Risk of Breast Cancer and Organochlorine Exposure[1]

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Abstract

A prospective investigation of breast cancer and organochlorine (OC) exposures was undertaken in the New York University Women's Health Study. Cases ($n = 148$) and individually matched controls ($n = 295$) were identified among women whose blood had been obtained 6 months or more prior to breast cancer diagnosis. In addition, among 84 cases and 196 controls, two or more consecutive annual blood samples were available to estimate half-lives of 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethene (DDE) and polychlorinated biphenyls (PCBs). Cases and controls had similar levels of DDE (geometric mean, 6.95 *versus* 7.27 ng/ml; lipid-adjusted geometric mean, 977 *versus* 1100 ng/g) and PCBs (5.04 *versus* 4.97 ng/ml; lipid-adjusted geometric mean, 683 *versus* 663 ng/g). These differences remained nonsignificant when estrogen receptor status of tumors was considered. DDE and PCB half-lives did not differ in case *versus* control patients. In control patients, DDE and PCB half-lives were strongly correlated ($r_s = 0.71$), and the half-life of DDE (but not that of PCB) was inversely correlated with body mass index (BMI), yet the blood serum levels of PCB (but not those of DDE) were correlated with BMI. We conclude that there is no evidence for an association of breast cancer risk with DDE or PCB levels in blood (based on samples collected during the period 1987–1992) nor with their elimination half-lives. However, changes in DDE and PCBs over time are influenced by metabolism, BMI, and current OC exposures, and each may affect interpretation of OC levels in risk assessment models.

Introduction

Following early reports of an association between DDT[4] exposure and breast cancer risk (1, 2), there have been a number of additional studies that failed to confirm these observations (3–5). In these investigations, DDT and PCB residues have been measured in blood or adipose tissue collected prospectively (1–15 years prior to cancer diagnosis) or near the time of diagnosis. A few recent reports suggest that lactation, genetic polymorphisms, or weight loss may affect the association of OCs with breast cancer (6). Other reports of cancer include positive associations of PCBs with non-Hodgkin's lymphoma (7) but not with endometrial cancer (8). Effects of OC exposures have also been linked with neuroendocrine-related health outcomes including early puberty and neurological impairment (9, 10).

Therefore, interest in human health effects of exposures to OCs continues, although the use of DDT and PCBs in developed countries has been banned for more than 20 years. Opportunities for exposures continue, inasmuch as DDT and other OCs are still widely used in developing countries. Another reason for continuing concern is that DDE and PCBs bioaccumulate in the environment and in the body. PCBs in North America still persist in significant amounts in freshwater fish and in estuarial sediments. However, during the past two decades, since the cessation of DDT and PCB use, levels in United States, Canadian, and European populations have declined (11). Nevertheless, there are very few reports that have measured elimination rates in individuals, and indeed, some reports have suggested that PCB levels are constant or increasing (12).

The fact that OC levels are variable over time is relevant to the issue of timing of hormonal and xenobiotic exposures. Timing of exposures has come to be recognized as an important aspect of their toxicological effects, including cancer risk (13), yet a single measurement of OCs has been assumed to be a reliable estimate of historical exposure because of their persistence and their cumulative properties. Little information is available on individual changes in OC levels over time. Two small studies have suggested that OC levels in blood are steady over the course of a few months (14, 15). In our population, we have shown that the reliability is good between sequential measurements of estrogen taken over several years (16).

We found an elevated risk for breast cancer and DDE levels in an earlier report on 58 women with breast cancer from New York City Women's Health Study who were diagnosed within 6 months of entry into the cohort (prevalent cases) compared with their 171 individually matched controls (1). In the current study, we have investigated levels of DDE and PCBs among incident breast cancer cases (diagnosed 6 months or more after enrollment in the study) and controls in this prospective cohort. Because some of these women had provided two or more sequential annual blood specimens, we were also able to evaluate persistence of these OCs in the body.

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[4] The abbreviations used are: DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; dichlorodiphenyltrichloroethane; BMI, body mass index; CI, confidence interval; DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethene; ER, estrogen receptor; GM, geometric mean; NYU, New York University; OC, organochlorine; OR, odds ratio; PCB, polychlorinated biphenyl.

Materials and Methods

Study subjects were participants in the NYU Women's Health Study, a prospective cohort study of hormonal and environmental factors and cancer in women (17). Between 1985 and 1991, the NYU Women's Health Study enrolled 14,275 healthy women ages 34–65 years at the Guttman Breast Cancer Institute, a breast cancer screening center in New York City. Women who had taken hormonal medications or been pregnant in the 6 months preceding their visit were not eligible. After written informed consent was obtained, demographic, medical, anthropometric, reproductive, and dietary data were collected through self-administered questionnaires. Thirty ml of nonfasting peripheral venous blood were drawn prior to breast examination. After centrifugation, serum samples were immediately stored at −80°C for subsequent biochemical analyses. Up to 1991, women who returned for annual breast cancer screening were invited to contribute additional blood donations. Approximately 25% of the participants contributed three or more blood donations.

Breast cancer cases were identified through active follow-up of the cohort by mailed questionnaires every 2 years and telephone interviews for nonrespondents, as well as record linkage with state cancer registries in New York, New Jersey, and Connecticut and with the National Death Index. A capture-recapture analysis estimated that the ascertainment rate for breast cancer in our cohort is 95% (18). Medical and pathology reports were obtained to confirm diagnosis.

Incident case subjects were included in an ongoing case-control study of sex hormones and breast cancer nested within the cohort, as described previously (17). For each case subject, controls were selected at random from the risk set of women who were alive and free of disease at the time of diagnosis of the case and who matched the case on menopausal status and age at enrollment (±6 months), number and dates of blood donations (±3 months), and day of the menstrual cycle for premenopausal women. Four controls were selected for each premenopausal case and two controls for each postmenopausal case.

Cases diagnosed up to October 1, 1994, and with a lag time of 6 months or more between blood donation and diagnosis were eligible for the present study on the association between serum levels of OCs and risk of breast cancer. Initially, participants were eligible irrespective of the number of blood donations, and either two or three yearly serum samples were assayed for OCs in cases and all of their individually matched controls. However, because we were also interested in assessing OC half-lives, after the first year of serum analyses, we decided that only cases with at least three yearly blood donations would be eligible for this study. In addition, we decided to reduce the number of controls to one per case. Therefore, one control was selected at random from the two (for postmenopausal case subjects) and from the four (for premenopausal case subjects) that were included in the study of sex hormones. As a result of these inclusion criteria, 148 cancer patients and 295 individually matched controls were selected for this study. Analyses involving lipid adjustment were conducted on the 110 cases and 213 controls for whom serum lipid measurements were available. OC half-lives were calculated for the 84 cases and 196 controls who had contributed more than one blood donation.

The method for determination of DDE and PCBs, including the quality control protocols, was the same as that described previously (19). Limits of detection were less than 0.5 ng/ml for DDE and less than 1 ng/ml for PCBs based on three times the SD of the levels found in the lowest quality control serum pools (average of 0.3–0.7 ng/ml DDE, 1 ng/ml PCB) over the course of the analyses ($n = 50$). For the two higher level pools (DDE = 9 and 17 ng/ml, PCB = 5 and 9 ng/ml; $n = 53$ and 49, respectively) overall CVs were <10%. Serum lipids were determined by a commercial laboratory. The laboratory was blind with respect to any information concerning study subjects; all individually matched and multiple specimens from the same individual were analyzed in the same laboratory batch.

DDE and PCB values were adjusted for total serum lipids using the method of Akins *et al.* (20) Lipid adjustment was also performed using the linear regression method described by Hunter *et al.* (3). Because the lipid-adjusted values calculated with the two different methods were very highly correlated for both DDE and PCB (Spearman correlation coefficients > 0.97), only results using the Akins method are presented.

Crude and lipid-adjusted DDE and PCB values were log transformed to reduce departures from the normal distribution. Mixed effects regression models were used to test for differences in continuous variables between case and control subjects, taking into account the matching design. The Kruskal-Wallis test was used to test for differences in the distribution of continuous risk factors for breast cancer within tertiles of DDE and PCB levels among the controls. For categorical variables, the χ^2 test or χ^2 test for trend was used.

DDE and PCB half-lives were calculated for women who contributed more than one blood donation, assuming that the rate of elimination from the body may be described by the one-compartment exponential decay model (21). For each woman, the half-life was therefore calculated by dividing ln (2) by the slope of the least squares regression of the logarithm of the OC levels *versus* time. Not all persons showed a decline in DDE and PCBs, which produced indeterminate or very long half-lives. Following the recommendation of Phillips (22), some analyses were conducted after recoding these values as infinite.

ORs were computed using conditional logistic regression analysis with DDE and PCB levels as both quartiles and continuous variables. Percentiles were based on the frequency distribution of controls. Some analyses were also conducted comparing women in the highest category of both DDE and PCB levels with those in the lower levels. To have sufficient numbers of participants in all exposure levels, these analyses were conducted using tertiles rather than quartiles. Adjustment was made for potential confounders (other than the matching criteria); those included age at menarche, number of full-term pregnancies, age at first full-term pregnancy, first-degree family history of breast cancer, months of lactation, height, BMI, and an interaction term for BMI and menopausal status (menopausal status was not included in the model because it was one of the matching criteria). Effect modification by menopausal status, lactation history, and lag time between exposure measurement and diagnosis was explored by including interaction terms between these variables and OC levels in the logistic model, as well as by conducting stratified analyses. Because of the relatively small sample size of our study, OC levels were included as continuous variables in these analyses. All reported *P*s are two-sided.

Results

Case and control subjects are described in Table 1. Two traditional risk factors, nulliparity and family history of breast cancer, were found to be significantly associated with breast cancer risk. Case subjects tended to have an older age at first pregnancy than controls, but this difference was not statistically

Table 1 Description of 148 breast cancer cases and 295 individually matched controls enrolled in the NYU Women's Health Study, New York City, 1987–1992

	Cases (n = 148)	Controls (n = 295)
Caucasian (%)	86.3	81.3
Age at first blood donation, median (range)	56.5 (34.1–65.8)[a]	54.0 (33.9–65.8)
Age at diagnosis, median (range)	60.3 (35.5–71.4)	
Postmenopausal (%)	63.5[a]	55.9
Age at menarche, median (range)	12 (9–16)	13 (8–17)
No. of full-term pregnancies (%)[b]		
0 (n = 64 cases, 106 controls)	43.2	35.9
1 (n = 20 cases, 34 controls)	13.5	11.5
>1 (n = 64 cases, 155 controls)	43.2	52.5
Age at first full-term pregnancy, median (range)	26.3 (16–41)	24.0 (16–43)
Ever breast feeding (%)[c]	33.3	36.0
Family history of breast cancer (%)[b]	31.5	19.8
Height in cm, median (range)	162.6 (147.3–177.8)	162.6 (149.9–182.9)
Weight in kg, median (range)	63.5 (40.8–122.5)	63.1 (39.5–124.7)
BMI (kg/m^2)		
Premenopausal women, median (range)[b]	22.5 (17.6–32.9)	23.1 (16.9–43.1)
Postmenopausal women, median (range)	25.5 (16.9–43.6)	24.1 (17.0–46.5)

[a] Apparent differences between cases and controls arise from variable number of controls, with 2.4 controls/premenopausal case and 1.8 controls/postmenopausal case; see Patients and Methods.
[b] $P < 0.05$.
[c] Among parous women, 84 cases and 189 controls.

Table 2 DDE and PCB levels at enrollment in serum for 148 breast cancer cases and 295 individually matched controls (NYU Women's Health Study 1987–1992)

Cases and controls did not have significantly different levels of any variables, using a mixed-effects regression model, controlling for the pair-matching variables.

	Cases			Controls		
	GM	GSD[a]	n	GM	GSD	n
DDE (ng/ml)	6.95	2.46	148	7.27	2.39	295
PCBs (ng/ml)	5.04	1.65	148	4.97	1.74	295
DDE, lipid adjusted	977	2.46	110	1097	2.29	213
PCBs, lipid adjusted (ng/g)	683	1.64	110	663	1.62	213
Cholesterol (g/liter)	2.26	1.21	110	2.23	1.24	213
Triglycerides (g/liter)	1.15	1.67	110	1.03	1.70	213
Total lipids (g/liter)[a]	7.01	1.23	110	6.83	1.25	213

[a] GSD, geometric SD.
[b] Computed as suggested by Akins *et al.* (20).

significant. Age at menarche and duration of lactation were similar in cases and controls. Case subjects had lower BMI than controls in premenopausal women ($P < 0.05$), consistent with other studies (23), whereas the reverse was true among postmenopausal women (>0.10). There were no major differences in known risk factors between participants for whom half-life estimates were available and others.

Levels of DDE and PCBs (lipid adjusted or not adjusted) were similar in cases and controls, in the overall group as well as in the smaller group for whom lipid measurements were available (Table 2). Cholesterol and triglyceride levels, used to compute serum lipids, were also similar. We examined the relationship of several variables with respect to tertiles of serum DDE and PCB levels among control subjects (Table 3). Age increased significantly across both the DDE and PCB tertiles. Family history of breast cancer was more prevalent in the lowest exposure tertiles, which we attribute to the younger age of women in this tertile. Younger women who had a family history of breast cancer may have been more likely to seek screening for breast cancer in the setting in which the cohort was enrolled. BMI was lower in the upper PCB tertile.

There was no evidence of a positive association between DDE serum levels and risk of breast cancer (Table 4). For PCBs, ORs were elevated in the three upper quartiles relative to the lowest one. However, none of the ORs was statistically significant, and there was no evidence of a trend. In addition, there was no association between PCB on the continuous scale with breast cancer risk. Finally, women for whom both DDE and PCB levels were in the highest tertiles did not have an elevated risk for breast cancer when compared to women in the lowest tertiles for both OCs (crude OR = 1.14, 95% CI = 0.49–2.66; adjusted OR = 1.60, 95% CI = 0.61–4.18; data not shown). There was no evidence of effect modification by menopausal status or lactation history (data not shown).

ER status was available for 89 women (Table 5). Levels of DDE and PCBs were higher in ER-negative cases than in their controls, but these differences were not statistically significant. Levels of DDE and PCB were very similar in the ER-positive cases and their controls. In addition, there were no statistically significant differences in OC levels between ER+ and ER– cases.

The first blood donation occurred in 1985–1986 for 90% of the study subjects and in 1987–1990 for the remaining 10%. Eighty-four case and 196 control subjects contributed two or more sequential blood specimens, with a median interval between first and last donations of 25.4 months (range, 5.8–70.6 months). DDE levels declined approximately 0.8 ng/ml on average over this time interval. The GM was 7.2 ng/ml at the first donation and 6.4 ng/ml at the last (n = 225). PCBs

Table 3 Risk factors (medians) according to tertiles of serum DDE and PCB levels among 213 control patients (NYU Women's Health Study 1987–1992)

Risk factors (medians)	Tertiles of lipid-adjusted serum DDE levels (ng/g)			p^a
	<803	803–1587	>1587	
Age	49.6	50.8	50.4	0.04
Age at menarche	13	13	13	0.71
Live births	1	2	1	0.38
Age at first birth	25	24	24	0.45
Ever lactated, parous only	34.1%	41.7%	38.3%	0.71
Height (cm)	160	160	162	0.78
Weight (kg)	60.6	62.6	63.5	0.13
BMI (kg/m^2)	23.1	24.0	24.8	0.24
Family history	25.0%	21.9%	12.3%	0.09
Serum lipids (g/liter)	6.57	6.83	6.99	0.58
	Tertiles of lipid-adjusted serum PCB levels (ng/g)			
	<528	528–773	>773	
Age	44.3	49.8	51.6	<0.001
Age at menarche	13	13	13	0.40
Live births	1	2	2	0.10
Age at first birth	23	25	24	0.49
Ever lactated, parous only	41.0%	36.2%	38.0%	0.79
Height (cm)	160	160	163	0.14
Weight (kg)	63.1	62.6	62.6	0.44
BMI (kg/m^2)	23.8	24.7	22.9	0.06
Family history	28.3%	17.7%	14.3%	0.05
Serum lipids (g/liter)	6.52	6.93	6.94	0.38

[a] Kruskal-Wallis test for continuous variables, χ^2 test for trend for categorical variables.

Table 4 Risk for breast cancer by quartiles of serum DDE and PCB levels

Quartile	Cutoff (ng/g lipid)	Cases (*n*)	Controls (*n*)	Unadjusted OR	Adjusted OR[a]	95% CI
DDE						
1	<664	31	53	1.00	1.00	
2	664–1172	30	53	0.90	0.81	(0.35–1.87)
3	1173–1934	24	54	0.72	0.60	(0.26–1.38)
4	>1934	25	53	0.73	1.30	(0.51–3.35)
P, trend				0.26	0.99	
PCB						
1	<478	21	53	1.00	1.00	
2	478–638	30	53	1.42	1.55	(0.59–4.12)
3	639–876	26	54	1.30	1.23	(0.49–3.08)
4	>876	33	53	1.65	2.02	(0.76–5.37)
P, trend				0.26	0.23	

[a] Adjusted for age at menarche, number of full-term pregnancies, age at first full-term pregnancy, family history of breast cancer, lifetime history of lactation, $\ln_e$ (height), $\ln_e$ (body mass index), $\ln_e$ (BMI)-menopausal status at blood donation interaction. Data are presented for 110 cases and 213 controls with lipid-adjusted DDE and PCB values.

decreased only slightly (GM, 5.0 *versus* 4.7). Serum levels were highly correlated between visits 1 and 2 (Spearman correlation coefficient, 0.93 for DDE and 0.81 for PCB) and between visits 1 and 3 (Spearman correlation coefficient, 0.95 for DDE and 0.83 for PCB).

We computed the half-life of DDE and PCBs for all women who contributed repeated samples. Indeterminate (*i.e.*, mathematically negative) half-lives were observed among participants whose later measurements were greater than or equal to their first measurement. For DDE, the half-life was indeterminate among 21 of 84 cases (25%) and in 40 of 140 controls (29%). The PCB half-life was indeterminate for 35 of 84 cases (42%) and 68 of 140 controls (49%). The half-lives of DDE and PCBs were almost identical among cases and controls who had positive values. The median half-life of DDE in the control subjects was 8.6 years, and that of PCB was 11.2 years. If indeterminate half-lives were assumed to be infinite (22), the median half-life of DDE was 13.0 years among cases and 15.0 years among controls (not significant); median half-life of PCB was 37 years among cases and indeterminate among controls. Risk for breast cancer was not associated with DDE or PCB half-life (data not shown).

We examined exposure-related information with respect to half-life among control patients with measurable OC elimination half-lives using age-adjusted Spearman correlations (Table 6). Half-lives of DDE and PCB were strongly correlated ($r = 0.71$; $n = 72$). DDE and PCB levels were moderately correlated ($r = 0.43$; $n = 72$). DDE levels in serum were weakly correlated with the DDE serum half-lives ($r = 0.20$; $n = 100$). DDE half-life (but not DDE level) was positively correlated with BMI. Also, the median BMI was higher in the group with indeterminate DDE half-life than in the group with positive half-life (26.0 *versus* 23.3 kg/m^2; $P < 0.01$, Wilcoxon test). PCB level (but not PCB half-life)

Table 5 Serum DDE and PCB levels with respect to ER status of breast tumors

No statistically significant differences between cases and controls, using mixed effects models adjusting for matching criteria. Data are presented for 89 cases and their pair-matched controls (lipid unadjusted) and 75 cases and their 125 controls (lipid adjusted). Findings were similar for the same 75 cases (lipid unadjusted); therefore, we include the larger number.

	ER-negative tumors				ER-positive tumors			
	Cases		Controls		Cases		Controls	
	GM (GSD[a])	*n*	GM (GSD)	*n*	GM (GSD)	*n*	GM (GSD)	*n*
DDE (ng/ml)	8.56 (1.87)	32	6.42 (2.36)	64	7.04 (2.51)	57	7.26 (2.21)	111
PCB (ng/ml)	5.46 (1.38)	32	4.95 (1.64)	64	4.96 (1.52)	57	5.00 (1.73)	111
DDE (ng/g lipid)	1300 (1.79)	23	1040 (2.14)	42	950 (2.41)	44	1040 (2.16)	83
PCB (ng/g lipid)	770 (1.43)	23	650 (1.52)	42	670 (1.50)	44	660 (1.65)	83

[a] GSD, geometric SD.

Table 6 Age-adjusted Spearman correlation coefficients for OC levels and half-lives and BMI in controls

	PCB (ng/g lipid)	DDE half-life	PCB half-life	BMI
DDE (ng/g lipid)	0.43[a]	0.20[b]	0.33[c]	−0.01
PCB (ng/g lipid)		0.18	0.08	−0.29[a]
DDE half-life			0.71[a]	0.26[c]
PCB half-life				0.02

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

was inversely correlated with BMI. We did not find any significant associations between duration of lactation and OC levels or OC half-lives. However, only 35.2% of our participants had a history of breastfeeding, and for 88% of those, breastfeeding was limited to 6 months or less.

Discussion

We found no association of DDE, PCBs, or their half-lives with risk of breast cancer in this cohort study. In contrast, we had earlier observed higher risk for DDE and nonsignificant elevated risk for PCB exposures among 58 cases and 171 controls in this same cohort who were diagnosed within 1 year after blood donation (1). We have considered several possible explanations for the difference between this and the earlier findings in the same cohort. We cannot exclude the possibility that the earlier finding was a chance observation. Other possible explanations were not borne out in our analyses. Average OC levels in the two studies were quite similar. Lipid adjustment for OC level was not done in the previous study, but it did not alter the results of the current investigation. This report includes primarily participants who contributed more than one blood donation prior to diagnosis. This is not expected to introduce bias in the assessment of the association of OC levels with breast cancer risk because controls were matched to cases on exact number of blood donations. These patients experienced a longer average interval between exposure measurement and diagnosis (2.6 years) than in the previous report (<6 months), but we found no evidence of effect modification by lag time between exposure measurement and diagnosis in this study. Elimination rates (half-lives) were similar for cases and controls, although our data are relevant only during the interval between first blood collection and diagnosis. It is possible that absorption/elimination rates at an earlier point in time were not similar for cases and controls, but we could not evaluate this possibility. Participants were largely Caucasian (83%), precluding our ability to examine race as an effect modifier. Because of the relatively small sample size of our study, we did not attempt to examine other effect modifiers, such as gene-environment interactions.

Our results add to a growing body of evidence suggesting that current, low levels of DDE and PCBs are weakly, if at all, associated with risk for breast cancer. There have been eight studies that included more than 100 cases of breast cancer during the past 5 years (3, 5, 6, 24–28). None found significant elevated risk associated with OC exposures alone. Of six cohort studies with blood collected before breast cancer diagnosis (1, 3–5, 24, 25), five found relative risks below 1 for DDE (one was statistically significant), and four had relative risks less than 1 for PCBs.

One recent report found a modest increase in risk with dieldrin but not with DDT or PCB levels among women whose blood had been obtained in 1976, as long as 17 years prior to diagnosis (24). In another study, increased risk was found among women with higher levels of PCBs if they had never lactated (6) or if they possessed the variant *CYP1A1* allele (29). However, these findings have not yet been widely duplicated. Clearly, large sample sizes will be needed to detect with confidence interactions between OC exposures and modifying factors.

Our data on relationships among serum OC levels, their half-lives, BMI, and age offer insight into the source and disposition of OCs in humans (Tables 3 and 6). The correlations of PCB and DDE with each other and with age (as seen in many previous studies) suggest that their absorption derives from common dietary sources over a long period of time. This evidence has led to the view that, because OCs are persistent and cumulative, a single measure is a biomarker that represents lifetime accumulation. However, other recent findings indicate that changes in OC levels over time may complicate interpretation of persistent body burden measures in epidemiological studies (4, 30)

Our observation that levels of PCBs were higher among leaner women is consistent with a simple pharmacokinetic model of uptake, implying concurrent exposure to PCBs that may be incremental to cumulative past exposures (31, 32). A simple model predicts just such a *negative* correlation between OC levels and BMI during a period when exposures are ongoing, as long as absorption (*a*) exceeds elimination rate and (*b*) is comparable across the population. [The rationale is mathematical: the body burden (*e.g.*, 20 mg DDT) is divided by the reservoir of adipose tissue (*e.g.*, 10 kg, giving 2 mg/kg or 2 parts per million). A larger adipose tissue reservoir would yield a lower concentration, *e.g.*, 20 mg/20 kg = 1 ppm.] Dorgan *et*

al. (25) also found a negative association between PCBs and BMI, whereas Hunter *et al.* (3) found no relationship.

Also consistent with the idea of concurrent PCB exposures, we found that PCB half-life was indeterminate in approximately one-half of our women (103 of 224) and that PCB half-life did not vary by BMI. Thus, if absorption of PCB-contaminated foods continues today (albeit lower than in earlier years), a falsely long or indeterminate (mathematically negative) half-life will be seen. An alternative explanation for our findings is that the half-life of PCBs be very long (>25 years). In that case, our interval of measurement (average, 2.5 years) is too short to obtain an accurate estimate of half-life; as demonstrated by Phillips *et al.* (25), to obtain a good estimate of half-life, the interval (in years) between two measurements must be similar to the half-life (in years). A very long half-life seems unlikely, because other studies, particularly of highly exposed occupational groups, have found a PCB half-life in the range 5–25 years, depending on specific congener make-up of the PCB mixtures (33). Longer half-lives may be expected for PCB levels that do not include the lower-chlorinated, more readily metabolized congeners. Moreover, whereas PCB half-life in our study was not associated with BMI, and the half-life for DDE was inversely correlated with BMI, PCB-DDE half-lives were strongly correlated. Taken together with data on the DDE half-life described below, this evidence suggests that individual metabolism rates of persistent chlorinated aromatic compounds are the same.

In contrast to PCBs, DDE levels were not associated with BMI in our study and DDE half-life was shorter among leaner women. Lopez-Carrillo *et al.* (26) also found no association between DDE and BMI, but other recent studies of OCs have found a *positive* correlation between BMI and DDE or dieldrin levels in serum or adipose tissue (3, 25, 27). Schildkraut *et al.* (30) examined DDE levels in relation to extremes of BMI and found a significant positive association of DDE with BMI and with African-American ethnicity; they found negative associations with weight loss and weight gain. Overall, these results are consistent with a proposed model in which (*a*) at the time of blood donation, more than one elimination half-life of DDE had elapsed since any prior significant DDE uptake, (*b*) less than three elimination half-lives had elapsed (because three half-lives would eliminate approximately 90% of the body burden (½ × ½ × ½), and (*c*) the half-life among more obese women was longer than half-life among leaner women (31, 32).

Our data on half-life of OCs provide additional knowledge about lifetime levels of OCs. This is to our knowledge the first report of half-life data on more than two serial samples in a normal population and is the first such report in a breast cancer study. Earlier studies of half-life had two measures (31, 32) or were of too short a duration to establish half-life (14, 15). The median half lives of DDE and PCBs in our study (7–11 years) are similar to reported half-lives of 6–15 years in other studies of OCs (dieldrin and 2,3,7,8-tetrachlorodibenzodioxin but not PCB) in North America, showing a dramatic decline over the past 40 years (11). Assembled data from several breast cancer studies also reflect the declining trend in OC levels in the United States and elsewhere (Table 7). Levels of DDE in blood of California women in the late 1960s were more than 4 times higher than most recent reports and approximately twice the levels obtained in a study of women in 1982 from Missouri (Table 7). Recent studies from different laboratories and from different countries show similar levels of DDE, within a factor of 2 (Table 7). Moreover, the half-life of DDE estimated from these cross-sectional data is 11 years, a rate of decline similar to that found in other reports and in the current study. However, average PCB levels shown in these varied reports over the past 30 years are all within 2–10 ppb and show no decline, consistent with other investigations (12, 34). Compared to these findings, higher OC pesticide levels can be expected in countries where there is continued agricultural use (35, 36).

Table 7 DDE and PCB levels among control women in reported studies of breast or uterine cancer[a]

Place and approximate yr. of blood collection (Ref.)	DDE		PCB	
	ng/ml	Lipid basis	ng/ml	ng/g, lipid basis
CA, 1967 (4)	43	(6000)	4.8	(670)
MD, 1974 (5)	11	1670	4.2	607
MO, 1982 (25)	(17)	2400	(2.6)	350
CT, 1987 (2)	(11)	1500	(10)	1400
NY, 1987 (1)	7.7	(1100)	6.7	(940)
Buffalo, NY, 1988 (6)	11	(1500)	4.1	(570)
MD, 1989 (5)	7.0	1180	1.7	270
NY, 1987 (this paper)	7.3	1100	5.0	660
United States, 1989 (8)	(9.7)	1360	(2.5)	350
United States, 1990 (3)	4.7	(660)	4.7	(660)
CT, 1996 (28)	(5.6)	784		
Europe, 1976 (24)	9.5	1330	7.8	1100
Europe, 1992 (27)	(11)	1500		
Mexico, 1995 (26)	2.9	419		
Estimated half-life[b]	11.7 yr	11.7 yr	NS[c]	NS
Estimated half-life (this study)		13 yr[d]		NS[d]
Half-life reported elsewhere (11)	6 yr		NS	

[a] Values in parentheses are estimated from lipid or wet weight basis using a factor of adipose/140 = serum.
[b] 11.0 yr using only United States data for either wet- or lipid-based values; half-lives were estimated using the years in the left-hand column and are not age adjusted.
[c] NS, no downward trend in values over time.
[d] For all data; for only those women with downward trend (positive half-life), the estimate for DDE was 8.6 and PCB 11.2 yr.

Inconsistent associations between BMI and OCs have been reported. It is possible that the sampling frames for OC measures differ among various epidemiological studies. In addition, these effects of sample timing and OC metabolism may partly explain different risks detected in different populations regarding OCs and breast cancer risk. For example, Dorgan *et al.* (25) reported lower risk for PCB exposures among women whose blood was collected further from diagnosis, but higher risk if blood was taken closer to diagnosis, and Helzlsouer *et al.* (5) found lower risks for PCBs in their more recent cohort (1989) compared with an earlier cohort (1976).

In summary, our results do not support a relationship between DDE or PCB levels and breast cancer in a prospective cohort of New York City women. Also, changes in OC levels over several years were similar for cases and controls, suggesting that OC elimination rates may not influence breast cancer risk. Correlations among DDE, PCBs, and age imply similar long-term accumulation of these residues by most women, but differences in correlations among DDE, PCBs, and BMI and their half-lives denote different intervals of exposure and rates of elimination across the population, whereas the strong correlation of DDE half-life with PCB half-life indicates similar individual rates of metabolism. Thus, a single OC measurement may not accurately represent the past exposure of a population. BMI may be a significant factor, causing marked disparities in circulating OC levels between lean and obese women and leading to interindividual variations that are not proportional over time. Therefore, although a measurement of persistent OC levels in the body may reflect lifetime exposure, these measures may not portray OC levels at a time that is relevant to cancer.

After further research into this question in other populations, it may be possible to examine the association between lipid-adjusted OC levels and BMI to obtain clues to the history of exposures in a sample observed at only one point in time.

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References

1. Wolff, M. S., Toniolo, P., Lee, E., Rivera, M., and Dubin, N. Blood levels of organochlorine residues and risk of breast cancer. J. Natl. Cancer Inst., *85:* 648–652, 1993.

2. Falck, F. Y., Ricci, A., Jr., Wolff, M. S., Godbold, J., and Deckers, J. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch. Environ. Health, *47:* 143–146, 1992.

3. Hunter, D. J., Hankinson, S., Laden, F., Colditz, G. A., Manson, J. E., Willett, W. C., Speizer, F. E., and Wolff, M. S. Plasma organochlorine levels and risk of breast cancer in a prospective study. N. Engl. J. Med., *337:* 1253–1258, 1997.

4. Krieger, N., Wolff, M. S., Hiatt, R. A., Rivera, M., Vogelman, J., and Orentreich, N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J. Natl. Cancer Inst., *86:* 589–599, 1994.

5. Helzlsouer, K. J., Alberg, A. J., Huang, H. Y., Hoffman, S. C., Strickland, P. T., Brock, J. W., Burse, V. W., Needham, L. L., Bell, D. A., Lavigne, J. A., Yager, J. D., and Comstock, G. W. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol. Biomarkers Prev., *8:* 525–532, 1999.

6. Moysich, K. B., Ambrosone, C. B., Vena, J. E., Shields, P. G., Mendola, P., Kostyniak, P., Greizerstein, H., Graham, S., Marshall, J. R., Schisterman, E. F., and Freudenheim, J. L. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prev., *7:* 181–188, 1998.

7. Rothman, N., Cantor, K. P., Blair, A., Bush, D., Brock, J. W., Helzlsouer, K., Sahm, S. H., Needham, L. L., Pearson, G. R., Hoover, R. N., Comstock, G. W., and Strickland, P. T. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet, *350:* 240–244, 1997.

8. Sturgeon, S. R., Brock, J. W., Potischman, N., Needham, L. L., Rothman, N., Brinton, L. A., and Hoover, R. N. Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). Cancer Causes Control, *9:* 417–424, 1998.

9. Gladen, B. C., Rogan, W. J., and Ragan, N. B. Growth and development at puberty and perinatal exposure to polychlorinated biphenyls (PCBs) and DDE. Organohalogen Comp., *30:* 215–216, 1996.

10. Jacobson, J. L., and Jacobson, S. W. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. New Eng. J. Med., *335:* 783–780, 1996.

11. Wolff, M. S. Organochlorine half-lives (Letter). Arch. Environ. Contam. Toxicol., *36:* 504, 1999.

12. Robinson, P. E., Mack, G. A., Remmers, J., Levy, R., and Mohadjer, L. Trends of PCB, hexachlorobenzene, and b-benzene hexachloride levels in the adipose tissue of the U. S. population. Environ. Res., *53:* 175–192, 1990.

13. Colditz, G. A., and Frazier, A. L. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol. Biomarkers Prev., *4:* 567–571, 1995.

14. Gammon, M. D., Wolff, M. S., Neugut, A. I., Terry, M. B., Britton, J. A., Greenebaum, E., Hibshoosh, H., Levin, B., Wang, Q., and Santella, R. M. Treatment for breast cancer and blood levels of chlorinated hydrocarbons. Cancer Epidemiol. Biomarkers Prev., *5:* 467–471, 1996.

15. Gammon, M. D., Wolff, M. S., Neugut, A. I., Terry, M. B., Papadopoulos, K., Levin, B., Wang, Q., and Santella, R. M. Temporal variation in chlorinated hydrocarbons in healthy women. Cancer Epidemiol. Biomarkers Prev., *6:* 327–332, 1997.

16. Toniolo, P., Koenig, K. L., Pasternack, B. S., Banerjee, S., Rosenberg, C., Shore, R. E., Strax, P., and Levitz, M. Reliability of measurements of total, protein-bound, and unbound estradiol in serum. Cancer Epidemiol. Biomarkers & Prev., *3:* 47–50, 1994.

17. Toniolo, P. G., Pasternack, B. S., Shore, R. E., Sonnenschein, E., Koenig, K. L., Rosenberg, C., Strax, P., and Strax, S. Endogenous hormones and breast cancer: a prospective cohort study. Breast Cancer Res. Treat., *18:* S23–S26, 1991.

18. Kato, I., Toniolo, P., Koenig, K. L., Kahn, A., Schymura, M. M., and Zeleniuch-Jacquotte, A. Comparison of active and cancer registry-based follow-up for breast cancer in a prospective study. Am. J. Epidemiol., *149:* 372–378, 1999.

19. Wolff, M. S., Toniolo, P., Lee, E., Rivera, M., and Dubin, N. Blood levels of organochlorine residues and risk of breast cancer. J. Natl. Cancer Inst., *85:* 648–652, 1993.

20. Akins, J. R., Waldrep, K., and Bernert, J. T., Jr. The estimation of total serum lipids by a completely enzymatic "summation" method. Clin. Chem. Acta, *184:* 219–226, 1989.

21. Kim, M., and Dubin, N. Sample size and study design considerations for half-life studies. Arch. Environ. Contam. Toxicol., *30:* 423–429, 1996.

22. Phillips, D. L. Propagation of error and bias in half-life estimates based on two measurements. Arch. Environ. Contam. Toxicol., *18:* 508–514, 1989.

23. Ballard-Barbash, R. Anthropometry and breast cancer. Body size: a moving target. Cancer (Phila.), *74:* 1090–1100, 1994.

24. Hoyer, A. P., Grandjean, P., Jorgensen, T., Brock, J. W., and Hartvig, H. B. Organochlorine exposure and risk of breast cancer. Lancet, *352:* 1816–1820, 1998.

25. Dorgan, J. F., Brock, J. W., Rothman, N., Needham, L. L., Miller, R., Stephenson, H. E., Jr., Schussler, N., and Taylor, P. R. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control, *10:* 1–11, 1999.

26. Lopez-Carrillo, L., Blair, A., Lopez-Cervantes, M., Cebrian, M., Rueda, C., Reyes, R., Mohar, A., and Bravo, J. Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: a case-control study from Mexico. Cancer Res., *57:* 3728–3732, 1997.

27. van't Veer, P., Lobbezoo, I. E., Martin, Moreno, J. M., Guallar, E., Gomez, Aracena, J., Kardinaal, A. F., Kohlmeier, L., Martin, B. C., Strain, J. J., Thamm, M., van Zoonen, P., Baumann, B. A., Huttunen, J. K., and Kok, F. J. DDT (dicophane), and postmenopausal breast cancer in Europe: case control study. Br. Med. J., *315:* 81–85, 1997.

28. Zheng, T., Holford, T. R., Mayne, S. T., Ward, B., Carter, D., Owens, P. O., Dubrow, R., Zahm, S. H., Boyle, P., Archibeque, S., and Tessari, J. DDE and DDT in Breast Adipose Tissue and Risk of Female Breast Cancer in Connecticut. Am. J. Epidemiol., *150:* 453–458, 1999.

29. Moysich, K. B., Shields, P. G., Freudenheim, J. L., Schisterman, E. F., Vena, J. E., Kostyniak, P., Greizerstein, H., Marshall, J. R., Graham, S., and Ambrosone, C. B. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prev., *8:* 41–44, 1999.

30. Schildkraut, J. M., Demark-Wahnefried, W., DeVoto, E., Hughes, C., Laseter, J. L., and Newman, B. Environmental contaminants and body fat distribution. Cancer Epidemiol. Biomarkers Prev., *8:* 179–183, 1999.

31. Wolff, M. S., and Anderson, H. A. Body mass and serum levels of organochlorines (Letter). Cancer Epidemiol. Biomarkers Prev., *8:* 951–952, 1999.

32. Wolff, M. S., and Anderson, H. A. Polybrominated biphenyls: sources and disposition of exposures among Michigan farm residents, 1976–1980. Eur. J. Oncol., *4:* in press, 1999.

33. Wolff, M. S., Fischbein, A., and Selikoff, I. J. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ. Res., *59:* 202–216, 1992.

34. Craan, A. G., and Haines, D. A. Twenty-five years of surveillance for contaminants in human breast milk. Arch. Environ. Contam. Toxicol., *35:* 702–710, 1998.

35. Schecter, A., Toniolo, P., Dai, L. C. Thuy, L. T. B., and Wolff, M. S. Blood levels of DDT and breast cancer among women living in the North of Vietnam. Arch. Environ. Contam. Toxicol., *33:* 453–456, 1997.

36. Waliszewski, S. M., Pardio, V. T., Chantiri, J. N., Infanzon, R. M., and Rivera, J. Organochlorine pesticide residues in adipose tissue of Mexicans. Sci. Total Environ., *181:* 125–131, 1996.