Organochlorine exposure and breast cancer risk in Colombian women

Exposição a organoclorados e risco de câncer de mama em mulheres colombianas

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Abstract *An epidemiological study was performed in Santafé de Bogotá, Colombia, with a total of 306 women enrolled, including 153 incident BC cases and 153 age-matched controls. The objective of this study was to evaluate the association between BC risk and serum dichlorodiphenyl-dichloroethene (DDE) levels. Sociodemographic and reproductive data, diet, and past exposure to pesticides were obtained through a structured questionnaire. Chemical analysis of samples was performed by high resolution gas chromatography-ECD. Likelihood of developing BC by exposure to these substances was evaluated through odds ratios (OR) adjusted for: first-child breast-feeding, family BC history, body mass index (BMI), parity, and menopausal status. Data analysis was performed by conditional logistic regression techniques. Adjusted OR for exposure to serum DDE and BC suggests an increase risk of BC in the higher category of DDE exposure (OR = 1.95; CI 1.10-3.52). The test for trend was not statistically significant (p = 0.09). We confirm that serum DDE levels bear a positive association to risk of BC and could support the association between risk of BC and burden of DDE exposure.*

Key words *Breast Neoplasms; Environmental Exposure; Pesticide Exposure; Logistic Regression; Case-Control Studies*

Resumo *Em estudo epidemiológico realizado em Santa Fé de Bogotá,Colômbia, 153 casos incidentes de câncer de mama (CM) foram comparados com 153 controles, pareados por idade. O objetivo deste estudo foi avaliar a associação entre o risco de CM e níveis séricos do pesticida DDT (DDE). Dados reprodutivos e sócio-demográficos, características da dieta e informação sobre exposição pregressa a pesticidas foram obtidos por meio de questionário. A análise química de amostras de sangue foi realizada através de cromatografia a gaz de alta resolução – ECD. A verossimelhança de desenvolver CM como decorrência de exposição a estas substâncias foi avaliada através de* odds ratios *(OR), obtidas por técnicas de regressão logística condicional, ajustadas para amamentação do primogênito, história familiar de CM, índice de massa corporal,paridade e presença de menopausa. As OR ajustadas sugerem um risco aumentado de CM no estrato de maior exposição a DDE (OR = 1,95; C.I. 1,10-3,52),embora o teste de tendência fosse estatisticamente não significativo (p = 0,09). Os resultados encontrados constataram que os níveis séricos de DDE estão positivamente associados com o risco de CM, e poderiam apoiar a hipótese desta associação.*

Palavras-chave *Neoplasias Mamárias; Exposição Ambiental; Exposição a Praguicidas; Regressão Logística; Estudos de Casos e Controles*

Introduction

Breast cancer (BC) is the most common cancer among women and is a growing problem (World Cancer Research Foundation/American Institute for Cancer Reserach, 1997). In Colombia it is the second leading cause of cancer-related deaths among women, as it is for American women (Instituto Colombiano Nacional de Cancerología, 1990). Inherited mutations in the BRCA1 or BRCA2 genes, increasing age, early menarche, late menopause, nulliparity, primiparity after age 30, personal or family history of BC, and possibly high-fat diet are the best documented risk factors to date. Mortality rates are falling among white women, especially those under 65 years of age, even in South American countries (World Cancer Research Foundation/ American Institute for Cancer Reserach, 1997). It has been suggested that some chemical contaminants such as DDT-related compounds, which possess estrogenic activity (as xenobiotic estrogens), could be associated with the incidence of this type of tumor (Wolff & Weston, 1997; Wolff et al., 1993; Krieger et al., 1994). The alternative estradiol pathway yields the genotoxic 16 alpha-hydroxyestrone (16 alpha-OHE1), which enhances breast cell growth, increases unscheduled DNA synthesis, and oncogene and virus expression and increases anchorage-independent growth (Wolff & Weston, 1997; Davis et al., 1993). Epidemiological studies comparing exposure to DDT and BC are inconclusive (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Van't Veer et al., 1997; Dewailly et al., 1994; López-Carrillo et al., 1997), probably because they have been performed in populations among whom DDT use has been prohibited for over 20 years (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Van't Veer et al., 1997; Dewailly et al., 1994). In Colombia DDT was used until 1986 in agriculture, principally for the production of cotton, rice, and flowers for export and has been restricted for vector control since 1994 (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Van't Veer et al., 1997; Dewailly et al., 1994). Some studies in Colombia have shown the presence of DDT and DDE levels in fish and animal tissues, water, and some foods (Ministerio de Salud de Colombia, 1992). In this context, an evaluation is needed of the potential effect of organochlorine pesticides on populations with higher exposure levels than those studied to date. The aim of the present study was to assess the association between BC and DDE (dichlorodiphenyldichloroethene), an organochlorine pesticide, in a group of Colombian women.

Materials and methods

Subjects

A hospital case-control study was carried out in Bogota, Colombia, from July 1995 to February 1996. Cases included 164 histologically confirmed incident BC patients identified in the main hospital of the capital city (Colombian National Cancer Institute), and those with no clinical indication of distant metastases at discharge were included. An age-matched control (±2 years) was selected for each case from a similar hospital that provides care for non-cancer patients from San Juan de Dios: Hospital Out-Patient Services: (Urology, Ophthalmology, Internal Medicine, and Ear, Nose, and Throat Departments). From a total of 328 patients interviewed, chemical analysis of blood samples was obtained for 306 participants, and the results are presented in this paper. Three questionnaires were used in the interviews with participants prior to signing the informed consent. The first questionnaire explored socioeconomic and reproductive characteristics, family and patient health history, and occupation. The second focused on diet, and the third explored prior pesticide-related and occupational exposure. Sample size was calculated to detect twice the risk for the factors to be evaluated, with a power of 80% and confidence level of 95% when such differences existed (Breslow & Day, 1980).

Blood samples

A 10 ml blood sample was obtained from each woman, using sterile vacutainers. We obtained the serum by centrifugation and stored it in glass vials (prewashed with hexane) covered with a Teflon cap. Serum specimens were kept in frozen storage at the National Oncology Institute in Bogota at -7ºC during the study period. Blood samples were drawn prior to any chemotheraphy in the cases.

Chemical analyses

Organochlorine compounds (DDT and metabolites DDD and DDE) were analyzed by high resolution gas chromatography-ECD following USA Environmental Protection Agency recommendations. A 2 ml serum sample was transferred to a 15 ml test tube and 6ml hexane were added. Extraction was performed for 2 hours in a low-speed rotator mixer. Transfer of 5ml hexane extract was made to a 4 ml vial and evaporated with nitrogen steam. One microliter was analyzed by electron capture high resolution gas

chromatography under standard conditions (Dale et al., 1996). Chemical results were reported on the basis of volume (ng/ml or ppb). DDE detection limit was 0.10 part per billion (ppb). In addition, laboratory personnel were blind to the healthy-versus-diseased status of the samples, so as not to bias measurement of exposure.

Statistical analysis

Data analysis was performed using STATA 5.0 software (Texas University). Although skewed distributions of DDE required log-transformations in data analysis, results are presented on their original scales. Center-adjusted means were calculated for DDE and major risk factors for BC, and the Wilcoxon matched-pairs signed ranks test was used for non-parametric comparisons of median concentrations and the matched test for the mean comparisons. Odds ratio (OR) was used as the principal measure of association. To identify potential confounders, mean levels of risk factors for BC were compared among tertiles of DDE concentration in controls: BMI (kg/m^2), parity, first-child breast-feeding (months), cumulative breast-feeding (months), family history of BC, and socioeconomic conditions. OR and 95% CI for BC were obtained from multivariate conditional logistic regression analysis (maximum likelihood ratio test) (Breslow & Day, 1980), modeling DDE first in tertiles and as a continuous variable, comparing risk for subjects in the first and last tertile. Test for trend was conducted through the exact test for trend (modified Wilcoxon test for trend), and we included the continuous DDE variable in the saturated model (p value for trend). Interaction terms between DDE and BMI, parity, cumulative breast-feeding (months), prior family BC, and geographic origin prior to 15 years of age (rural, periurban, or urban) were tested, but none appeared to be statistically significant. Other authors have adjusted the models to some of these variables (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Van't Veer et al., 1997; Dewailly et al., 1994; López-Carrillo et al., 1997), making our results more comparable.

Results

The case-control DDE analysis included 153 women with BC and 153 healthy matched controls. Age of women enrolled in the study varied from 26 to 75 years, with a mean age of 50. Table 1 describes adjusted reproductive risks associated with BC, and risk factors associated with the event were found to be nulliparity as compared to women with over three children, age at first childbirth (over 25 as compared to under 20), and family history of BC. Protective factors for BC included first-child breast-feeding and cumulative breast-feeding; the latter provided 70% protection as compared to those that had children but had not breast-fed (OR = 0.30; CI 0.14-0.64). We also found that socioeconomic level determines life styles and reproductive events in women, based on which we calculate that middle class women present a risk of BC 3.82 times higher than low-income women. BMI was associated with the disease, but was not statistically significant. Early menarche was assessed as a possible risk factor for this neoplasm. Mean age at menarche was 13 years and there was no positive association with BC in the study population.

As for the questionnaire including indirect exposure to pesticides, we found that women referring frequent (weekly) past use of pesticides/insecticides had a BC risk of 1.88 (CI 0.90-3.55) as compared to those using such substances very rarely (few times a year). Risk for women using insecticides monthly to quarterly was 1.33 (CI 0.75-2.36) as compared to those using them only very rarely. The most frequently used insecticide group was the carbamates, followed by pyrethroids and then organochlorines, generally used inside the home without any kind of individual protection (data not shown). Such data could be considered surrogates for organochlorine use.

Table 2 shows mean serum pesticide. Total population mean DDE was 2.90 ppb, and mean serum pesticide was higher in cases (3.30 ppb) as compared to controls (2.90 ppb), reaching statistical significance in the comparison of the means transformed into natural logarithms. The difference in the medians between the cases and controls also proved to be statistically significant, and this association was only maintained for premenopausal women with the data stratified for menopausal status.

Table 3 describes the adjusted odds ratio for the effect of DDE on BC in the Colombian population. Risks for BC in the case group were higher than those in the controls, but only for the last tertile as compared to those with lowest exposure (adjusted OR = 1.95; CI 1.10-3.52). Upon stratifying the data according to menopausal status, the association disappears between environmental exposure to organochlorine pesticides and the risk of developing this type of neoplasm, as shown in table 3. On the other hand, we did not find a linear trend for this association in any case (p value for trend > 0.05).

Table 1

Adjusted Odds Ratios for the reproductives variables and the breast cancer risk in the colombian women.

Suspected factor	OR	CI95%	Value p[5]
Age at menarche (years)*			
8-13	1.02	0.50 - 2.14	0.40
14-15	1.42	0.82 - 2.50	–
≥ 16	1.0	–	–
Parity**			
Yes	2.34	1.1 - 5.44	0.001
No	1.0	–	–
Age at birth first child*			
≥ 25	3.1	1.21 - 3.0	–
20-25	1.56	0.84 - 2.60	0.636
< 20	1.0	–	–
Breast feeding at first child (months)*			
13-max	0.76	0.30 - 1.90	–
1-12	0.60	0.24 - 0.14	0.40
0	1.0	–	–
History of lactation lactation (months)**			
≥ 24	0.63	0.30 - 1.25	–
1-23	0.30	0.14 - 0.64	0.001
0	1.0	–	–
Familial breast cancer*			
Yes	8.0	2.0 - 34.0	–
No	1.0	–	–
Place of origen before 15 years*			
Area rural	2.35	1.32 - 4.20	–
Area suburban	3.0	1.16 - 7.22	–
Area urban	1.0	–	–
Quetelet index (Kg/m²)*			
≥ 30	1.20	0.91 - 3.0	–
25-29	1.60	0.62 - 2.30	0.96
24	1.0	–	–
Menopausal status			
No	1.0	–	–
Yes	0.62	0.22 - 1.73	–

OR = Odds ratio; CI95% = confidence Intervals, p[5] = value for trend, n = 306.
* Adjusted for: familial breast cancer, place of origen before 15 years (rural, suburban, urban), breast feeding at first child (months), parity, Quetelet index, age at birth first child and menopausal status.
** Adjusted for: familial breast cancer, place of origen before 15 years, Quetelet index, age at birth first child ad menopausal status.

The fundamental difference of a 95% excess risk for cases as compared to controls was found in the final tertile, where the highest levels are observed, especially among younger women. The association between DDE and BC in this group of Colombian women was similar within strata of age at birth of first child, parity, and history of breast-feeding, as well as geographic origin prior to 15 years of age.

Discussion

DDT and metabolites have been called "endocrine disrupters" because evidence suggests that they can disrupt the endocrine system and contribute to the development of BC (Wolff & Weston, 1997; Wolff et al., 1993; Davis et al., 1993; MacLachlan & Arnold, 1996; Allen et al., 1997; Wolff & Landrigan, 1994; Hansey, 1994). One way DDT influences BC risk is by increasing the production and circulating blood levels of certain types of estrogens (Wolff & Weston, 1997; Davis et al., 1993; Allen et al., 1997; Wolff & Landrigan, 1994). In this sense, DDT may act as a promoter of breast tumors induced by other carcinogens (Wolff & Weston, 1997). The observation that DDT could behave as an estrogen provided a framework for the understanding that chemicals not specifically designed to have hormonal activity may in fact display it (MacLachlan & Arnold, 1996). In this sense, we

Table 2

Plasma levels of DDE among case patients ad controls in the columbian study.

DDE (ng/ml)*	Case patients and controls (n)	Mean (± SD) value	Median value	p**
Entire study population				
Case patients	153	3.30 ± 4.12	1.60	0.025
Controls	153	2.50 ± 3.60	0.94	–
Menopausal status				
Premenopausal				
Case patients	60	3.02 ± 4.35	1.46	0.040
Controls	60	2.1 ± 2.80	0.80	–
Postmenopausal				
Case patients	93	3.45 ± 3.0	1.72	0.22
Controls	93	3.0 ± 4.03	1.10	–

* Values were transformed to log (DDE).
** Wilcoxon matched – Pairs signed-ranks tes.
n = 306

Table 3

Adjusted Odds Ratio for the effect of DDE on breast cancer in the columbian women.

DDE (ng/ml) serum levels	Cases	Controls	OR* CI 95%	OR** CI 95%	p- value***
Total study population					
0.10-0.14	39	55	1.0	1.0	–
0.15-1.96	45	47	1.26 0.72-2.22	1.20 0.64-2.25	0.09
1.97-19.2	69	51	1.82 1.10-3.10	1.95 1.10-3.52	–
Premenopausal					
0.10-0.14	15	22	1.0	1.0	–
0.15-2.06	20	21	1.25 0.54-3.0	1.40 0.55-3.43	0.08
2.07-19.2	25	17	1.84 0.82-4.13	2.46 0.96-6.30	–
Postmenopausal					
0.10-0.19	24	33	1.0	1.0	–
0.20-1.90	25	26	1.30 0.60-3.0	1.14 0.50-2.75	0.24
0.91-19.0	44	34	1.81 0.90-4.0	1.85 0.84 -4.05	–

* Matched pairid by age.
** Adjusted for breastfeeding at first child, familial history of BC (yes/no), parity (as continuous variable), Quetelet index (Kg/mt^2), menopausal status (yes/no).
*** p-value for trend (Wilcoxon rank-sum test for trend).
n = 306

found a risk association between BC and DDE serum levels for high DDE burden (i.e., the highest tertile compared to the lowest). We confirm that serum DDE levels bear a positive association with duration of breast-feeding, BMI, and age, as in previous studies (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; López-Carrillo et al., 1997). The same authors confirm that the longer the cumulative duration of breast-feeding and in some cases the greater the woman's parity, the lower the serum pesticide levels. In the opposite direction, increased age and BMI were associated with greater accumulation of DDE in serum and adipose tissue (Hunter et al., 1997; Van't Veer et al., 1997; Dewailly et al., 1994; López-Carrillo et al., 1997). With regard to menopausal status and serum pesticide concentrations, the results did not allow for a precise assessment, due to the diversity of results; on the other

hand, BC risk due to DDE exposure has been demonstrated for hormone-responsive breast cancers (López-Carrillo et al., 1997). In the current investigation, upon stratifying for menopausal status, a stronger association was shown between the disease and higher concentrations of DDE for both premenopausal and postmenopausal women, but without reaching statistical significance; the risk was slightly higher in younger women. In an aggregate evaluation of the study group (n = 306), a BC risk of 2 times was shown for the high exposure category (see table 3). The reason the values suggest higher exposure in younger women is probably that we are evaluating the damage to undifferentiated cells in younger women, with greater exposure due to delayed primiparity, shorter cumulative breast-feeding, and greater use of hormonal contraceptives, added to the presence of DDE at earlier stages in life (Kelsey et al., 1993; Wolff et al.,1993) in addition to the fact that DDE could contribute to an increase in circulating estrogens resulting from a summation of exposures (both endogenous and environmental). In the case of postmenopausal women, the action mechanism of DDE may be more related to the increase in circulating estrogens, along with peripheral production of the same (Kelsey et al., 1993). We can thus conclude that the effect of DDE can potentiate traditional risk factors, especially in younger women (Wolff & Weston, 1997). Our results are consistent with and similar to those presented by other authors (Wolff et al., 1993; Krieger et al., 1994; Hunter et al., 1997; Dewailly et al., 1994; López-Carrillo et al., 1997). In this sense, 61% of our DDE values were below 5.2 ppb, similar to the levels reported by López-Carrillo et al. (1997), according to whom out of the total serum DDE observed in their subjects, 77% (as compared to 46% in Wolff et al., 1993) were below this figure, corresponding in turn to the second quintile from the study by Krieger et al. (1994); in the latter, on the contrary, none of the study subjects had serum DDE values lower than 5.2 ppb. In Colombia, both the mean and the range of DDE concentrations were not as high as those reported by previous studies (Colombia mean for cases was 3.30 ppb as compared to 11.0 ppb in Wolff et al. and 4.75 ppb in Mexico). Our results confirm the hypothesis raised by Wolff et al., with similar characteristics in the pattern of the results (Wolff et al., 1993). The pesticide values reported for Colombia were lower, but this is explained by the fact that Colombian women reflect more recent exposures, and as has been documented it is a country where the use and production of DDT has declined dramatically (Ministerio de Salud de Colombia, 1992) as compared to other Latin American countries (Yuan et al., 1995). In order to approach the differences found in these studies as compared to the current investigation, one should consider the variability of the participants' sociodemographic characteristics, since these in turn determine reproductive patterns, diet, life styles, and family history of BC in women in the different geographic areas studied (i.e., Europeans versus Mexicans and Americans versus Colombians). One of these differences pertains to diet; it has been well-documented that women with a diet rich in phytoestrogens, antioxidants, and carotenes (vegetables, especially leafy vegetables, and fruits) are at lower risk of BC as compared to women with diets rich in protein and animal fat (World Cancer Research Fundation/American Institute for Cancer Reserach, 1997; Willet, 1997; Yuan et al., 1995; Goodman et al., 1997). The latter can be considered intervening factors in the bioaccumulation of pesticides and increased risk of developing BC. Likewise, exposure to pesticides in general (and especially DDE) varies, even among Latin American countries (Finkelman et al., 1994). The Mexican study concludes that there was no association between BC and exposure to organochlorines with a smaller sample size than that used in the current study and other recent ones (Hunter et al., 1997; Van't Veer et al., 1997; López-Carrillho et al., 1997). In addition, exposure was measured in women residing for at least 20 years in Mexico City, who had not been exposed to malaria eradication campaigns, in a society displaying changes in demographic, cultural, and diet patterns similar to those in developed countries (Romieu et al., 1997). Exposure to organochlorine pesticides in urban areas comes mainly from ingestion of foodstuffs (López-Carrillo et al., 1996). Although it is reported that agricultural DDT use in Mexico was suspended in the 1980s, DDT contamination was found in 1994, especially in meat and dairy products (López-Carrillo et al., 1996). The explanation for the different DDT exposures among Latin American countries might be difference in diet, since in Mexico a wide variety of fruits, vegetables (especially leafy vegetables), and grains are used in the daily diet, unlike the diet in urban areas of Colombia (Bogota, specifically). Special mention should be made of the high diet fiber consumption in Mexico (in grains, fruits, vegetables, and seeds), which has proven to display major risk-reducing capacity for cancer overall and breast and endometrial cancer in particular (World Can-

cer Research Foundation/American Institute for Cancer Reserach, 1997; Goodman et al., 1997). Such assessments are soon to be published.

There is some concern among researchers that cancer can affect body metabolism, including increasing the breakdown of fat stores. Since DDT and DDE can be stored in fatty tissues, this breakdown of fat stores could result in an increased release of DDT or DDE into the blood and even to some decrease in DDE levels in adipose tissue, perhaps due to a combination of chance and mobilization of energy from fat stores in cases (Falck et al., 1992). This would result in falsely elevated blood levels of this pesticide in BC patients and low breast fatty tissue DDE concentrations. In this sense, the European study, concluded that "*The lower DDE concentrations observed among the women with BC may be secondary to disease inception*" (Van't Veer et al., 1997:81), and in fact, they did not support the hypothesis that DDE increases risk of BC in postmenopausal women in Europe, contrary to the Canadian study (Van't Veer et al., 1997; López-Carrillo et al., 1997). Another relevant aspect of the European study is that it did not take into account the duration of breast-feeding to adjust the results of the association under study, and in regard to history of breast-feeding, different results agree that DDE levels in maternal milk decreased with increased duration of breast-feeding (Wolff et al., 1993; Hunter et al., 1997; Gladen & Rogan, 1995), also supporting the idea that this situation would reduce risk of BC (Wolff & Weston, 1997; Wolff et al., 1993; Hunter et al., 1997).

With regard to the methodological aspects of the current study, we might think that an imperfect measurement of the exposure of interest (DDE levels) among all women enrolled in the study would lead to nondifferential misclassification and attenuate the measures of effect (ORs for breast cancer). Thus, any laboratory error is likely to be nondifferential.

Due to different exposures to environmental factors including chemical compounds, diet, and highly local cultural aspects (genetically and/or geographically determined) that could explain differences in the results from exposure to DDE and risk of developing BC, one can conclude that this relationship is subject to the interdependence of these factors on individual susceptibility to BC, and that such interdependent factors have still not been fully incorporated into research. Evidence for this was the association observed between pesticide exposure and BC when comparing ethnic groups in the study by Krieger et al. (1994), a result that had not been observed when evaluating the group as a whole (Wolff & Weston, 1997; Krieger et al., 1994). Recent studies provide evidence that the synergistic activity of many common pesticides may be significant (Wolff & Weston, 1997; MacLachlan & Arnold, 1996; Allen et al., 1997; Wolff & Landrigan, 1994). In addition, interactions of chemicals in the body are not well understood. Simple additive models may approximate biological effects at one moment of exposure, but such models cannot take into account relative rates of metabolism, susceptibility due to inherited metabolic capacity, susceptibility due to breast epithelial development, or synergistic interactions of chemicals (Wolff & Weston, 1997; MacLachlan & Arnold, 1996; Allen et al., 1997; Hansey, 1994). Because of the absence of studies on women with known exposures to DDT and the inconsistent results in the studies examining levels of DDT/DDE in BC patients and women without the disease, and taking into account all these interrelationships, there is currently not enough evidence to affirm that DDT or DDE does or does not cause BC in humans. However, exposure to organochlorines in Latin America requires further evaluation in order to determine especially the potential damage to women's health. Enforcement of the current legislation on pesticide use should thus be strengthened.

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