood and adipose tissue measurements and removes variability in organochlorine residues attributable to fasting and postprandial states (2).

Several epidemiological studies have investigated the association of DDE and PCBs in human adipose tissue or blood samples and risk of breast cancer (reviewed in Refs. 1–5). The first large epidemiological study linking DDE and PCBs to breast cancer was conducted by Wolff *et al.* (6), who reported a strong association for serum DDE and a weaker association for total PCBs in a case-control study of New York City women. In a nested case-control study in the San Francisco Bay Area, Krieger *et al.* (7) reported an OR of 3.85 (95% CI, 0.93–16.05) comparing African-American women in the highest to the lowest third of serum DDE and an OR of 2.21 (95% CI, 0.70–6.98) comparing African-American women in the highest to lower third of total PCBs. A weak positive association was observed for DDE in white women, whereas inverse associations were found for total PCBs in white women and DDE and total PCBs in Asian-American women. No additional studies of African-American women have been reported. Most subsequent studies reported no association between DDE or PCBs and breast cancer risk, including nested case-control studies of nurses from the United States (8) and women from Copenhagen, Denmark (9); Washington County, MD (5); and Columbia, MO (10). Case-control studies conducted in Connecticut (11), Mexico City (12), and several large European cities (13) also failed to detect an association with DDE. However, a case-control study in Bogota, Columbia showed a weak positive association between DDE and breast cancer (14).

To examine the relationship between DDE and PCBs and breast cancer risk, we analyzed plasma samples collected from a population-based, case-control study. The study includes African-American women and was conducted in a rural area

[3] The abbreviations used are: DDE, dichlorodiphenyldichloroethene; PCB, polychlorinated biphenyl; OR, odds ratio; CI, confidence interval; BMI, body mass index; WHR, waist:hip ratio; CBCS, Carolina Breast Cancer Study; DDT, dichlorodiphenyltrichloroethane; HRT, hormone replacement therapy.

engaged in intensive agricultural production (15). We examined the association of DDE and total PCBs with breast cancer risk among African-American and white women separately, as well as among subgroups of women defined by parity and lactation status, BMI, WHR, farming history, and reported pesticide exposure. Among cases, we investigated the roles of stage at diagnosis and estrogen receptor status. We also studied the relationship of low to moderate and high chlorination PCB congeners and breast cancer risk.

Materials and Methods

Study Population. The CBCS is a population-based, case-control study of breast cancer conducted in 24 counties of central and eastern North Carolina (15). Cases with a first diagnosis of histologically confirmed, invasive breast cancer were ascertained using a rapid case ascertainment system implemented in cooperation with the North Carolina Central Cancer Registry, whereas controls were identified using Division of Motor Vehicles and Medicare beneficiary lists (16). Randomized recruitment (17) was used to identify approximately equal numbers of African-American and white women and women <50 and ≥ 50 years of age. During Phase I of the CBCS (May 1993–December 1996), 889 cases and 841 controls were interviewed. Overall response proportions (number of completed interviews/number of eligible participants) were 74% for cases and 53% for controls (18). The interview included a variety of known and potential risk factors for breast cancer. Race was classified according to self-report. For the present analysis, we classified women as African-American or white. We included as white seven Native Americans, three Asian-Americans, and three women who listed their race as "multiracial." Women who had ever lived or worked on farms completed a more extensive telephone interview regarding farming practices and exposure to pesticides (19). Information regarding stage at diagnosis, estrogen receptor status, and breast cancer treatment for cases was obtained from medical records.

Approximately 98% of participants who were interviewed agreed to provide three 10-ml blood samples collected in acid citrate dextrose-anticoagulated tubes. Each tube was centrifuged at 700–900 $\times$ *g* (2600 rpm) at 4°C for 20 min. The plasma layer was transferred in three aliquots to polypropylene freezer tubes and stored at −70°C. All blood samples were processed within 48 h of collection.

Laboratory Methods. Plasma levels of organochlorines were used as an estimate of total body burden of these compounds (6, 20–22). Organochlorine analyses were conducted at Research Triangle Institute (Research Triangle Park, NC). Plasma samples (2.0 ml) were treated with methanol (1.0 ml), spiked with two surrogate standards (PCB 198 and *o*,*p*′-DDT), and then extracted sequentially with three 2.5-ml portions of hexane: diethyl ether (1:1). Extraction was performed using rotary mixing (15 min at 60 rpm) and centrifugation (15 min at 1800 rpm). The combined extracts were fractionated using Florisil (R) open-column chromatography. The first fraction was eluted with 35 ml of hexane and contained all of the PCBs, as well as *p*,*p*′-DDE, *o*,*p*′-DDE, and DDT. This fraction was concentrated to 0.5 ml and spiked with octachloronaphthalene as an external quantitation standard. Extracts were analyzed by gas chromatography/electron capture detection using a DB-5 column and Hewlett-Packard Model 6890 instrument. Individual compounds were identified based upon chromatographic retention times relative to the internal standards and pattern recognition in the sample extract. Individual PCB congeners were quantitated using calibration curves generated for the chromatographic peak area ratio of the congener to the internal standard *versus* solution concentrations. Calibration solutions were prepared from certified standard solutions (AccuStandard, New Haven, CT) for each of the 35 individual congeners measured in this study (IUPAC numbers 74, 99, 101, 105, 114, 118, 137, 138, 141, 146, 149, 153, 156, 157, 158, 167, 170, 171, 172,174, 177, 178, 180, 182, 183, 185, 187, 190, 194, 195, 196, 197, 200, 201, and 203).

Quantitation limits were 0.125 ng/g for *o*,*p*′-DDE and other pesticides and 0.025 ng/g for individual PCB congeners. Quantitation limits were based upon the lowest calibration standard in the calibration curve (0.1 ng/ml) that met the following criteria: signal:noise ratio of 10:1 and a measured value within 20% of the prepared value. The quantitation limit was considered to be the detection limit $\times$ 2. Coefficients of variation were 12% for total PCBs, with individual congeners showing coefficients of variation of $<10\%$, and 16% for *p*,*p*′-DDE.

Plasma lipid profiles were determined at the Core Laboratory for Clinical Studies at Washington University School of Medicine (St. Louis, MO). Automated enzymatic assays using cholesterol esterase and lipoprotein lipase were performed on a Technicon RA-1000 analyzer. Replicate samples were included with each shipment to determine coefficients of variation (3.4% for net triglycerides and 2.1% for total cholesterol).

Organochlorine and lipid measurements were available on 748 cases (84%) and 659 controls (78%). Reasons for failure to obtain laboratory measurements included insufficient plasma and interference in the sample. Participants with organochlorine and lipid measurements did not differ significantly from participants without such measurements based upon age, race, disease status, or breast cancer risk factors (23). The time between blood draw and blood processing ranged from 3 to 24 h. We determined in a pilot study that varying the time between blood draw and blood processing from 30 min to 24 h did not result in appreciable differences in measured organochlorine levels (23). A small proportion of samples showed moderate hemolysis; however, the presence or degree of hemolysis was not correlated with measured DDE or total PCB levels (23).

Among the 1407 study participants, 99.7% had detectable levels of *p*,*p*′-DDE. Only 1% of participants had detectable levels of *o*,*p*′-DDE, and 40% had detectable levels of DDT. Results are presented for *p*,*p*′-DDE only (hereafter referred to as DDE). All participants had detectable levels of one or more PCB congeners.

Statistical Methods. Raw values for DDE and total PCBs were analyzed, as well as imputed values. Imputation was conducted to facilitate log transformation and was performed by setting zero values and values below the detection limit (0.0625 ng/ml for DDE and 0.0125 for individual PCB congeners) to the detection limit divided by the square root of 2. We used this method of imputation to compare our results with the Northeast and Mid-Atlantic Breast Cancer Studies Group.[4] Total PCBs were determined by summing the individual PCB congeners (raw or imputed) for each person. To compare our results with other studies, we also created a modified total PCBs restricted to the congeners 118, 138, 153, and 180. In addition, we used the methods described by Moysich *et al.* (24, 25) to classify PCB congeners according to the degree of chlorination. Relatively few women had detectable levels of

[4] Francine Laden, personal communication, 1998.

low chlorination PCBs; therefore, we grouped PCB congeners in two groups, high chlorination (IUPAC numbers 194, 195, 196, 197, 200, 201, and 203) *versus* low to moderate chlorination (remaining congeners). Similar to Moysich *et al.* (24), we did not detect sufficient numbers of the relevant PCB congeners to use the classification system based upon enzyme induction suggested by Wolff *et al.* (26).

Lipid adjustment was performed by dividing DDE or total PCB levels by total lipids to yield μg/g lipid (Ref. 27, Eq. 2 therein). We used an additional method for lipid adjustment wherein separate terms for cholesterol and triglycerides (centered around their respective means) were entered into logistic models when calculating ORs for breast cancer. Because results were unchanged, only results using the lipid adjustment method of Phillips *et al.* (27) are presented. The distributions of DDE and total PCBs were compared in cases and controls using raw values (without imputation or lipid adjustment), imputed values (with and without lipid adjustment), and log-transformed imputed values (with and without lipid adjustment). Because the distributions of untransformed DDE and total PCBs were skewed, the Wilcoxon rank sum test for unpaired data were used to compare medians for raw and lipid-adjusted DDE and total PCBs. *t* tests were used to compare geometric means for log-transformed values of lipid-adjusted imputed DDE and total PCBs.

To calculate ORs for breast cancer, DDE and total PCBs were categorized into thirds as well as quartiles, based upon the distribution in controls. We used each of the possible values for DDE and total PCBs: raw, imputed, lipid-adjusted, and log-transformed. Results were similar, regardless of the method of classification; therefore, ORs for DDE and total PCBs include imputed values, after lipid adjustment and without log transformation. Distributions of organochlorines divided into thirds are presented to compare with previous studies (*e.g.*, Ref. 7) and to maximize power in subgroup analyses. For analyses of African-Americans and whites, ORs for organochlorines are presented using race-specific cutpoints, because the distributions of DDE and total PCBs were different in these groups.

Unconditional logistic regression was used to calculate adjusted ORs for breast cancer and 95% CIs. PROC GENMOD of the software package SAS (version 6.11; SAS Institute, Cary, NC) was used to adjust for age (continuous) and race (African-American and white), as well as to incorporate offset terms derived from the sampling probabilities used to identify eligible participants (17). To provide additional adjustment for age, we added an age-squared term to logistic models. The following factors were tested as potential confounding variables: height, weight, BMI, WHR, menopausal status, parity, breastfeeding, age at first full-term pregnancy, oral contraceptive use, HRT use, yearly household income, level of education, smoking, alcohol consumption, and dietary variables (fruit, vegetable, and fish consumption).

To assess confounding, we evaluated whether the β coefficient for either the uppermost or middle third of organochlorines changed by 10% or more after controlling for each variable separately in logistic models adjusted for age, age-squared, race, and sampling fractions. Confounding was assessed in the entire dataset and among African-American and white women separately. The addition of income resulted in a change of 10% or greater in β coefficients for DDE and total PCBs. Adjustment for the remaining covariates made little or no difference in OR estimates but led to wider CIs. To compare our results with other studies, we present results adjusted for the common list of variables used by the Northeast and Mid-Atlantic Breast Cancer Studies Group:[4] age, age-squared, race (African-American and white), menopausal status (pre- and postmenopausal), BMI ($\leq$24.9 kg/m^2, 25–39.9, and $\geq$30), parity and breastfeeding composite (nulliparous, parous never breastfed, and parous ever breastfed), and HRT use (ever and never). In addition, we adjusted for yearly household income ($<$\$15,000, \$15,000 to $<$\$30,000, \$30,000 to $<$\$50,000, and $\geq$\$50,000 per year).

To address the effect of missing values for covariates, we calculated ORs for DDE and total PCBs in the subset of participants with complete covariate information while controlling for age, age-squared, and race. Results were similar to those obtained in the entire dataset. We calculated ORs for thirds of DDE and total PCBs after including both variables simultaneously in logistic models, but results were unchanged.

Analyses were stratified by race, parity, history of breastfeeding, menopausal status, BMI, and WHR. For women $<$50 years, postmenopausal status was assigned to women who had undergone natural menopause, bilateral oophorectomy, or irradiation to the ovaries; in women $\geq$50 years, menopausal status was assigned on the basis of cessation of menstruation. We used three methods to create strata for BMI: (*a*) race-specific cutpoints in thirds based upon distributions in controls ($<$28.16 kg/m^2, 28.16 to $<$34.2, and $\geq$34.2 for African-Americans; $<$23.50, 23.50 to $<$27.94, and $\geq$27.94 for whites); (*b*) absolute cutpoints for the entire dataset based upon the latest United States obesity standards (normal, $<$25 kg/m^2; overweight, 25–29.9; and obese, $\geq$30)[5]; and (*c*) cutpoints in thirds based upon African-American controls, applied to the entire dataset. The first method yielded maximal power to evaluate the effects of organochlorines across strata of BMI within each racial group, because values of BMI were substantially higher among African-American controls (median, 30.7 kg/m^2) compared with white controls (median, 25.7 kg/m^2). We stratified on WHR a measure of body fat distribution (higher values of WHR indicate central adiposity), using race-specific cutpoints in thirds (African-Americans: $<$0.78, 0.78–0.87, and $>$0.87; whites: $<$0.74, 0.74–0.81, and $>$0.81).

To evaluate whether plasma DDE levels exhibited a different relationship with breast cancer risk among women engaged in agriculture, we stratified women based on having lived or worked on a farm. A farm was defined as "any place that raises crops or livestock and sells them to earn money." Women with a history of farming were asked about specific agricultural activities, including exposure to pesticides. Women who reported having mixed, loaded, or transported pesticides, applied pesticides to crops, or cleaned pesticide applying equipment were classified as having potential pesticide exposure (19).

To address potential disease-related changes in body mass and distribution of organochlorine residues, we conducted stratified analyses based upon self-reported loss or gain of at least 5 pounds in the year preceding the date of blood collection in cases and controls. ORs were also calculated after subdividing cases based upon stage at diagnosis and presence or absence of estrogen receptors. ORs for total PCBs were also calculated using the modified PCB total specified by the data analysis consortium and after grouping PCB congeners according to level of chlorination (see "Laboratory Methods," above). We also calculated ORs comparing women in the highest third of DDE and total PCBs compared with women in the lowest third of both, as suggested by Hunter *et al.* (8).

[5] National Heart, Lung, and Blood Institute (NHLBI). First federal obesity guidelines released. Internet address: http://www.nhlbi.nih.gov/new/press/obese14f.htm, 1998.

Table 1 Plasma levels of DDE and total PCBs among cases and controls in the CBCS

	Cases		Controls		P^a
	Mean (SD)	Median	Mean (SD)	Median	
African-Americans	$n = 292$		$n = 270$		
DDE[b]	9.96 (11.1)	6.64	8.82 (8.9)	5.66	0.45
Lipid-adjusted DDE[c]	1.96 (2.2)	1.31	1.69 (1.7)	1.17	0.29
Total PCBs[d]	2.79 (2.2)	2.17	2.56 (2.3)	1.97	0.21
Lipid-adjusted total PCBs[e]	0.56 (0.4)	0.45	0.51 (0.4)	0.43	0.08
Whites	$n = 456$		$n = 389$		
DDE	3.52 (4.4)	1.91	3.94 (5.8)	2.32	0.09
Lipid-adjusted DDE	0.66 (0.8)	0.40	0.76 (1.2)	0.43	0.18
Total PCBs	1.89 (1.7)	1.47	1.89 (1.2)	1.63	0.16
Lipid-adjusted total PCBs	0.38 (0.2)	0.33	0.38 (0.2)	0.35	0.42

[a] Wilcoxon rank sum test comparing medians in cases and controls.
[b] *p,p′*-DDE in parts per billion (ng/ml), unadjusted for lipids.
[c] *p,p′*-DDE adjusted for lipids (μg/g).
[d] Total PCBs in ppb (ng/ml), unadjusted for lipids.
[e] Total PCBs adjusted for lipids (μg/g).

Results

For analysis of organochlorines, the study population consisted of 292 African-American cases, 270 African-American controls, 456 white cases, and 389 white controls. The mean age was 50.2 years (range, 23–74) for cases and 51.5 years (range, 21–74) for controls. Cases were 51.1% premenopausal (n = 382) and 48.9% postmenopausal (n = 366). Controls were 46.4% premenopausal (n = 306) and 53.6% postmenopausal (n = 353). Characteristics of participants in the CBCS have been presented previously (28). Briefly, onset of menarche prior to age 12, nulliparity, first full-term pregnancy at ≥26 years, breast cancer in a first-degree relative, and smoking cigarettes for >20 years were positively associated with breast cancer, whereas breastfeeding of any duration showed an inverse association. Risk factors among participants with organochlorine and lipid measurements did not differ from the CBCS as a whole (data not shown). Detailed results regarding predictors of DDE and total PCBs among participants in the CBCS will be presented elsewhere.[6, 7]

Mean and median levels of DDE and total PCBs among African-American and white cases and controls are presented in Table 1. To compare our results with previous studies, raw values (without imputation, adjustment for lipids, or log transformation) and lipid-adjusted imputed values are presented. Case-control differences were minimal among African-American and white participants (Table 1). There were also no significant differences between cases and controls for lipid-adjusted, imputed, or log-transformed values (geometric means) of DDE or total PCBs (data not shown).

ORs for breast cancer according to thirds of DDE and total PCBs are presented in Table 2. Among all participants, there was no association between increasing levels of DDE or total PCBs and breast cancer. For African-American women, ORs were elevated slightly across thirds of DDE and total PCBs, with some evidence of a dose-response gradient, particularly for total PCBs. Among white women, only a slight elevation for the middle *versus* lowest third was observed for total PCBs.

Table 2 ORs for lipid-adjusted DDE and PCBs and breast cancer, overall and stratified by race

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
All participants				
DDE[c]				
<0.394	274	220	Referent	Referent
0.394 to <1.044	231	219	0.96 (0.73–1.25)	1.05 (0.79–1.40)
≥1.044	243	220	1.00 (0.74–1.36)	1.09 (0.79–1.51)
Total PCBs[d]				
<0.283	239	219	Referent	Referent
0.283 to <0.469	266	220	1.29 (0.98–1.69)	1.29 (0.97–1.72)
≥0.469	243	220	1.21 (0.89–1.65)	1.09 (0.79–1.52)
African-Americans				
DDE				
<0.71	89	90	Referent	Referent
0.71 to <1.8	90	90	1.11 (0.72–1.72)	1.12 (0.70–1.77)
≥1.8	113	90	1.37 (0.87–2.17)	1.41 (0.87–2.29)
Total PCBs				
<0.312	79	90	Referent	Referent
0.312 to <0.54	97	90	1.48 (0.95–2.33)	1.35 (0.84–2.16)
≥0.54	116	90	1.79 (1.07–3.01)	1.74 (1.00–3.01)
Whites				
DDE				
<0.30	176	130	Referent	Referent
0.30 to <0.66	146	129	0.91 (0.65–1.27)	0.97 (0.68–1.40)
≥0.66	134	130	0.87 (0.62–1.24)	0.98 (0.67–1.43)
Total PCBs				
<0.265	149	130	Referent	Referent
0.265 to <0.417	172	129	1.32 (0.94–1.85)	1.32 (0.92–1.90)
≥0.417	135	130	1.19 (0.81–1.74)	1.03 (0.68–1.56)

[a] Adjusted for age, age-squared, and race (all participants).
[b] Adjusted for age, age-squared, race (all participants), menopausal status, BMI, parity/lactation, HRT use, and income.
[c] *p,p′*-DDE in μg/g lipid.
[d] Total PCBs in μg/g lipid.

Results for DDE and total PCBs stratified by parity and breastfeeding are presented in Table 3. Nulliparous women showed slightly stronger associations for both DDE and total PCBs than parous women. Similarly, parous women who never breastfed showed slightly stronger associations than women who reported a history of breastfeeding. Results were similar for African-American and white women.

ORs for DDE and breast cancer stratified by BMI are presented in Table 4, using race-specific cutpoints for BMI. Results are presented using race-specific cutpoints for BMI,

[6] E. DeVoto, R. Millikan, C-K. Tse, and D. Savitz. Predictors of plasma PCB levels among African-American and white women, manuscript in preparation, 2000.
[7] E. Duell, R. Millikan, E. DeVoto, C-K. Tse, and D. Savitz. Predictors of plasma DDE levels among African-American and white women in North Carolina, manuscript in preparation, 2000.

Table 3 ORs for lipid-adjusted DDE and PCBs and breast cancer, stratified by parity and history of breastfeeding

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
Nulliparous				
DDE[c]				
<0.394	41	25	Referent	Referent
0.394 to <1.044	36	23	1.28 (0.59–2.78)	1.24 (0.54–2.82)
≥1.044	35	17	1.87 (0.67–5.20)	1.48 (0.49–4.46)
Total PCBs[d]				
<0.283	37	25	Referent	Referent
0.283 to <0.469	39	21	1.51 (0.69–3.33)	2.06 (0.88–4.85)
≥0.469	36	19	1.74 (0.67–4.54)	1.62 (0.57–4.58)
Parous, never breastfed				
DDE				
<0.394	131	102	Referent	Referent
0.394 to <1.044	122	123	0.86 (0.59–1.26)	0.96 (0.65–1.42)
≥1.044	134	111	1.07 (0.91–2.15)	1.23 (0.80–1.89)
Total PCBs				
<0.283	115	112	Referent	Referent
0.283 to <0.469	159	125	1.51 (1.04–2.20)	1.50 (1.01–2.23)
≥0.469	113	99	1.40 (0.91–2.15)	1.30 (0.82–2.06)
Parous, ever breastfed				
DDE				
<0.394	102	93	Referent	Referent
0.394 to <1.044	73	73	0.94 (0.60–1.48)	1.16 (0.70–1.90)
≥1.044	74	92	0.71 (0.41–1.21)	0.80 (0.45–1.44)
Total PCBs				
<0.283	87	82	Referent	Referent
0.283 to <0.469	68	74	0.92 (0.58–1.47)	0.90 (0.55–1.48)
≥0.469	94	102	0.95 (0.57–1.57)	0.84 (0.49–1.44)

[a] Adjusted for age, age-squared, and race.
[b] Adjusted for age, age-squared, race, menopausal status, BMI, HRT use, and income.
[c] *p,p′*-DDE in μg/g lipid.
[d] Total PCBs in μg/g lipid.

Table 4 ORs for lipid-adjusted DDE and breast cancer, stratified by BMI

	Case no.	Control no.	OR[a] (95% CI)	OR[b] (95% CI)
Lowest third of BMI[c]				
African-Americans				
DDE[d]				
<0.71	37	35	Referent	Referent
0.71 to <1.8	29	21	1.31 (0.62–2.73)	1.25 (0.57–2.73)
≥1.8	36	31	1.14 (0.55–2.35)	1.54 (0.58–3.49)
Whites				
DDE				
<0.30	89	51	Referent	Referent
0.30 to <0.66	38	40	0.61 (0.34–1.08)	0.69 (0.37–1.28)
≥0.54	45	37	0.91 (0.50–1.64)	0.99 (0.52–1.88)
Middle third of BMI				
African-Americans				
DDE				
<0.71	27	29	Referent	Referent
0.71 to <1.8	35	31	1.13 (0.51–2.49)	0.80 (0.33–1.92)
≥1.8	38	27	1.17 (0.49–2.79)	1.07 (0.41–2.76)
Whites				
DDE				
<0.30	48	43	Referent	Referent
0.30 to <0.66	59	51	1.15 (0.64–2.05)	0.91 (0.48–1.74)
≥0.54	52	35	1.53 (0.81–2.91)	1.29 (0.63–2.64)
Highest third of BMI				
African-Americans				
DDE				
<0.71	21	23	Referent	Referent
0.71 to <1.8	23	34	0.98 (0.41–2.34)	0.98 (0.37–2.55)
≥1.8	37	31	1.86 (0.77–4.49)	1.90 (0.71–5.09)
Whites				
DDE				
<0.30	35	35	Referent	Referent
0.30 to <0.66	48	36	1.30 (0.68–2.50)	1.66 (0.81–3.39)
≥0.54	37	58	0.62 (0.32–1.19)	0.89 (0.43–1.82)

[a] Adjusted for age and age-squared.
[b] Adjusted for age, age-squared, menopausal status, parity/lactation, HRT use, and income.
[c] Cutpoints for BMI (kg/m^2) are race specific: <28.16, 28.16 to <34.2, and ≥34.2 in African-Americans; <23.50, 23.50 to <27.94, and ≥27.94 in whites.
[d] *p,p′*-DDE in μg/g lipid. Cutpoints for DDE are race specific, based upon controls.

because this approach maximized power to evaluate modification of ORs by BMI within each racial group. There were no pronounced differences in ORs across strata of BMI. However, using a single BMI cutpoint in both racial groups, fully adjusted ORs for DDE in African-American women with BMI <25 ("normal weight") were 1.00 (referent), 2.74 (0.78–9.65), and 3.84 (0.98–15.08). ORs for white women with BMI <25 were 1.00 (referent), 0.70 (95% CI, 0.41–1.18), and 0.88 (95% CI, 0.51–1.52). Thus, the thinnest African-American women showed a stronger association between DDE and breast cancer. ORs for DDE did not differ when we stratified on WHR (data not shown).

ORs for total PCBs and breast cancer stratified by BMI are presented in Table 5. Using race-specific cutpoints, ORs for African-American women in the middle and especially the uppermost third of BMI were elevated relative to women in the lowest third, and ORs for white women were elevated slightly in the uppermost third of BMI. Similar results were obtained using the cutpoints for BMI in both racial groups based upon National Heart Lung and Blood Institute obesity standards.[5] For example, among participants with BMI ≥30 kg/m^2 ("obese"), fully adjusted ORs were 1.00 (referent), 1.69 (95% CI, 0.82–3.46) and 4.31 (95% CI, 1.78–10.39) for African-American women and 1.00 (referent), 1.99 (95% CI, 0.85–4.63), and 1.49 (95% CI, 0.53–4.22) for white women. Using the cutpoints based upon thirds in African-American controls, ORs for white women with BMI ≥34.2 kg/m^2 were 1.00 (referent), 3.98 (95% CI, 1.01–15.67), and 7.89 (95% CI, 1.39–44.88). Thus, white women and especially African-American women at the highest levels of obesity exhibited positive associations for total PCBs and breast cancer. ORs for total PCBs were elevated slightly among African-American women in the highest third of WHR compared with the middle and lower thirds, but the association was diminished after controlling for BMI (data not shown).

ORs for DDE and breast cancer stratified by farming history are presented in Table 6. ORs were not elevated substantially among women who lived or worked on farms compared with non-farming women. For the two racial groups combined, fully adjusted ORs for DDE in farming women were 1.00 (referent), 1.26 (95% CI, 0.81–1.96), and 1.50 (95% CI, 0.93–2.42). For farming women who reported potential pesticide exposure, ORs for DDE were 1.00 (referent), 0.79 (95% CI, 0.23–2.68), and 1.49 (95% CI, 0.41–5.42). However, the number of farming women with potential pesticide exposure was small (47 cases and 54 controls).

No important differences in ORs for DDE or total PCBs were found when we stratified by menopausal status (data not shown). ORs for DDE and total PCBs were slightly higher among postmenopausal women who used HRT compared with non-users (data not shown). We found no significant differences in ORs for DDE or total PCBs when we subdivided cases based upon stage at diagnosis: age- and race-adjusted ORs for the top *versus* lowest third of DDE were 0.80 (95% CI, 0.54–

Table 5 ORs for lipid-adjusted total PCBs and breast cancer, stratified by BMI

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
Lowest third of BMI[c]				
African-Americans				
Total PCBs[d]				
<0.312	29	24	Referent	Referent
0.312 to <0.54	38	30	1.13 (0.54–2.40)	1.22 (0.54–2.73)
≥0.54	35	33	0.90 (0.38–2.11)	0.82 (0.32–2.08)
Whites				
Total PCBs				
<0.265	54	36	Referent	Referent
0.265 to <0.417	69	35	1.50 (0.82–2.74)	1.28 (0.67–2.42)
≥0.417	49	57	0.90 (0.47–1.71)	0.72 (0.36–1.46)
Middle third of BMI				
African-Americans				
Total PCBs				
<0.312	24	29	Referent	Referent
0.312 to <0.54	32	31	1.31 (0.59–2.90)	1.11 (0.48–2.60)
≥0.54	44	27	1.65 (0.63–4.36)	2.51 (0.85–7.45)
Whites				
Total PCBs				
<0.265	53	38	Referent	Referent
0.265 to <0.417	50	47	0.83 (0.45–1.52)	0.81 (0.41–1.62)
≥0.417	56	44	0.95 (0.49–1.85)	0.77 (0.36–1.65)
Highest third of BMI				
African-Americans				
Total PCBs				
<0.312	23	33	Referent	Referent
0.312 to <0.54	25	28	2.09 (0.87–5.05)	2.20 (0.86–5.63)
≥0.54	33	27	3.83 (1.42–10.34)	4.92 (1.63–14.83)
Whites				
Total PCBs				
<0.265	39	55	Referent	Referent
0.265 to <0.417	52	45	1.79 (0.99–3.25)	1.85 (0.97–3.54)
≥0.417	29	29	1.79 (0.85–3.79)	1.82 (0.79–4.20)

[a] Adjusted for age, age-squared.
[b] Adjusted for age, age-squared, menopausal status, parity/lactation, HRT use, and income.
[c] Cutpoints for BMI (kg/m^2) are race specific: <28.16, 28.16 to <34.2, and ≥34.2 in African-Americans; <23.50, 23.50 to <27.94, and ≥27.94 in whites.
[d] Total PCBs in μg/g lipid. Cutpoints for total PCBs are race specific, based upon controls.

Table 6 ORs for lipid-adjusted DDE and breast cancer, stratified by farming history

	Cases	Controls	OR[a] (95% CI)	OR[b] (95% CI)
Never farmed				
African-Americans				
DDE[c]				
<0.71	47	50	Referent	Referent
0.71 to <1.8	41	37	1.23 (0.64–2.37)	1.26 (0.61–2.62)
≥1.8	29	29	1.05 (0.49–2.23)	1.14 (0.51–2.58)
Whites				
DDE				
<0.30	115	87	Referent	Referent
0.30 to <0.66	93	71	1.09 (0.71–1.66)	1.19 (0.75–1.89)
≥0.66	57	66	0.73 (0.46–1.18)	0.76 (0.45–1.28)
Lived or worked on farms				
African-Americans				
DDE				
<0.71	42	40	Referent	Referent
0.71 to <1.8	49	53	0.93 (0.51–1.68)	0.93 (0.49–1.77)
≥1.8	84	61	1.48 (0.82–2.68)	1.65 (0.86–3.17)
Whites				
DDE				
<0.30	61	43	Referent	Referent
0.30 to <0.66	53	58	0.68 (0.39–1.18)	0.74 (0.41–1.34)
≥0.66	77	64	0.99 (0.58–1.68)	1.19 (0.66–2.14)

[a] Adjusted for age, age-squared, and race.
[b] Adjusted for age, age-squared, race, menopausal status, BMI, parity/lactation, HRT use, and income.
[c] *p,p′*-DDE in μg/g lipid.

1.21) for stage 1 breast cancer *versus* controls and 1.19 (95% CI, 0.83–1.71) for stages 2 through 4 breast cancer *versus* controls. For total PCBs, the respective ORs were 1.35 (95% CI, 0.90–2.03) and 1.13 (95% CI, 0.78–1.64). We also did not observe differences in ORs according to estrogen receptor status of breast tumors in cases: for DDE, top to bottom ORs were 1.01 (95% CI, 0.70–1.45) for estrogen receptor-positive breast cancer and 0.96 (95% CI, 0.64–1.45) for estrogen receptor-negative breast cancer. For total PCBs, the respective ORs were 1.07 (95% CI, 0.74–1.56) and 1.35 (95% CI, 0.90–2.04). There were no appreciable differences in ORs when we stratified cases and controls based upon weight change within the past year (data not shown).

ORs for thirds of modified total PCBs (congeners 118, 138, 153, and 180 only) were 1.00 (referent), 0.98 (95% CI, 0.61–1.58), and 1.30 (95% CI, 0.77–2.17) in African-American women and 1.00 (referent), 1.02 (95% CI, 0.73–1.42), and 0.85 (95% CI, 0.57–1.25) in white women. For both racial groups combined, ORs were 1.00 (referent), 0.96 (95% CI, 0.73–1.27), and 0.99 (95% CI, 0.73–1.35) for low to moderate chlorination PCB congeners and 1.00 (referent), 1.41 (95% CI, 1.05–1.87), and 1.35 (95% CI, 0.97–1.88) for high chlorination PCB congeners. Results were similar in African-American and white women.

We did not observe evidence for a combined effect of DDE and PCBs. ORs for women in the highest third of DDE and total PCBs compared with women in the lowest third for both were 1.08 (95% CI, 0.54–2.15) in African-American women and 1.03 (95% CI, 0.60–1.77) in white women.

Discussion

We observed no overall association between plasma levels of DDE and total PCBs and breast cancer among African-American and white women in North Carolina. Raw and lipid-adjusted levels of DDE and total PCBs were higher among African-American women compared with whites, as reported previously (11, 29–31). DDE and total PCB levels were slightly higher in African-American cases compared with controls, but ORs did not approach the magnitude reported previously by Krieger *et al.* (7). Among white women, levels of DDE were slightly higher among controls compared with cases, as reported by three recent studies (5, 8, 13). The number of women in our study was sufficient to detect weak to moderate effects for DDE and total PCBs in each racial group.

Stratified analyses were conducted to determine whether subgroups of women might exhibit stronger associations between organochlorines and breast cancer. ORs for DDE and total PCBs were greater among nulliparous women compared with parous women. Hunter *et al.* (8) reported no significant differences in ORs for DDE or total PCBs across strata defined by parity or lactation. None of the remaining epidemiological studies presented analyses stratified by parity. Interestingly, in our study 19% of controls were nulliparous, whereas in the

study of Wolff *et al.* (6), ~36% of controls were nulliparous.[8] A high prevalence of nulliparous women could have contributed to the strong associations observed in the Wolff *et al.* (6) study, as well as other positive studies. In our study, ORs for total PCBs were higher among parous women who never breastfed than parous women who ever breastfed, in agreement with Moysich *et al.* (24). Breastfeeding might lower body burden of organochlorines during a time period of susceptibility to breast cancer and render breast epithelial cells less susceptible to carcinogens by inducing terminal differentiation (24).

We found that African-American and white women at the highest levels of obesity (BMI of 34.2 kg/m^2 or greater) exhibited strong positive associations between increasing levels of total PCBs and breast cancer. Conversely, the thinnest African-American women showed a stronger positive association for DDE. ORs did not differ strongly based upon WHR. Thus, our results suggest that the degree of obesity (rather than the distribution of body fat) modifies the association of organochlorines and breast cancer. A potential explanation for our findings with DDE may be found in a recent letter by Wolff and Anderson (32). According to a pharmacokinetic model presented by these authors, individuals with low BMI had higher tissue concentrations of DDE in the past (one to two decades earlier) compared with obese women. In the present study, BMI was based upon current measurements. However, current BMI was highly correlated with self-reported levels of obesity in the past among women in the CBCS (33). Our results for PCBs are more difficult to explain. It may be that for exposures that are on-going, such as PCBs, obese persons maintain higher tissue concentrations because of slower elimination in comparison with thin persons. Data on the relationship of BMI and organochlorine levels in blood are needed from prospective studies that measure intake and absorption of these compounds. Such information would be useful for assessing the potential health effects of PCBs and other fat-soluble chemicals.

In our study, women who lived or worked on farms exhibited ORs for DDE and breast cancer similar to those of women who never farmed. Among women who farmed, we did not observe a stronger association for those with potential pesticide exposure compared with women without such exposure. We stratified on farming history and pesticide exposure to address the possibility that plasma DDE levels could reflect exposure to DDT by a more direct route among farming women, *e.g.*, via aerosols or dermal contact. Our analyses are limited by the small number of women with reported pesticide exposure and the fact that we did not collect detailed information regarding pesticide exposure among non-farming women.

We did not observe evidence for a combined effect of DDE and total PCBs, in agreement with Hunter *et al.* (8) and Hoyer *et al.* (9). In our study, ORs for high chlorination PCB congeners were elevated compared with low and moderate chlorination PCB congeners. These results are in contrast to the findings of Moysich *et al.* (24), who reported stronger associations for low chlorination PCBs congeners, compared with moderate or high chlorination PCBs. Analysis of specific congeners is complicated by incomplete knowledge regarding biological activity (26), relatively short half-life for many congeners (24), and strong correlations among congeners in human blood samples (34). We did not observe stronger associations for estrogen receptor-positive breast cancer, in agreement with Hunter *et al.* (8) but in contrast to DeWailly *et al.* (35) and Liljegren *et al.* (36). The latter authors reported stronger associations for DDE and some PCB congeners for estrogen receptor-positive compared with estrogen receptor-negative breast cancer.

Our study has the advantage of including large numbers of African-American women and women from the rural South. Only one previous study examined organochlorines in relation to breast cancer in African-American women (7). In the past, levels of DDE in serum and breast milk from women residing in the South ranked among the highest in the United States (31, 37). Only the study of Moysich *et al.* (24) reported residential history. Although the study was conducted in upstate New York, only 16% of controls reported living in a rural area. In the CBCS, 48% of controls lived or worked on farms.

One limitation of our study is the potential for selection bias, given the lower response proportion in controls compared with cases. In a previous analysis (18), we determined that participants who completed a full interview and provided a blood sample were similar to women who consented to a brief telephone interview, based upon comparison of a variety of breast cancer risk factors. We were unable to compare organochlorine levels in responders and nonresponders; however, the distribution of DDE and PCB values among controls in our study was similar to recent surveys (reviewed in Ref. 2). An additional limitation is the fact that we used blood samples drawn after the diagnosis of breast cancer in cases. A recent study (38) suggested that treatment for breast cancer may alter blood levels of organochlorines. To address the possibility of disease and/or treatment-related effects, we stratified by history of weight loss or gain, as well as stage of disease, and did not observe any differences in ORs for DDE or total PCBs. An additional limitation of our study is the fact that we had incomplete information on socioeconomic status. Women of higher socioeconomic status are often reported to have higher risk of breast cancer (reviewed in Ref. 39). In the CBCS, we obtained information on yearly household income and level of education. Education was not associated with breast cancer, whereas increasing income showed a slight inverse association (data not shown). Data collected from partial interviews suggest that controls with lower income were less likely to participate in the CBCS (18). This may have biased the income distribution upward in controls relative to cases, leading to an inverse association between income and breast cancer. Increasing income showed strong inverse correlations with DDE and total PCB levels among controls in the CBCS, in agreement with surveys of other populations (29, 31). Thus, income exhibited characteristics of a potential confounding variable. Controlling for income resulted in a slight change in ORs but probably provided only partial adjustment for the confounding effects of socioeconomic status. It is possible that after adjustment for better measures of socioeconomic status, ORs for DDE and total PCBs would be elevated further (Tables 4–6). Finally, although we had adequate power to conduct analyses among subgroups of women, our findings should be interpreted with caution pending evaluation in other studies.

On the basis of our study, combined with previous studies, it appears that DDE and PCBs are unlikely to play a major role in increasing the risk of breast cancer. Some subgroups of women exhibited stronger effects, but these effects remained quite weak in absolute terms. One exception is the strong association in our study between total PCBs and breast cancer among women with high BMI. Further investigation of the relationship between obesity and susceptibility to the adverse health effects of PCBs and other fat-soluble compounds is warranted, particularly among African-American women. Our

[8] M. Wolff, personal communication, 1997.

results suggest that race, parity, breastfeeding, obesity, and socioeconomic status may influence the relationship between organochlorine levels and breast cancer risk. Differing distributions of these variables across studies may help to explain some of the inconsistencies in results.

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Dichlorodiphenyldichloroethene, Polychlorinated Biphenyls, and Breast Cancer among African-American and White Women in North Carolina

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