REPORTS

Blood Levels of Organochlorine Residues and Risk of Breast Cancer

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Background: Organochlorines such as DDT [2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane] and PCBs (polychlorinated biphenyls), which have been used extensively as insecticides and as fluid insulators of electrical components, respectively, are known to be persistent environmental contaminants and animal carcinogens. These agents have been found in human tissue due to their inefficient metabolism and their solubility in lipids, which lead to lifelong sequestration in adipose tissue. Their association with human cancer occurrence, however, has been explored only marginally, with most studies having 20 or fewer cases. *Purpose:* This blinded study was designed to determine whether exposure to PCBs and to DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene], the major metabolite of DDT, is associated with breast cancer risk in women. *Methods:* We analyzed sera from the stored blood specimens of 14290 participants enrolled between 1985 and 1991 in the New York University Women's Health Study, a prospective cohort study of hormones, diet, and cancer. Cohort members who developed breast cancer were included as case patients in our nested case–control study. DDE and PCBs were measured by gas chromatography in the sera of 58 women with a diagnosis of breast cancer 1-6 months after they entered the cohort and in 171 matched control subjects from the same study population who did not develop cancer. *Results:* Mean levels of DDE and PCBs were higher for breast cancer case patients than for control subjects, but paired differences were statistically significant only for DDE ($P = .031$). After adjustment for first-degree family history of breast cancer, lifetime lactation, and age at first full-term pregnancy, conditional logistic regression analysis showed a fourfold increase in relative risk of breast cancer for an elevation of serum DDE concentrations from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile). For PCBs, the relative risk for a change in serum levels from 3.9 ng/mL (10th percentile) to 10.6 ng/mL (90th percentile) was less than twofold, a nonsignificant association that was further reduced after adjustment for DDE. *Conclusion:* In this population of New York City women, breast cancer was strongly associated with DDE in serum but not with PCBs. *Implications:* These findings suggest that environmental chemical contamination with organochlorine residues may be an important etiologic factor in breast cancer. Given the widespread dissemination of organochlorine insecticides in the environment and the food chain, the implications are far-reaching for public health intervention worldwide. [J Natl Cancer Inst 85:648–652, 1993]

Environmental factors have long been suspected to play a prominent role in breast cancer etiology. Both diet and hormones have been implicated, but specific agents have not yet been identified, and the recognized risks explain only a small proportion of the disease. Furthermore, breast cancer incidence has been steadily rising in the United States, and it has been suggested that part of the increase may be due to unexplained environmental factors.

The possibility that organochlorine residues may be related to breast cancer arises from several observations. DDT [2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane], its metabolite DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene], similar pesticides, and related chemicals (PCBs [polychlorinated biphenyls] and PBBs [polybrominated biphenyls]) are known animal carcinogens (*1,2*) and suspected human carcinogens (*1*) and may compromise immune function (*3*). Both DDT and PCBs have been shown to be tumor promoters (*1,2*) and to have estrogenic activity (*1,2,4*). Moreover, they have become ubiquitous in the environment and in human tissues, due to their inefficient metabolism and their high solubility in lipids, which leads to lifelong sequestration in adipose tissue. Previous studies have been unable to establish a clear connection between exposure to these chemicals and breast cancer (*5*), or indeed other cancers (*1,6*), although some studies (7-9) have reported possible associations with breast cancer.

A large prospective cohort study designed to investigate the role of endogenous hormones and environmental factors in cancer among women offered us an opportunity to examine the association of breast cancer with individual exposure to DDE and PCBs, as estimated by measurement of levels in blood serum.

Subjects and Methods

Subjects. Study subjects were a subset of the participants in the New York University Women's Health Study, a cohort study of hormonal and environmental factors and cancer in women (*10*). Between 1985 and 1991, 14290

*See "Notes" section following "References."

New York City women were enrolled while attending a mammography screening clinic and after consenting to having 30 mL of venous blood drawn. Serum specimens were stored at -80 °C. Study subjects were aged 35-65 years (median age, 50.7 years), and 80% were Caucasian. Cohort members developing breast cancer were included as case patients in a case-control study nested within the cohort. Control subjects were selected at random from risk sets consisting of all cohort members who were alive and free of cancer at the time of the cancer diagnosis in a case patient and who matched the case patient on menopausal status, age at entry into the study (±0.5 year), number and dates (±0.25 year) of blood donations, and, if premenopausal, day of menstrual cycle at the time of first blood drawing. Two control subjects were selected for each postmenopausal case patient (n = 34), and four were selected for each premenopausal case patient (n = 24). Case and control subjects did not differ with regard to socioeconomic status (as defined by years of school). DDE and PCB analyses were performed on specimens from the 58 breast cancer case patients who were diagnosed within 6 months after entry into the study (prevalent cases) and their 171 matched control subjects. (For seven matched sets, one extra control had been selected in the parent project, and all were used in the present study.) The laboratory investigators were blinded with respect to any information concerning study subjects.

Determination of levels of DDE and PCBs. The method for determination of the levels of DDE and PCBs, including the quality-control protocols, was the same as that described elsewhere (*11*), with minor modifications to obtain satisfactory results with the use of 1-mL aliquots of serum. The cleanup step used a 9-mL fraction of 1% methanol in hexane eluted from 1.2 g Florisil (U.S. Silica Co., Berkeley Springs, W. Va.), and gas chromatography was performed with electron capture detection on a 0.53 μm × 30 m 5% methylphenyl silicone column in the temperature program mode with direct injection of 0.5 μL on an Autosystem gas chromatograph (Perkin-Elmer Corp., Norwalk, Conn.). Results are reported as nanograms per milliliter (parts per billion [ppb]) of *p,p'*-DDE and of the higher PCB congeners, those with retention time longer than that of DDE. The calculations were based on the peak percentages reported for Aroclor 1260 by Webb and McCall (*12*). Since certain of these peaks were resolved into two or three components with our modified gas chromatography technique, the method of calculation was revised by use of the data of Mullin et al. as reported by Burse et al. (*13*). The Webb and McCall peaks (*12*) (and their revised percentages) were 203 (4.9%, 3.3% in order of retention time), 232 (4.5%, 3.3%, 2.2%), and 372 (2.1%, 1.9%). Limits of detection were approximately 1 ng/mL for DDE and 2 ng/mL for PCBs based on three times the standard deviation of the results from the lowest quality-control serum pool over the course of the analyses (n = 18). Statistical computations performed at the Mount Sinai School of Medicine as part of the laboratory analyses utilized the facilities of the City University of New York Computing Center.

Statistical analysis. Statistical comparisons of DDE and PCB levels in case patients and their matched control subjects were made by paired Student's *t* tests. Relative risks, as estimated by the odds ratios (ORs), were determined by use of conditional multiple logistic regression with DDE and PCB exposure as both quintiles and continuous variables. Quintiles were based on the frequency distribution of cases and controls combined. Adjustment was made for potential confounders (other than the matching criteria). Potential confounders included body mass index (kg/m^2), age at menarche, age at first full-term pregnancy, first-degree family history of breast cancer, history of benign breast disease, months of lactation, history of tobacco smoking and/or alcohol drinking, and race. There was no apparent modification of effect by age. Final models included only those covariates that altered the regression coefficients for either of the continuous exposure variables by at least 15%. Covariates included in the final models were first-degree family history of breast cancer (yes or no), lifetime months of lactation, and age at first full-term pregnancy (<21 years, 21-29, >29, nulliparous). Similar results were obtained in models that included all of the potential confounders. Confidence intervals (95%) were obtained from the standard errors of the pertinent regression coefficients.

Results

The mean levels of both DDE and PCBs were higher among the breast cancer case patients than among their matched control subjects. The paired differences were statistically significant only for DDE (Table 1). DDE was approximately 35% (or 2.7 ng/mL) higher in patients than in control subjects; PCBs were 15% higher (by 1.0 ng/mL).

In conditional logistic regression analyses, after adjustment for first-degree family history of breast cancer, lifetime lactation, and age at first full-term pregnancy, the ORs for breast cancer increased markedly with increasing quintile of DDE concentration (Fig. 1). The adjusted OR for the upper quintile, compared with the lowest, was 3.68 (95% confidence interval = 1.01-13.50); the chi-square for trend for quintiles was 4.44 (P = .035). When serum DDE was examined as a continuous risk factor, there was a 1.09 increase (9%) in the adjusted OR for breast cancer per unit increase in DDE (regression coefficient = 0.0823 ± 0.0301 [±SE]; P for trend = .0037). This increase corresponded to a four-fold risk for an elevation of serum DDE from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile; OR = 4.08; 95% confidence interval = 1.49-11.20).

The effect of adjusting for lactation history was to strengthen the association between DDE and breast cancer. (Regression coefficient for DDE as a continuous variable = 0.0509 ± 0.0218 [±SE] without adjustment for lifetime duration of lactation compared with 0.0823 ± 0.0301 in the model described above.) However, the effect of lactation itself was protective. When we examined months of lactation as a continuous variable, the decrease in OR for breast cancer per additional month of lactation was 0.88 (regression coefficient = –0.1308 ± 0.0556 [±SE]; P for trend = .0069 in a conditional logistic regression model adjusting for DDE, PCBs, first-degree family history of breast cancer, and age at first full-term pregnancy).

For PCBs, the adjusted ORs for breast cancer rose from 5.18 in the second quintile to 7.02 in the third, but they decreased thereafter to 4.10 and 4.35 in the two upper quintiles. The chi-square for trend of the PCB quintiles was 1.99 (P = .16). When serum PCBs were examined as a continuous variable, the increase in OR per unit change was 1.08 (regression coefficient = 0.0795 ± 0.0587 [±SE]; P for trend

Table 1. Serum concentrations of DDE and PCBs in breast cancer case patients and in individually matched control subjects

	Mean ± SD, ng/mL		Mean difference, ng/mL*		
	Case patients (n = 58)*	Control subjects (n = 171)*		t†	P
DDE	11.0 ± 9.1	7.7 ± 6.8	2.7	2.22	.031
PCB	8.0 ± 4.1	6.7 ± 2.9	1.0	1.94	.058

*As the difference between a case patient and the mean of her matched control subjects.
†Paired Student's *t* test, two-tailed.

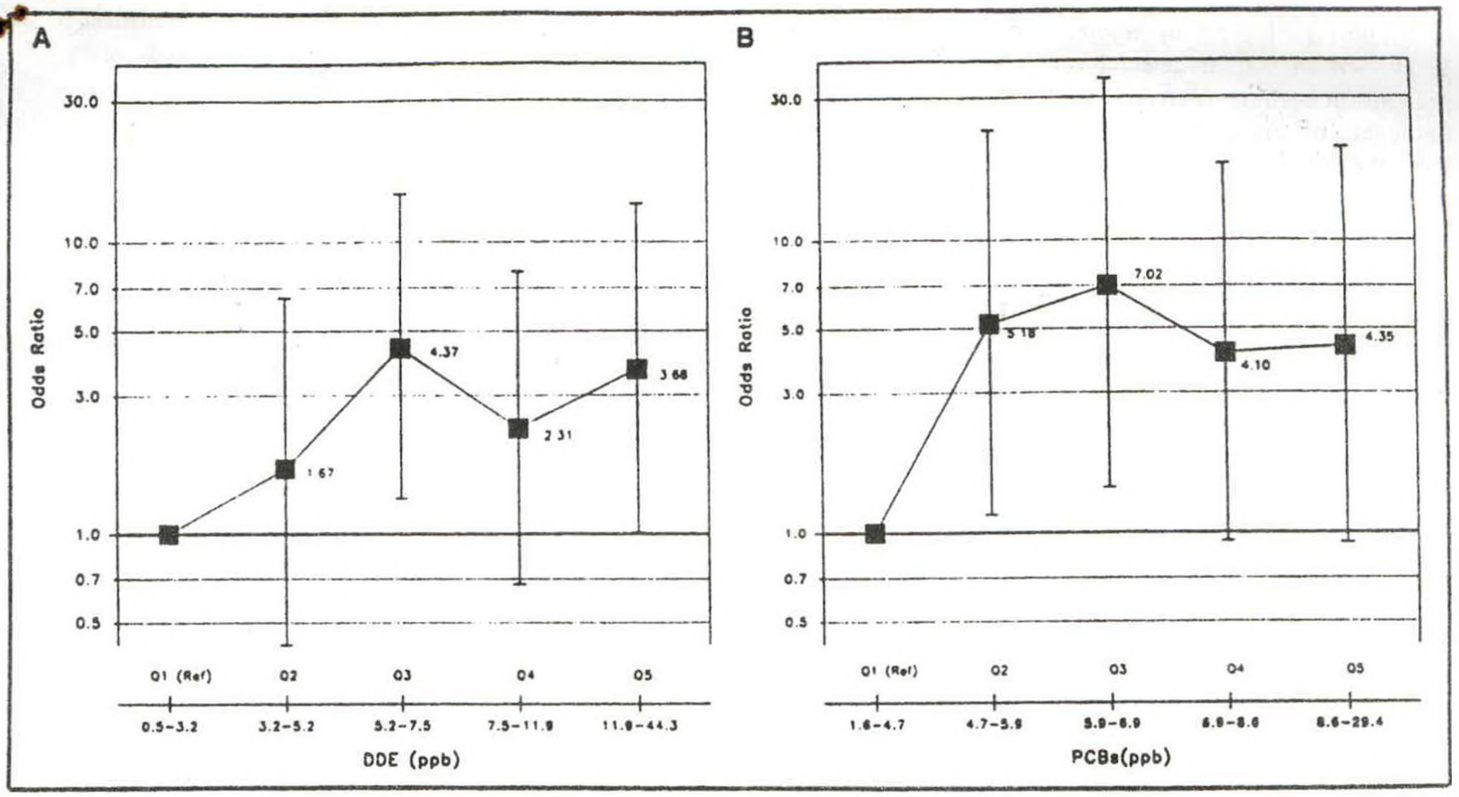

Fig. 1. Relative risk (odds ratio) of breast cancer by quintiles of DDE and PCB concentrations in serum. Quintiles are based on the frequency distribution of case patients and control subjects combined. Of the 58 case patients, only 49 had complete data for the conditional logistic regression analyses. Case–control frequencies for DDE quintiles were as follows: Q1 (low) = 6-39, Q2 = 6-34, Q3 = 16-27, Q4 = 8-33, and Q5 (high) = 13-26. Case–control frequencies for PCB quintiles were as follows: Q1 = 4-38, Q2 = 12-33, Q3 = 10-29, Q4 = 12-30, and Q5 = 11-29. A) For DDE (continuous variable), the regression coefficient (±SE) was 0.0823 ± 0.0301 (P = .0037); chi-square for trend for DDE quintiles = 4.44 (P = .035). B) For PCB (continuous variable), the regression coefficient (±SE) was 0.0795 ± 0.0587 (P = .16); chi-square for trend for PCB quintiles = 1.99 (P = .16).

= .16), corresponding to less than a twofold risk for an elevation of levels of serum PCBs from 3.9 ng/mL (10th percentile) to 10.6 ng/mL (90th percentile; OR = 1.70; 95% confidence interval = 0.79-3.68). When both DDE and PCBs were included in the model as continuous variables, DDE remained essentially unchanged, but the coefficient for PCBs was greatly reduced in magnitude (by 53%) and in statistical significance (chi-square adjusted for DDE = 0.360; P = .55).

Discussion

Previous studies (*5,7-9*) have raised the question of organochlorine residues and their possible association with breast cancer, but the results of these studies have been inconsistent. All of these studies had methodological limitations. None adequately adjusted for known breast cancer risk factors, and only one study (*9*) had more than 20 case patients. In our study, it was possible to individually match case patients for some risk factors and to statistically adjust for others.

A strong association between DDE and breast cancer was found, with higher DDE levels among women who developed breast cancer than among their matched control subjects. The relative risk rose in an approximately log-linear fashion with increasing levels of DDE (Fig. 1, A). With PCBs, the trend for breast cancer risk with increasing levels was not statistically significant. Moreover, even though certain individual ORs were significantly elevated within quintiles of PCBs, the pattern of increase was characterized by a flattened dose–response curve along the upper quintiles (Fig. 1, B). This trend, which may have arisen from an imbalance in the numbers of case patients and control subjects within the lowest quintile, was less consistent with the stepwise incremental function typical of a biological dose–response. The nominal association of PCBs with breast cancer may have been due mainly to its relationship with DDE, since inclusion of both in the model greatly reduced the effect of PCBs. The risk calculations showing twofold to fourfold increases across the range of serum concentrations are comparable to those calculated from a smaller study (*7*) and are also similar to cancer rate estimates obtained from risk assessment computations using animal data (*2,14*).

Organochlorine residues may be found throughout the body and in concentrations proportional to the lipid content of a tissue. The primary site of organochlorine storage in the body is adipose tissue, which has been obtained from autopsy and biopsy specimens to measure organochlorine residues in several studies (*5,7-9*). However, blood serum concentration is a more convenient means of estimating body burden, since it is easier to obtain from humans and to process in the laboratory. Blood serum was used in our study because archival sera, having been collected over a period of several years, were already available for a large cohort of

women. A number of previous studies (*15,16*) have shown that, if detectable, concentrations in serum accurately reflect the levels of organochlorines in fat. Thus, the partition between the adipose and serum compartments is approximately 200 to 1, the ratio of their respective lipid contents (90% and 0.4%) (*17*). Because fluctuations in serum lipids can introduce minor variations (*18*), it is preferable to adjust serum concentrations for serum lipid content. We plan to make this adjustment when serum lipid data become available from other stages of the investigation.

In terms of mechanism, the possible relationship between organochlorines and breast cancer is based on studies of animal carcinogenesis as well as on a number of experimental observations that are consistent with breast cancer etiology. Induction of the cytochrome P-450 mixed-function oxidase enzymes, a phenomenon widely investigated in animals (*2,3*), has been observed in humans exposed to such chemicals (*19,20*). Through this pathway, organochlorines may alter the metabolism of xenobiotics and steroid hormones. In addition, DDT and its metabolites, especially the *o,p'*-isomers, exert estrogenic effects that are epitomized by eggshell thinning and reproductive failure in birds (*21*) and that are also shown by the ability to interact with estrogen-binding protein (*21,22*) and to promote estrogenic tumors (*23,24*). Also, an inverse association has been reported in humans between levels of DDE in breast milk at birth and subsequent duration of lactation (*25*), which offers additional indirect evidence for an effect of some organochlorines on the endocrine balance.

Lactation exerted a strong effect on the association between DDE and breast cancer in our data. Without adjustment for a woman's lifetime breast-feeding history, the coefficient for DDE would have been reduced by 38%. Thus, among women who had breast-fed, DDT exposures prior to nursing may have been elevated, but lactation would have reduced their serum DDE levels (*25*), and an effect of DDE could have been overlooked if information on lactation were omitted from statistical analyses. Although lactation has not been found consistently to be associated with risk for breast cancer, one report (*26*) suggested that women with lactation failure were at greater risk than women who were able to breast-feed for longer periods. The interrelationship of curtailed lactation and DDE or DDT residues might bear further investigation in terms of their relationship to breast cancer and estrogenic effects.

Environmental factors have been invoked to explain rates of breast cancer in developed countries, and nutrition especially has received much attention as a potential determinant of this disease (*27*). That breast cancer is sex hormone dependent is also widely acknowledged. However, although the relationship among diet, sex hormones, and risk of breast cancer has been examined in many studies (*27-29*), a consistent picture has yet to emerge. Moreover, the relative risks observed are low (1.2-1.5) in studies (*28,29*) that find an effect for dietary fat or caloric intake.

Overall, the epidemiologic data suggest that estrogens exert a cancer-promoting effect (*30*) and that a diet rich in animal products and fat may increase a woman's risk of breast cancer (*28*). Our data suggest that organochlorine residues and, in particular, DDE are strongly associated with breast cancer risk. These observations are important in light of the fact that DDE is a widespread contaminant of animal food products and that human absorption is related to the ingestion of animal fat. Once absorbed, DDE may affect breast cells through binding to either cytosol or nuclear receptors (thereby modifying cell regulation), through the mediation of the cytochrome P-450 oxidative enzymes that are intimately involved in steroid hormone metabolism, or by interference with sex hormone metabolism at the hypothalamic level.

While these findings are novel and suggest a number of potential follow-up studies, the conclusions require confirmation, ideally in an expanded study design that will allow examination of confounding factors. Of particular merit for further study would be country of origin, estrogen receptor status, lactation, and diet. Statistical power was not sufficient to study diet in this investigation of 58 case patients. It would also be desirable to have knowledge of blood or adipose levels at a point long before diagnosis of cancer, in case organochlorine concentrations change near the time of cancer onset because of variations in lipids or body weight. Confirmation of our findings among incident cases (those diagnosed >12 months after blood was drawn) would be important in this regard. Moreover, since the risk associated with organochlorines may be merely a surrogate for other agents in the diet, the question of fat or chemical carcinogens is also an important one to pursue.

Breast cancer incidence has been steadily rising during the past two or three decades, a trend characterized by increasing rates among estrogen-responsive tumors, by continuing increases among older women, and by growing numbers in both developed and developing countries (*29*). Between 1973 and 1980, the incidence of breast cancer in the United States increased a modest 8.0% among women under 50 years of age, while it rose 32.1% among women in the age group 50 years or older (*31*). Although this increase can be explained in part by enhanced screening (*32*), the upward shift is also consistent with the historical pattern of accumulation of organochlorine residues in the environment; i.e., older women who had the greatest potential cumulative exposure to DDT between 1945 and 1972 may now experience a higher risk of breast cancer than women much older or younger who were not similarly exposed. Likewise, diminishing rates of breast cancer in Israel have paralleled a precipitous decline in environmental contamination with DDT and benzene hexachloride (*33*). The existence of a limited exposure window would provide an explanation for an earlier negative study (*5*) and would suggest that the risk of cancer can be expected to decline as the levels of organochlorine residues continue to decline in human tissues (*34*).

Environmental accumulation of DDT and PCB residues has been documented for at least three decades. Levels in the

United States and Europe have diminished since the late 1970s as a result of government regulation, but human exposure is still common. Since elimination of body burden is slow, taking several decades, consequent health risks may continue for a long time after exposure; therefore, cancer, with its long latency, has been of particular concern.

Our observations provide important new evidence relating low-level environmental contamination with organochlorine residues to the risk of breast cancer in women. Given the widespread dissemination of organochlorines in the environment, these findings have immediate and far-reaching implications for public health intervention worldwide.

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