Treatment for Breast Cancer and Blood Levels of Chlorinated Hydrocarbons[1]

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Abstract

Small studies have examined, with conflicting results, whether breast cancer risk is increased among women exposed to high levels of chlorinated hydrocarbons, as measured in breast fat tissue or peripheral blood collected prior to treatment (pretreatment blood). For a population-based, case-control study, collection of pretreatment blood is a labor-intensive effort. An alternative is to collect blood from cases at interview, as is done for controls, after breast cancer treatment has commenced (posttreatment blood). It is unknown whether treatment affects blood levels of the organochlorines 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) or polychlorinated biphenyls (PCBs). The purpose of this study was to determine whether pretreatment *versus* posttreatment blood samples yielded significantly different estimates of cumulative exposure to DDE and PCBs among newly diagnosed breast cancer patients. Two-ml blood samples were collected prior to and after treatment for breast cancer from 22 nonfasting women, ages 45–87 years, newly diagnosed with invasive disease. Treatment was defined as major surgery (mastectomy or node removal), radiation, hormones (tamoxifen), or chemotherapy. Pretreatment and posttreatment blood samples were assayed for DDE and PCBs in blinded, matched pairs. The reported concentrations (volume basis) were adjusted for estimated total plasma lipids. For DDE, mean differences in unadjusted [0.99 ng/ml; 95% confidence interval (CI), −0.36 to 2.34 ng/ml] and lipid-adjusted (0.05 μg/g lipid; 95% CI, −0.04 to 0.13 μg/g lipid) levels were small. For PCBs, the unadjusted (0.68 ng/ml; 95% CI, 0.05 to 1.30 ng/ml) and adjusted (0.070 μg/g lipid; 95% CI, −0.009 to 0.149 μg/g lipid) mean differences were of borderline statistical significance. The mean percent change in lipid-adjusted organochlorine levels did not vary substantially between treatment groups, except for those patients receiving chemotherapy [*n* = 5; 15.8% (DDE), 29.4% (PCBs)]. Adjusted mean differences also increased with increasing time between the pretreatment and posttreatment blood draws. In multiple regression models that included treatment, age, race, stage, and time between blood draws, only chemotherapy appeared to predict the percent change in adjusted pretreatment and posttreatment levels of DDE or PCBs (*P* = 0.10 and 0.06, respectively). Posttreatment blood samples drawn within 3 months of pretreatment samples, with the exception of those drawn after the commencement of chemotherapy, provide similar measures of DDE body burden levels among breast cancer cases. The use of blood samples collected after treatment, rather than before treatment, for characterizing PCB levels may lead to misclassification of exposure.

Introduction

Since 1990, several small studies have reported an increase in breast cancer risk among women with high body levels of chlorinated hydrocarbons, primarily DDE[2], a metabolite of the pesticide 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) (1–4), or PCBs, used as fluid insulators of electrical components (1–3). However, the one study (5) that found no statistically significant association between breast cancer and DDE or PCBs was well conducted and analyzed, shedding doubt on these associations.

A number of case-control studies have recently been undertaken to address this controversial issue. In those studies that are population based, body levels of chlorinated hydrocarbons are assessed using blood samples. Blood levels of these compounds are highly correlated with fat levels (6–8), which are cumulative surrogates of lifetime exposure. However, it is currently unknown whether any breast cancer treatment modality affects blood levels of DDE or PCBs among newly diagnosed cases. Thus, the timing of the blood draw among case women, prior to or after treatment has commenced, could cloud interpretation of these studies.

Collection of blood samples prior to breast cancer treatment among newly diagnosed cases (pretreatment blood) in a population-based study is challenging, due primarily to the short 1–3-week lag time between diagnosis and major surgery. An alternative is to collect blood samples for cases at interview, as is done for controls. In past studies, the time between

Received 11/29/95; revised 2/27/96; accepted 2/28/96.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] This research was supported by National Cancer Institute-National Institutes of Environmental Health Sciences Grants 2P30CA13696-22 (principal investigator, Dr. I. Bernard Weinstein) and R21-CA S66244-01 (principal investigator, Dr. Karen Antman) to Columbia-Presbyterian Medical Center.

[2] The abbreviations used are: DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene; CI, confidence interval; PCB, polychlorinated biphenyl.

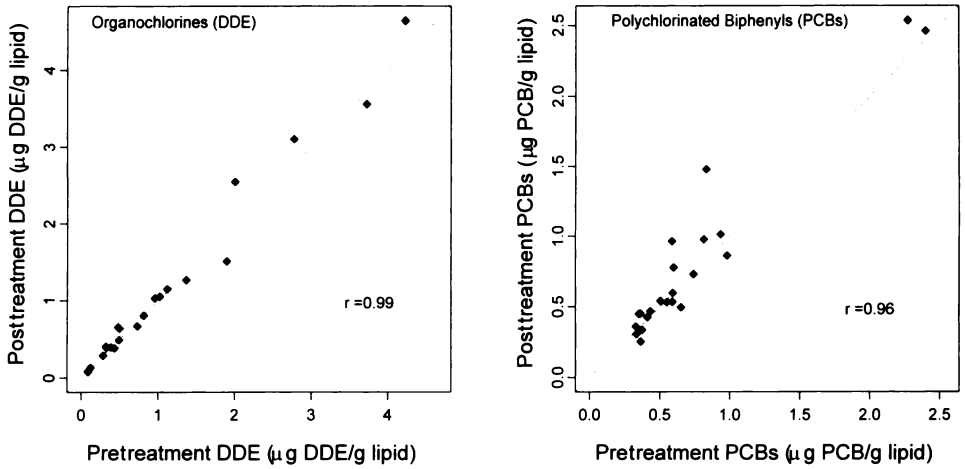

Fig. 1. Correlations between pretreatment and posttreatment blood levels of chlorinated hydrocarbons adjusted for lipids among 22 women newly diagnosed with breast cancer, Columbia-Presbyterian Cancer Center, 1994–1995.

diagnosis and interview was commonly between 30 and 90 days (9). Thus, if blood is collected at the interviews, cases would most likely have already begun treatment (posttreatment blood). To determine whether breast cancer treatment significantly alters chlorinated hydrocarbon levels among newly diagnosed women, we conducted a pilot study.

Materials and Methods

Subjects. Eligible cases included women newly diagnosed with invasive breast cancer at Columbia-Presbyterian Medical Center from July through December 1994 and who returned to that institution for follow-up treatment. Each eligible woman must have had available a pretreatment and a posttreatment blood sample of sufficient quantity for the laboratory analyses of the study. Potential cases were identified through daily contact with the cytology and pathology laboratories of the hospital. Each patient's treatment was determined from medical records, her oncologist, and the radiotherapy department. Of 91 women identified with newly diagnosed breast cancer, 63 had pretreatment blood available for the study assays, and 22 also had posttreatment blood available.

Blood Sample Collection. Plasma was derived from blood samples from nonfasting patients ordered by the patients' surgeons or oncologists. Samples were obtained by daily computer surveillance of the hematology laboratory to determine whether potentially eligible cases had remaining samples of sufficient quantity (2 ml or more) in heparin-preserved lavender-top or EDTA-preserved green-top tubes available for the study assays. Pretreatment blood was defined as a sample drawn prior to major surgery (modified or radical mastectomy or node removal) or other treatment modalities (radiation, hormones, or chemotherapy). Posttreatment blood was defined as a sample drawn at least 3 weeks after diagnosis; all patients had undergone major surgery, and for half of the women, radiation, hormones (tamoxifen), or chemotherapy had commenced.

Laboratory Analyses. Samples were randomly numbered and centrifuged, and plasma was stored at −80°C. Analyses were conducted in blinded pretreatment and posttreatment subject pairs. Assay methods for DDE and PCBs have been described previously (1). Briefly, the method for organochlorine compounds is a polar extraction, cleanup, and analysis by gas chromatography with electron capture detection. The limits of detection were approximately 1 ng/ml for DDE and 2 ng/ml for the PCBs; the coefficients of variation were 6.3% and 7.8%, respectively. Total cholesterol and triglyceride measurements were conducted using standard enzymatic procedures on a Hitachi 704 chemistry analyzer.

Statistical Analyses. In nonfasting subjects, blood levels of chlorinated hydrocarbons adjusted for total lipids, compared with unadjusted levels, have been determined to yield results closer to those in fasting subjects (10). Because blood levels from fasting subjects are highly correlated with adipose tissue levels (6–8), lipid-adjusted values are comparable to levels in adipose tissue. Variations in plasma lipids may contribute 10–20% to the variance of organochlorine plasma concentrations that are unadjusted for lipids (10). Therefore, the statistical analyses include DDE and PCB plasma levels adjusted for estimated total lipids using the method (Eq. 2) described by Phillips and colleagues (10).

Statistical analyses were performed on a personal computer using the S-Plus statistical package (11). Subject pretreatment and posttreatment blood levels were compared using Pearson's product moment correlation coefficient (r), two-tailed, paired Student's t test, and Wilcoxon's signed-rank test (12). Results from the latter nonparametric method were very similar to those of the parametric methods; thus, only the parametric results are presented. Comparisons on the percent change and the difference between pretreatment and posttreatment levels were evaluated using multiple regression (13). Because multiple regression on the difference did not yield substantially different results from those comparing the percent change, only those derived from the latter models are shown.

Results

The ages of the 22 newly diagnosed breast cancer patients ranged from 45 to 87 (mean, 61; SD, 12) years. Of the 22 participants, 14 (63.6%) were white, 5 (22.7%) were black, 2 (9.1%) were Hispanic, and 1 (4.5%) was of unknown ethnicity. Five of the 22 women were diagnosed with lobular disease. The interval between the pretreatment and posttreatment blood draws was 25–91 (mean, 56; SD, 22) days. Mean total plasma lipid levels varied little between pretreatment and posttreatment samples [6.8 (SD, 1.58) and 6.8 (SD, 1.27) g/L, respectively].

Pretreatment and posttreatment blood levels of DDE and PCBs, unadjusted for estimated lipids, among the 22 women with breast cancer were highly correlated (r = 0.96 and 0.97, respectively). The corresponding lipid-adjusted values were similarly high (r = 0.99 and 0.96; Fig. 1). For DDE, there was

Table 1 Unadjusted and lipid-adjusted pretreatment *versus* posttreatment blood levels of DDE and PCBs among 22 newly diagnosed breast cancer cases, Columbia-Presbyterian Medical Center, 1994–1995

Total plasma lipids	Compound	Mean ± SD		Difference		Paired *t* test (*P*)[a]	Mean % change ± SD
		Pretreatment	Posttreatment	Mean ± SD	95% CI		
Unadjusted (ng/ml)							
	DDE	6.82 ± 6.88	7.81 ± 8.93	0.99 ± 3.04	−0.36 to 2.34	1.53 (0.14)	7.4 ± 24.6
	PCB	4.75 ± 3.42	5.42 ± 4.51	0.68 ± 1.41	0.05 to 1.30	2.24 (0.04)	11.3 ± 28.9
Adjusted (μg/g lipid)[b]							
	DDE	1.10 ± 1.16	1.15 ± 1.23	0.05 ± 0.19	−0.04 to 0.13	1.18 (0.25)	4.6 ± 14.7
	PCB	0.728 ± 0.557	0.798 ± 0.622	0.070 ± 0.178	−0.009 to 0.149	1.85 (0.08)	9.0 ± 25.3

[a] Two-tailed.
[b] Adjusted for each subject's pretreatment and posttreatment estimated total plasma lipid levels (Eq. 2, Phillips *et al.*; Ref. 9).

Table 2 Lipid-adjusted pretreatment *versus* posttreatment blood levels of DDE and PCBs among 22 newly diagnosed breast cancer cases by treatment type and number of days between sample collection, Columbia-Presbyterian Medical Center, 1994–1995

Covariate (sample size) Compound	Adjusted Mean + SD (μ/g lipid)[a]		Adjusted Difference[a]		Paired *t* test (*p*)[b]	Mean % change ± SD	Multiple regression *p*[c]
	Pretreatment	Posttreatment	Mean ± SD	95% CI			
Treatment type							
Surgery alone (*n* = 11)							
DDE	1.00 ± 1.20	1.00 ± 1.29	0.00 ± 0.18	−0.12 to 0.13	0.94	−1.5 ± 10.7	Referent
PCB	0.713 ± 0.561	0.735 ± 0.638	0.022 ± 0.114	−0.055 to 0.099	0.53	0.8 ± 15.9	Referent
Surgery + radiation (*n* = 3)							
DDE	1.67 ± 1.81	1.66 ± 1.67	0.00 ± 0.14	−0.35 to 0.34	0.97	9.1 ± 14.2	0.25
PCB	1.31 ± 0.96	1.42 ± 0.91	0.11 ± 0.06	−0.05 to 0.26	0.10	13.7 ± 14.3	0.42
Surgery + chemotherapy ± radiation (*n* = 5)							
DDE	0.782 ± 0.685	0.941 ± 0.902	0.160 ± 0.231	−0.127 to 0.446	0.20	15.8 ± 20.7	0.03
PCB	0.602 ± 0.172	0.797 ± 0.431	0.195 ± 0.318	−0.201 to 0.590	0.24	29.4 ± 42.4	0.04
Surgery + hormones ± radiation (*n* = 3)							
DDE	1.42 ± 1.33	1.50 ± 1.50	0.08 ± 0.22	−0.47 to 0.63	0.60	3.9 ± 10.0	0.56
PCB	0.407 ± 0.030	0.410 ± 0.067	0.004 ± 0.037	−0.088 to 0.095	0.88	0.4 ± 9.3	0.98
No. of days between pretreatment and posttreatment samples [in tertiles (T)]							
T1, 25–41 days (*n* = 7)							
DDE	0.391 ± 0.285	0.387 ± 0.273	−0.004 ± 0.036	−0.037 to 0.029	0.80	−1.5 ± 10.1	Referent
PCB	0.467 ± 0.161	0.453 ± 0.163	−0.014 ± 0.063	−0.072 to 0.044	0.58	−2.5 ± 17.0	Referent
T2, 42–71 days (*n* = 7)							
DDE	1.95 ± 1.67	1.99 ± 1.77	0.04 ± 0.28	−0.22 to 0.30	0.72	2.9 ± 16.3	0.58
PCB	1.07 ± 0.89	1.10 ± 0.97	0.03 ± 0.14	−0.10 to 0.16	0.62	2.4 ± 16.7	0.69
T3, 72–91 days (*n* = 8)							
DDE	0.970 ± 0.553	1.072 ± 0.673	0.102 ± 0.192	−0.059 to 0.263	0.18	11.5 ± 15.6	0.10
PCB	0.654 ± 0.188	0.836 ± 0.354	0.182 ± 0.228	−0.009 to 0.372	0.06	24.9 ± 31.0	0.03

[a] Adjusted for pretreatment and posttreatment estimated total plasma lipid levels (Eq. 2, Phillips et al.; Ref. 9).
[b] Two-tailed.
[c] Multiple regression comparing mean percent changes.

no significant difference (0.99 ng/ml; 95% CI, −0.36 to 2.34 ng/ml) in the mean unadjusted pretreatment and posttreatment levels (Table 1). For PCBs, however, the unadjusted mean difference (0.68 ng/ml; 95% CI, 0.05 to 1.30 ng/ml) was statistically significant. After adjustments were made for lipid levels, however, there was no large difference between mean pretreatment and posttreatment levels for DDE (0.05 μg/g lipid; 95% CI, −0.04 to 0.13 μg/g lipid) or PCBs (0.070 μg/g lipid; 95% CI, −0.009 to 0.149 μg/g lipid).

After the first blood draw but before the second, 11 women underwent major surgery alone; 3 underwent surgery plus radiation; 5 underwent surgery plus chemotherapy and possibly radiation; and 3 underwent surgery plus hormone therapy and possibly radiation. Correlation coefficients for lipid-adjusted pretreatment and posttreatment levels of DDE and PCBs varied little across treatment groups, with the exception of chemotherapy: $r = 0.99$ and 0.99, respectively, for surgery alone; 0.99 and 0.99 for surgery plus radiation; 0.99 and 0.77 for surgery plus chemotherapy; and 0.99 and 0.99 for surgery plus hormones (scatter plots not shown). Treatment-specific mean differences in organochlorine levels were small except among the group that underwent surgery plus chemotherapy, but no difference was statistically significant (Table 2). Between-treatment group comparisons showed that the percent change between pretreatment and posttreatment levels among the chemotherapy group was significantly higher for DDE (15.8%) and PCBs (29.4%) compared with the surgery alone group (−1.5 and 0.8%, respectively).

Lipid-adjusted mean differences of the chlorinated hydrocarbons did not significantly vary with age, race, or tumor stage (data not shown) but appeared to vary with the length of time between the two blood draws (Table 2). The lipid-adjusted mean differences in the samples that were collected 25–71 days apart (representing the first two tertiles of time) were not large;

however, those that were drawn 72–91 days apart (the highest tertile of time) were large and of borderline statistical significance for the PCBs but not for DDE. Between-group comparisons showed that for those women whose second blood samples were collected from 72–91 days after the first, the percent change was significantly higher for DDE (11.5%) and PCBs (24.9%) than among those with a shorter time interval (25–41 days, −1.5 and −2.5%, respectively).

Breast cancer treatment was associated with time between blood draws and the subject's age (Fisher's exact test, $P = 0.05$ and 0.07, respectively) but not with the subject's race or stage of disease (corresponding $P = 0.33$ and 0.23, respectively). We explored the possible confounding effects of these variables on the relation between treatment and organochlorine blood levels. In a simple regression model to estimate the mean percent change in lipid-adjusted pretreatment and posttreatment levels, the term representing the effect of chemotherapy (*versus* no chemotherapy) was statistically significant for DDE ($P = 0.05$) and PCB ($P = 0.04$). In multiple regression models that included terms for treatment (chemotherapy/no chemotherapy), age (continuous), race (nonwhite/white), stage of disease (stages II and III/stage I), and number of days between blood draws (tertile 3/tertiles 1 and 2), only chemotherapy appeared to predict the percent change for DDE ($P = 0.10$) and PCB ($P = 0.06$). Due to the limited power available to perform multiple regression analyses in these data, an effect due to a longer time interval (72–91 days) between the two blood draws could not be completely ruled out for PCB ($P = 0.13$).

Discussion

Considering DDE first, there were no large differences in pretreatment and posttreatment blood levels among the 22 newly diagnosed breast cancer cases in this study, regardless of whether the results were adjusted for estimated total blood lipid levels. Subgroup comparisons by treatment type revealed that chemotherapy, as compared with surgery alone, significantly increased lipid-adjusted DDE levels. However, treatment-specific results are based on very small numbers. For PCBs, unadjusted for total plasma lipids, mean differences between pretreatment and posttreatment levels were small (<1 ppb increase) but statistically significant. After adjustments were made for lipid levels, however, pretreatment *versus* posttreatment mean PCB differences were still of borderline significance. Comparisons of differences between specific treatment types are based on small numbers, but the percent change in the adjusted mean pretreatment and posttreatment PCB levels was significant only among women who had received chemotherapy prior to the second blood draw.

To assist in the interpretation of these data, examination of the magnitude of the mean difference in blood levels of chlorinated hydrocarbons noted between breast cancer cases and controls might be instructive. In a previous study by Wolff *et al.* (1) that compared chlorinated hydrocarbon levels in blood from nonfasting subjects, the mean difference between breast cancer cases and controls was 2.7 ng/ml for DDE and 1.0 ng/ml for PCBs. As shown in Table 1 of this report, the CIs for the mean differences between pretreatment and posttreatment blood levels exclude the mean difference for DDE noted by Wolff *et al.* (95% CI, −0.36 to 2.34 ng/ml; Ref. 1) but include the mean value for PCBs (95% CI, 0.05 to 1.30 ng/ml; Ref. 1). This comparison adds support for using posttreatment blood samples to assess DDE levels but casts considerable doubt on their use to assess PCBs.

Lack of statistical power is an unlikely explanation for the main findings of our study. *A priori* sample size estimates demonstrated that assuming a correlation of 0.95 between pretreatment and posttreatment samples, an α level of 0.05, and power of 90%, a sample size of only three was required to evaluate the correlation between pretreatment and posttreatment levels. Thus, a type II error, failing to find a high correlation if one existed, is not an issue when correlating levels within groups. Power, however, for the comparison of mean differences was limited. Also, a larger sample size to explore the differences between treatment modalities, in other words, formal evaluation of effect modification, would have been more informative. Due to our small sample size, evaluation of whether treatment or the time interval between the two blood draws predicted the percent change in pretreatment and posttreatment levels using multiple regression was restricted and should be interpreted cautiously.

For example, treatment of breast cancer among patients in our study was highly associated with the time between the pretreatment and posttreatment blood collection. Due to the limited sample size, results from multiple regression analyses could only marginally help disentangle the effects of time *versus* treatment on the mean percent change in PCB levels. A longer posttreatment time could lead to an increase in blood levels if there were significant new exposure to PCBs or significant loss of body fat (14). A 25% increase in average PCB levels could arise if women in our study had eaten more than 6 pounds of highly contaminated fish during this time; if this were the case, it is unlikely that the increases would be limited to women having chemotherapy or to women followed for 3 months.

The magnitude of the increases in DDE and PCBs among women receiving chemotherapy could also be explained by an average 2–3-pound loss of body fat (assuming total body fat of 10 kg before treatment). Changes in weight were not recorded in the medical records of our patients. However, weight gain, not loss, has been reported as a side effect of adjuvant chemotherapy for breast cancer (15). Weight gain would result in decreased blood levels of PCBs (16, 17). In the absence of additional exposure or weight changes, organochlorine levels should show a 1–2% decrease over this short interval. Therefore, the observed increases in chlorinated hydrocarbons in chemotherapy patients cannot be explained at this time.

Blood samples collected prior to or after treatment for breast cancer, with the exception of those samples collected after commencement of chemotherapy, will provide similar estimates of DDE body burden levels among women newly diagnosed with invasive disease. However, the use of blood samples collected after treatment, rather than before, for characterizing PCBs may lead to exposure mismeasurement or misclassification.

Acknowledgments

We thank Drs. Walter Willett and Peter Schiff for valuable comments on earlier presentations of these data.

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Cancer Epidemiol Biomarkers Prev 1996;5:467-471.