[CANCER RESEARCH 57, 3728–3732, September 1, 1997]

Dichlorodiphenyltrichloroethane Serum Levels and Breast Cancer Risk: A Case-Control Study from Mexico[1]

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ABSTRACT

Some, but not all, epidemiological studies have suggested that dichlorodiphenyltrichloroethane (DDT) may play a role in the development of breast cancer. These investigations have been conducted in countries where this substance has been banned for at least 20 years. We conducted a study in Mexico, a country in which DDT is still being used to control malaria. In a hospital-based case-control study, we compared 141 histologically confirmed cases of breast cancer with 141 age-matched controls (±3 years). All subjects were identified at three referral hospitals of Mexico City between March 1994 and April 1996. Reproductive histories and other variables were obtained by structured interviews, DDT/DDE levels were determined in serum by gas-liquid chromatography. The arithmetic mean of serum DDE in lipid basis was 562.48 ± 676.18 ppb (range, 10.24–4661.44) for the cases and 505.46 ± 567.22 ppb (range, 0.004 to 4361.75) for the controls, but this difference was not statistically significant. The age-adjusted odds ratios for breast cancer regarding the serum level of DDE were 0.69 (95% confidence interval, 0.38–1.24) and 0.97 (confidence interval, 0.55–1.70) for the contrasts between tertile 1 (lowest level) and tertiles 2 and 3, respectively. These estimates were unaffected by adjustment for body mass, accumulated time of breast-feeding and menopause, and other breast cancer risk factors. These results do not lend support to the hypothesis that DDT is causally related to breast cancer at the body-burden levels found in our study population but do not exclude the possibility that higher levels of exposure could still play a role in the etiology of this tumor.

INTRODUCTION

Because of the estrogenic activity of DDT,[3], it has been hypothesized that exposure to this organochlorinated pesticide may lead to an increased risk of developing breast cancer (1). The results of epidemiological studies published thus far are suggestive but inconclusive (2–7). Some of these studies were small and were unable to control completely for the effects of other risk factors for breast cancer. Furthermore, previous studies were carried out in populations of countries where DDT use was banned more than 20 years ago.

In Mexico, DDT is still used to control malaria. Although a diminishing trend of DDT use has been observed since 1971, when 8000 tons were used, during 1994 about 2000 tons of this substance were sprayed in parts of the country. Studies in Mexico have also reported the presence of DDT and its metabolites (DDE and *o'p'*-DDT) in biological samples (blood, adipose tissue, and milk) obtained from individuals not directly exposed to the pesticide, indicating that contaminated foods are a locally important source of exposure for many individuals (8).

To evaluate the risk of breast cancer from DDT exposure, we conducted a case-control study among Mexican women.

MATERIALS AND METHODS

The present study used a hospital-based case-control study design. The study population was assembled from women seeking care at three referral public hospitals of the Secretariat of Health in Mexico City (Instituto Nacional de Cancerología, Hospital General, and Hospital Gea González) between March 1994 and April 1996.

Cases. Our cases were women between 20 and 79 years of age who had a histologically confirmed diagnosis of breast cancer, who were being seen for the first time at any of the participating hospitals, who were free from any other cancer, and who were residents of the Mexico City metropolitan area for at least 20 years. Breast cancer cases are referred to the three participating hospitals from other hospitals or primary care physicians with or without a definitive diagnosis. Upon confirmation or establishment of diagnosis at the participating hospitals, only those cases without previous treatment for breast cancer were included in the study. The 20-year residence requirement was used to avoid the practical difficulty of selecting appropriate controls for cases who may have recently migrated to Mexico City. The tumor stage was classified following the TNM system (10). From a total of 174 eligible cases, 141 agreed to participate in the study (giving a response rate of 81%).

Controls All of the controls came from the clinical services of the participating hospitals except gynecology and oncology. For each case, we selected one age-matched control (±3 years), who had no history of cancer or any other breast disease and who had resided in the Mexico City metropolitan area for at least 20 years. To assemble a group of 141 age-matched controls, a total of 196 eligible subjects were approached (response rate, 72%). The most frequent diagnoses among the controls were: injuries (17.0%), digestive tract disorders (11.3%), ill-defined conditions (4.2%), diseases of the blood and the circulatory system (4.2%), osteomuscular and connective tissue disorders (3.5%), and diseases of the nervous system (2.8%). Other categories accounted for smaller proportions of subjects, such as infectious diseases, endocrine disorders, blood disorders, diseases of the circulatory system, diseases of the respiratory system, diseases of the genitourinary system, diseases of the skin and the connective tissue, and some benign tumors.

Interviews. After signing an informed consent statement, all of the subjects were interviewed using a structured questionnaire to obtain their reproductive histories as well as information on their socioeconomic characteristics, diet, and occupation. Every woman was measured and weighed to estimate the body mass index (Quetelet index, kg/m^2).

On the basis of the reported history of breast-feeding, we estimated both the length of breast feeding for the first child and the total amount of time that a woman lactated for all her children (in months). Also, the time of exposure to endogenous estrogen was assessed by a variable that expresses the time elapsed since age at first birth and the age at the date of interview. This variable was 0 for nulliparous women, thus preventing the deletion of this subgroup from the analysis, as would happen if only age at first birth is used in the models.

Blood Samples. Ten ml of blood were drawn from each woman during diagnostic workup, but before any treatment, using sterile Vacutainers. The serum was separated by centrifugation and frozen at −20°C in glass vials (prewashed with hexane) covered with a Teflon cap.

Received 3/4/97; accepted 7/7/97.

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[1] This study was supported by grants from The John D. and Catherine T. MacArthur Foundation, the Secretariat of Health of Mexico, the United States National Cancer Institute, and the Committee for Studies on Environmental Recovery (COPERA) of Mexico City.

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[3] The abbreviations used are: DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene; OR, odds ratio; CI, confidence interval.

Chemical Analysis. Levels of DDE, *p'p*-DDT, and *o'p*-DDT were determined in serum samples (1–2 ml) by gas-liquid chromatography according to the protocol recommended by the United States Environmental Protection Agency (10). Concentrations were reported on the basis of ppb of lipid weight (ng/g) as well as ppb of wet weight (ng/ml). The former unit is preferable, given that its results can be compared across studies; ppb of lipid weight takes into account the variation of circulating lipids, to which most of the DDT and its metabolites are actually linked.

Results for 72 quality control samples (*i.e.*, bovine serum fortified with DDE) showed a 92 ± 8.3% of recovery. In addition, each human serum sample was fortified with aldrin; the average recovery rate was 94.2 ± 9.6%.

Statistical Analyses. To obtain normal distributions, serum levels of DDE were transformed, either by taking the natural logarithm for levels obtained on the basis of wet weight or taking the square root for levels obtained on the basis of lipid weight. The more detailed results reported in this paper use the latter transformations, which were evaluated by selected reproductive variables using ANOVA. We also tested for trends across levels of the reproductive variables by fitting simple regression models to the transformed values of the determinations based on lipid weight for cases and controls separately.

ORs for breast cancer from DDE levels were estimated using conditional logistic regression models. For these analyses, DDE levels (lipid weight basis) were categorized in tertiles based on the distribution of the total study population. All analyses were performed using the statistical software STATA 4.0 (Stata Corp., College Station, TX).

RESULTS

Table 1 displays the age-adjusted ORs for known determinant factors for breast cancer in the study population. Age at menarche increased the breast cancer risk among those women whose menarche started before 12 years of age compared to those whose menarche started at 12 or more years of age.

Nulliparous women and those who had one to three children had higher breast cancer risk compared to those women who had four or more children. This risk increased when the age at first birth or the Quetelet index increased, and it was higher among those women with a familial history of breast cancer compared with those with no familial history of breast cancer.

Table 1 *Age-adjusted ORs for known breast determinant factors in the study population*

	OR	95% CI[a]
Age at menarche (yr)		
≥12	1.0	
<12	1.65	0.98–2.77
Parity[a]		
≥4	1.0	
1–3	2.50	1.21–5.18
Nulliparous	1.94	1.15–3.29
Age at first birth (yr)		
<20	1.0	
20–24	1.82	0.91–3.63
≥25	4.07	1.54–10.74
Breastfeeding at first birth (months)		
0	1.0	
1–6	0.55	0.26–1.17
7–12	0.46	0.21–1.01
>12	0.44	0.16–1.18
Breastfeeding all births (months)		
0	1.0	
1–6	0.39	0.11–1.31
7–12	0.43	0.13–1.38
>12	0.26	0.09–0.74
Menopausal status		
No	1.0	
Yes	0.93	0.45–1.97
Familial breast cancer		
No	1.0	
Yes	2.14	0.87–5.25
Quetelet index (kg/m^2)		
<20–24	1.0	
25–29	0.89	0.52–1.13
≥30	1.64	0.83–3.25

[a] Five women who had had three abortions and two birth deaths were included.

Table 2 *DDE and p'p'-DDT serum levels in the study population (ppb)*

DDE/*p'p'*-DDT	Cases	Controls	*P*
DDE			
Lipid weight basis (ng/g)			
Arithmetic mean	562.48	505.46	0.444
SD	676.18	567.22	
Range	10.24–4661.44	0.004–4361.75	
n	141	141	
Geometric mean[a]	20.92	20.46	0.706
SD	11.21	9.36	
Range	3.2–68.27	0.063–66.04	
n	141	141	
Wet weight basis (ng/ml)			
Arithmetic mean	4.75	4.07	0.211
SD	5.04	4.12	
Range	0.5–35.35	0.25–29.72	
n	141	141	
Geometric mean[b]	1.23	1.06	0.081
SD	0.79	0.82	
Range	−0.69–3.56	−1.38–3.39	
n	141	141	
p'p'-DDT			
Lipid weight basis (ng/g)			
Arithmetic mean	61.45	84.53	0.233
SD	139.77	180.95	
Range	0.012–993.12	0.012–1262.68	
n	140	140	
Wet weight basis (ng/ml)			
Arithmetic mean	0.529	0.712	0.261
SD	1.05	1.62	
Range	0.012–5.67	0.012–13.7	
n	141	141	

[a] DDE values were transformed to $\sqrt{\text{DDE}}$.
[b] DDE values were transformed to ln(DDE).

Breast feeding showed a protective effect for breast cancer risk. A significant reduction of about 66% in the risk of breast cancer was observed among those women who breast-fed their first child for more than 12 months, compared to those who did not lactate their first child. The protective effect of lifetime lactation was estimated to be about 74% for women who breast-fed more than 12 months compared to those who did not breast-feed their children.

Finally, the proportion of menopausal women was similar for both groups; thus, the OR was very close to the null value.

The serum levels of DDE and *p'p'*-DDT are shown in Table 2. The arithmetic mean value for DDE measured on the basis of lipid weight was 562.48 ± 676.18 ppb for the case group (range, 10.24–4661.44), and 505.46 ± 567.22 ppb for the controls (range, 0.004–4361.75). This difference was not statistically significant. The mean for the case group using normalized values (square root of the crude values) was 20.92 ± 11.21, and the mean for the controls was 20.46 ± 9.36.

On the basis of wet weight, the arithmetic mean values of DDE for the cases were 4.75 ± 5.04 and 4.07 ± 4.12 ppb for the controls. The geometric means for cases and controls were 1.23 and 1.06, respectively, which was not statistically significant. No statistically significant differences between the groups occurred for comparisons of *p'p'*-DDT values measured on the basis of lipid or wet weight.

In Table 3, the results of the ANOVA models fitted on the transformed DDE values are presented. DDE levels increased steadily with age among cases and controls. By contrast, in the control group, the DDE levels decreased significantly with increasing duration of lactation for the first child. These results hold even after excluding the nulliparous women from the referent category. There were, however, no significant differences between case and control comparisons for DDE levels by age at menarche or age at first birth.

DDE levels were lower among those women who had four or more children compared to nulliparous women; the same pattern was observed among women who lactated all births for more than 25 months

Table 3 *Arithmetic means of serum DDE (ng/g) by selected variables in the study population*

Variable	Cases			Controls			P^b
	$\bar{X}^a$	SD	*n*	$\bar{X}^a$	SD	*n*	
Age (yr)							
20–29	422.52	839.94	9	421.13	588.08	7	0.395
30–39	288.98	185.53	27	355.91	279.68	26	
40–49	597.94	596.36	40	487.38	607.83	49	
50–59	744.59	793.32	31	470.92	413.04	30	
60–69	355.13	232.68	16	593.89	437.72	16	
70–79	834.59	1046.39	18	888.97	1001.79	13	
P for trend	0.026			0.021			
Age at menarche (yr)							
≤12	548.43	767.81	60	555.02	700.15	45	0.322
>12	579.92	604.70	80	485.16	500.04	94	
P for trend	0.247			0.683			
Parity							
Nulliparous	685.39	854.47	26	672.85	876.02	15	0.787
1	722.19	1139.92	18	760.84	504.32	8	
2 or 3	503.68	493.19	47	450.19	381.20	43	
≥4	479.57	478.83	47	462.63	577.60	73	
P for trend	0.494			0.153			
Age at first pregnancy (yr)							
<20	532.07	638.38	39	456.51	430.06	59	0.720
20–24	564.12	713.26	44	498.97	666.17	45	
≥25	497.42	502.61	32	535.87	406.04	22	
P for trend	0.330			0.398			
Duration of lactation, first live birth (months)							
Nulliparous	685.39	854.47	26	672.85	876.02	15	0.290
0	745.74	937.73	33	646.92	545.71	19	
1–6	414.43	299.36	35	459.39	305.77	42	
7–12	403.36	494.76	33	524.02	710.83	46	
>12	647.47	521.39	14	288.74	178.04	19	
P for trend	0.434			0.023			
Duration of lactation, all births (months)							
Nulliparous	685.39	854.47	26	672.85	876.02	15	0.496
0	651.83	712.80	23	854.77	604.31	10	
1–12	542.32	788.11	33	590.40	398.44	30	
13–24	494.61	406.42	18	336.58	200.00	20	
>25	480.43	523.14	41	427.06	592.46	66	
P for trend	0.810			0.070			
Menopausal status							
No	491.82	558.47	70	453.47	561.58	69	0.944
Yes	632.15	772.72	71	555.30	572.04	72	
Family history of breast cancer							
No	563.90	699.49	126	513.40	579.26	134	0.508
Yes	550.51	450.95	15	353.43	202.47	7	
Quetelet index (kg/m^2)							
<20	435.57	416.20	6	885.71	1054.25	12	0.110
20–24	460.45	574.42	36	526.18	783.62	29	
25–29	629.00	653.21	59	393.04	265.76	67	
≥30	575.22	818.21	40	565.89	508.93	30	
P for trend	0.546			0.512			

[a] $\bar{X}$, arithmetic mean.
[b] Two-way ANOVA test, using the geometric mean values.

compared to nulliparous women and to women who had children but did not breast feed.

The mean values of DDE were lower before than after menopause among the cases (491.82 *versus* 632.15) and the controls, (453.46 *versus* 555.30), but these differences did not reach statistical significance. With regard to familial history of cancer or body mass, again the differences between cases and controls were not significant. Serum DDE levels increased slightly with the Quetelet index among cases but decreased among controls.

ORs for breast cancer by serum levels of DDE measured on the basis of lipid weight are shown in Table 4. After categorizing DDE values in tertiles, the corresponding age-adjusted ORs for the contrast of tertile 2 and tertile 3 *versus* tertile 1 were 0.69 (95% CI, 0.38–1.24) and 0.97 (95% CI, 0.56–1.70), respectively. These values remained nonsignificant, although they became smaller after adjusting for Quetelet index, the total amount of time that the woman breast-fed her first child, parity, familial history of breast cancer, and time elapsed since first birth. Fitting separate logistic regression models for menopausal and nonmenopausal women did not uncover any significant differences in either groups. The results also remained essentially the same when equivalent models were fitted using age at first birth instead of time elapsed since first birth, thus excluding the subgroup of nulliparous women (data not shown in tables).

Finally, the mean values of DDE serum levels were not statistically different across diagnostic categories to which the controls belonged. The mean DDE levels ranged from 211.72 ± 70.98 ppb for infectious diseases to 848.57 ± 258.98 for disorders of the nervous system (one-way ANOVA; $P = 0.7482$; data not shown in tables)

DISCUSSION

In this study, an increasing level of serum DDE was not associated with a higher risk of breast cancer. In fact, the ORs for breast cancer were slightly lower among women with higher serum levels. Adjust-

Table 4 *Adjusted ORs for the effect of DDE on breast cancer risk*

DDE (ng/g)	Cases	Controls	O.R.[a] (95% CI)	O.R.[b] (95% CI)	O.R.[c] (95% CI)
All subjects					
<242.11	50	44	1.0	1.0	1.0
242.11–509.25	42	52	0.69 (0.38–1.24)	0.58 (0.30–1.09)	0.60 (0.31–1.16)
>509.25	49	45	0.97 (0.56–1.70)	0.79 (0.43–1.46)	0.76 (0.41–1.42)
Number of pairs			141	138	138
Premenopausal					
<242.11	27	23	1.0	1.0	1.0
242.11–509.25	22	28	0.83 (0.34–2.02)	0.59 (0.22–1.60)	0.67 (0.24–1.90)
>509.25	21	18	0.76 (0.29–1.97)	0.63 (0.23–1.76)	0.64 (0.22–1.90)
Number of pairs			56	55	55
Postmenopausal					
<242.11	23	21	1.0	1.0	1.0
242.11–509.25	20	24	0.85 (0.30–2.41)	0.68 (0.22–2.09)	0.82 (0.24–2.82)
>509.25	28	27	1.07 (0.46–2.49)	0.75 (0.28–2.04)	0.79 (0.27–2.28)
Number of pairs			58	56	56

[a] Adjusted by age.
[b] Adjusted by age, Quetelet index (kg/m^2), and breast feeding with first birth.
[c] Adjusted by age, Quetelet index (kg/m^2), and breast feeding with first birth, parity, familial history of breast cancer, and time elapsed since first birth (years).

ment for various breast cancer risk factors had little effect on the ORs. The results of previously published epidemiological case-control studies have been inconsistent, with positive associations reported by Falck *et al.* (3), Wolff *et al.* (4), and Dewailly *et al.* (5), and mixed results by Krieger *et al.* (6) and Savitz (7). Interpretation of the results from the Krieger study (6) is complicated because positive associations were observed among blacks and whites, but an inverse association was observed among Asians (7). Our findings most closely resemble those Krieger observed among Asians (6).

In case-control studies such as this, various methodological issues need to be considered. To account for potential confounding, factors related both with breast cancer and DDT metabolism, such as obesity and lactation, and other potential confounders, were taken into consideration when fitting multiple conditional logistic regression models. Therefore, the absence of an association between serum DDE levels and breast cancer in these data could hardly be explained by the lack of control of these variables. The positive association reported by Wolff *et al.* (4), however, was also adjusted for several potential confounders, including lactation.

Our results could be biased if the diseases affecting the women recruited as controls were also associated with the DDE levels. We are unaware of any association between DDE levels and the conditions observed among our controls. Furthermore, levels of DDE were similar among the diagnostic categories of the controls, suggesting that no particular condition was associated with DDT.

An imperfect measurement of the exposure of interest (DDE levels) among the entire study population would induce misclassification. Nondifferential (*e.g.*, similar for cases and controls), misclassification would most likely attenuate the measures of effect (ORs for breast cancer). Procedures used to diminish measurement error included blinding the laboratory chemists with regard to case or control status and the study hypothesis and the inclusion of additional reference material, blanks, and samples with DDE added to them. Thus, any laboratory error is likely to be nondifferential.

Differential errors could arise because of effects of breast cancer or treatment on serum levels. Chemotherapy does appear to increase serum levels (11), but it is not a problem in our study, because blood samples were drawn prior to any treatment. Information on levels of DDT/DDE on blood drawn before and after breast cancer diagnosis is not available. In contrast, if the onset of cancer resulted in reduced serum, levels our results could be biased toward the null value.

The estrogenic activity of *o'p*-DDT is greater than that of DDE (12). It was not possible, however, to relate serum DDT levels with breast cancer, because our limit of detection for *o'p*-DDT was 1 ppb (ng/ml), and only 3% of our study population had serum values above this level.

According to the National Health and Nutrition Examination Survey II carried out between 1976 and 1980, the median level of DDE measured on the basis of wet weight was 11.8 ppb (13). Taking this value as reference, we observed that in the study by Krieger *et al.* (1964–1969), approximately 97% of the subjects had DDE levels above that cutoff point; in contrast, only 18.75% of the subjects studied by Wolff *et al.* (1985–1991) and 4.25% in our study population (1994–1996) surpassed the reference set by National Health and Nutrition Examination Survey II. Thus, the fact that our study did not find an association does not preclude the possibility that DDT could still be a risk factor for breast cancer at higher levels of exposure. The situation is complicated further, because the exposure has generally decreased over time in most regions of the world, as has happened in Mexico since 1972 (8).

The serum DDT/DDE levels in our subjects were low. We anticipated that levels in the Mexico City population would be similar to others reported previously elsewhere in the country and higher than those observed in the United States. The reason for this expectation was that DDT is still used for malaria control in most regions of Mexico. However, to explain why DDT/DDE serum levels in Mexico City were not higher that those in the United States, we must consider that in spite of DDT still being used in Mexico, the amount consumed has declined considerably since the 1970s. The Mexico City valley, where our study subjects reside, does not harbor the mosquito transmitting malaria because of its altitude, and therefore, a DDT spraying program has not been mounted there. Finally, the amount of DDT exposure occurring through the food chain, the route most relevant to our subjects, may be similar in most countries.

In regard to history of breast-feeding, our results agree with those reported by Gladen and Rogan (14), who also found that DDE levels in maternal milk decreased with an increasing duration of lactation.

Overall, our findings do not lend support to the hypothesis that DDT is causally related to breast cancer at the body-burden levels found in our study population but do not exclude the possibility that higher levels of exposure could still play a role in the etiology of this tumor.

ACKNOWLEDGMENTS

We express our gratitude for his technical advice to Dr. Robert Dubrow; for field coordination and supervision to Drs. Laura Torres-Arreola and Luisa Torres-Sánchez, for her participation in the statistical analysis to Patricia Olaya; for laboratory work to Rosa M. García and Marisela Uribe Ramirez; and to Dr. Dolores Saavedra and Dr. Alfonso Torres-Lobatón for granting access to their hospital patients. Finally, we acknowledge Reina Collado and Matilde Fuentes for typing the manuscript.

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