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Organochlorine Pesticides in the Females Suffering from Breast Cancer and its Relation to Estrogen Receptor Status

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Abstract

Breast cancer is one of the most common types of cancer that occurs in females. Approximately 70% of breast tumors express the estrogen receptor. To date, established risk factors for breast cancer are only partially able to explain the causes for this disease. There have always been researchers' interests in evaluating the role of environmental chemicals, especially those with evidence of being hormonally active agents, which play an important role in breast cancer development. Organochlorine pesticides are one of those chemical which have received the most attentions because of their ability to concentrate onto food chain, fat-soluble and estrogenic activity while remaining persistent in the human body and environment. The present study is an attempt to explore the possibility and role of organochlorine pesticides in the development of estrogen receptor breast cancer.

A hospital-based case-control study was administered on 93 women, who underwent various surgeries for breast diseases, to observe the association between organochlorine pesticide exposures with reference to estrogen receptor status in the subjects suffering from breast cancer. Samples of blood, tumor and surrounding adipose tissue of the breast were collected from the subjects with estrogen positive, estrogen negative and benign breast lesions. The samples were then analyzed to determine the presence of organochlorine pesticides by using a gas–liquid chromatography equipped with an electron capture detector.

The α, β, γ and δ isomers of HCH (Hexachlorocyclohexane) and metabolites of DDT (Dichlorodiphenyltrichloroethane) such as p,p'-dichlorodiphenyltrichloroethane (p,p-DDT), o,p'- dichlorodiphenyltrichloroethane (o,p'-DDT), p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), and p,p'-dichlorodiphenyldichloroethane (p,p'-DDD) were frequently detected in the samples at significant level.

The result of this study shows that the exposure to potential estrogenic organochlorines may cause the development of estrogen receptor positive breast cancer. A possible mechanism on prognosis of hormone responsive breast cancers needs to be clarified.

Keywords: Organochlorine pesticides; Estrogen-receptor; Gas-chromatography; Benign breast disease

Introduction

Breast cancer is one of the most common cancers worldwide. Alarmingly, the incidence is raising rapidly, approximately 83,000 women who develop breast cancer approximately 45,000 women die every year because of this disease in India [1]. Breast cancer accounts for 23% of all the female cancers followed by cervical cancers (17.5%) in metropolitan cities such as Mumbai, Calcutta and Bangalore [2]. Although the incidence is lower as compare to the developed countries, the burden of breast cancer in India is alarming [3].

There are a number of well-established factors causing for the development of breast cancer such as increasing age, menarche<11 years, menopause>55 years, age at first birth>30 years, total number of children, nulliparity, absence of lactation, use of hormone replacement therapy, personal history of breast cancer, family history of breast cancer, prior history of radiation exposure or prior biopsy and known carriers of BRCA 1 and BRCA 2 mutations. But these factors do not fully explain the incidence or geographic variation in the disease [4]. It is estimated that as many as 80–90% of all cancers can be attributed to life-style and environmental factors are thought to be involved [5,6] although approximately 50% women who develop breast cancer have no identifiable risk factors beyond increasing age and gender [7].

It is known that DDT is a xenoestrogen, mimicking the action of estrogen [8]. The two organochlorines DDT and HCH persist in the environment, high concentration in the crops continually detected in the food chain [9], accumulate in human tissues and body fluids due to their lipophilic nature and also are excreted in breast milk [10-12]. Due to the human and environmental risks associated with the use of such organochlorine pesticides, they have been banned in several countries but are still used in India [13]. Human epidemiological studies on DDT exposure and the risk of breast cancer further introduced the concept of the estrogenic property of DDT [14-16] found as increased the risk of breast cancer with higher levels of DDE in plasma and breast adipose tissue. Krieger and Hunter [17,18] did not find any significant association with high DDE levels and breast cancer. The presence of Estrogen Receptors (ER) in breast tumors was associated with the risk

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for breast cancer [16] because estrogenic action of DDT and the risk of breast cancer postulated the possible interaction between DDT and ER. The studies on animals have shown that DDT increases the interaction of the receptor with the growth promoting genes in breast tissue, which enhanced breast epithelial cell proliferation *in vivo* and *in vitro* [19]. Increasing epithelial cell proliferation was also evident in human breast cancer epithelial cells in culture (MCF-7 cells) exposed to DDT [19-21]. Even though the exact mechanism of the estrogenic action of DDT is not known and the fact that DDT binds or interacts with human estrogen receptors in body would have further implications on the pathophysiology of the estrogenic response in tissues.

Estrogen stimulates proliferation of ER positive breast cell lines and may therefore be associated with ER positive human breast cancers [22]. Previous studies of potential effect of estrogenic organochlorines on breast cancer risk shows inconsistent results [15,17,18,23-32] and only few has taken into account estrogen receptor status [16,33,34]. The results of the study on small no. of Canadian women with estrogen receptor positive (ERP) tumors, but not those with estrogen receptor negative (ERN) tumors, had a higher DDE body burden as compared to women with benign breast disease [16].

Materials and Methods

Subject selection

The females presented to the General Surgery and Surgical Oncology OPD at Sir Ganga Ram Hospital, New Delhi with a palpable lump in the breast was included in the study.

These patients were from the population residing in and around New Delhi and were representative of the population. Sample size was calculated for statistically significant conclusion. Total ninety three (n=93) subjects were selected for present study, the immuno-histochemical estrogen receptor analysis were performed on fifty five (n=55) women. All subjects were categorized in to three groups, in which patients having estrogen receptor positive (n=34) and estrogen receptor negative (n=21) and 38 cases of benign breast disease serve as control group. The inclusion criteria for the estrogen receptor positive or estrogen receptor negative females with a palpable lump in the breast indicating the excision of lump, consent for surgery and histopathology confirming a malignant lesion and immuno-histochemical analysis of receptors were either negative or positive. Breast cancer is generally a disease of the elderly, being rare below the age of 35 years; we included only patients above 30 years in the benign group to allow a proper age matching. The other cases excluded from the study group were patients who had a mamographically detected non palpable lesion or a lump <1 cm in size. These were excluded as adequate tumor tissue could not be obtained for pesticide analysis after histopathological processing. Each case of malignant and benign group comprised samples of blood, tumor, and surrounding breast adipose, i.e., three samples. Prior to the commencement of research, ethical approval was obtained from the Institutional Human Ethics Committee of the Indian Institute of Toxicology Research, (IITR) Lucknow and Sir Ganga Ram Hospital, New Delhi.

Data collection: Personal details of the subjects including the factors that influence the risk of breast cancer such as age at menarche and menopause, total duration of breast feeding were recorded. Family history, if any, of breast carcinoma was noted together with use of tobacco and alcohol. Females after the age of 40 years until the age of menopause were categorized as peri-menopausal while others were categorized as pre or postmenopausal. A detailed clinical examination was performed. The lump, skin, nipple areola complex, chest wall, axilla for lymph node, abdomen, and any sites of bone pain were thoroughly examined.

Sample collection: The lumps were excised under general anesthesia and their sizes were noted in the maximum dimension. Adipose tissue from the breast was also obtained through the same incision from a site at least 2 cm away from the tumor site. At the time of surgery, 0.5–1.0 g of breast adipose tissue and tumor tissue were collected for the analysis. Samples were labeled with identification numbers to conceal malignity status and stored until analysis in a glass vial previously washed in hexane. The specimens was stored in 40% formaldehyde solution and kept in refrigerator. Approximately 5 ml of blood also withdrawn from all patients and stored in pre-heparinized pesticide free vials. All the samples of adipose tissue, tumor, and blood from the two groups of women were coded and transported to the Analytical Toxicology Lab, IITR, Lucknow for pesticide analysis. The analytical toxicologist was totally blind to the medical history and final diagnosis of the subjects. All the chemicals used in the process were from Merck and of high purity grade (98%) and checked for any contamination before being used for extraction. Extraction method of pesticide residues was carried out as reported by Saxena and Siddiqui [33] with some modification. Samples were analyzed on a GLC Nucon 5765, equipped with 63Ni ECD under the conditions described by Siddiqui et al. [12]. Comparing peaks with those of standards enabled quantification and tentative identification of pesticides. Further confirmation of pesticides was based on dual column gas chromatography/mass spectrometry. Recovery experiments were conducted to check the analytical quality control. Six samples of each blood, tumor, and adipose tissue in triplicate were spiked with mixed standards of organochlorine pesticides at 5 and 20 ppb. The average recovery varied from 85% to 94%. Repeated analyses gives the variation coefficients of 14% at 5 ppb and 10% at 20 ppb, further controlled the accuracy of methods for pesticide estimation by participating in an inter laboratory quality assurance program (IITR, Lucknow) wherein variation coefficients 15% at 5 ppb and 12% at 15 ppb were observed. A quality check sample was always run with each set of samples for pesticide analysis to maintain accuracy and the confirmatory GC-MS analysis was performed only for qualitative determination of pesticides in samples, so after the GC analysis some samples were randomly selected. These selected samples were prepared by exchanging their solvent phase hexane to dichloromethane (DCM) for GC-MS analysis.

Statistical analysis: Kruskal-Wallis test was carried out to compare the distributions of selected variables between the control, ER-positive and ER-negative. The accepted level of type I error was $p<0.05$. The data were analyzed with the STATA statistical software package (Stata Corp, 1997).

Results

The characteristics of subjects (female), in control, ER-positive and ER-negative groups are described in Table 1. Significant differences between three groups were observed for age and were found higher and statistically significantly in ER-positive group. For abode 94.74% of patients in the control group, 90.48% in the ER-negative and 88.24% in the ER- positive group were drawn from urban areas in and around Delhi, rural or urban depending on the majority of time of stay in the past 30 years. One case in benign breast disease group, two cases in ER-negative group and three cases in ER-positive group had a positive family history of breast carcinoma (Table 1). The distribution of the risk factors age of menarche and menopause were similar in the three groups as the average months of breast feeding. Figures 1-3,

Characteristics		Control group (n=38)	Study group	
			ER-negative (n=21)	ER-positive (n=34)
Age* (Years)		37.34 ± 8.70	53.52 ± 11.98	55.26 ± 11.11
Height (Cm)		157.70 ± 5.98	154.34 ± 4.18	156.72 ± 4.43
Weight (Kg)		59.28 ± 11.74	62.55 ± 9.10	64.29 ± 11.28
BMI		24.12 ± 4.69	26.25 ± 3.69	26.08 ± 4.0
Menarche (Years)		13.57 ± 1.08	14.19 ± 1.03	14.31 ± 1.46
Menopause (Years)		44.57 ± 5.76	48.85 ± 2.28	46.76 ± 3.58
Breast feeding (Months)		27.44 ± 24.52	39.19 ± 18.65	37.88 ± 29.03
Number of children		2.15 ± 1.91	2.52 ± 0.67	2.55 ± 1.28
Lump size (Cm)		3.39 ± 1.45	4.57 ± 2.37	3.89 ± 1.89
Side of lump	Left	17(44.74%)	14(66.67%)	24(70.59%)
	Right	21(55.26%)	7(33.33%)	10(29.41%)
Abode	Rural	2(5.26%)	2(9.52%)	4(11.76%)
	Urban	36(94.74%)	19(90.48)	30(88.24)
Family history	Yes	1(2.63%)	2(9.52%)	3(8.82%)
	No	37(97.37%)	19(90.48%)	31(91.18%)
Menstrual status	Pre	24(63.16%)	1(4.76%)	2(5.89%)
	Peri	7(18.42%)	6(28.58%)	7(20.58%)
	Post	7(18.42%)	14(66.66%)	25(73.53%)

Values represented as mean ± SD and %age
Kruskal-Wallis test was applied
*p<0.001.

Table 1: Characteristics of the subjects of three groups with benign breast disease (Control subjects) and breast cancer with or without estrogen receptors.

respectively, present the levels of different organochlorine pesticides in the blood, adipose tissue, and tumor tissue of the breast as mean ± SD in women with benign breast disease (control subjects) and breast cancer with or without estrogen receptors. Levels of HCH and its isomers were found higher in ER-negative cases than in their controls. In case of DDT, its isomers were found higher in ER-positive cases. Levels of DDE and HCH were very much similar in the ER-positive cases and their controls. Additionally, there were no statistically significant differences in organochlorine pesticide levels between ER-positive and ER–negative cases. None of the pesticide levels were found statistically significant. The β-HCH ($p<0.05$), total HCH ($p<0.05$), p, p-DDE ($p<0.001$) and total DDT ($p<0.05$) were found statistically significant in tumor tissue. The β-HCH and total HCH were higher in ER-negative cases but p, p-DDE and total DDT were higher in ER-positive cases. In adipose tissue the p,p-DDE ($p<0.05$) was found significantly higher in ER-negative cases and total DDT ($p<0.05$) were found significantly higher in ER-positive cases.

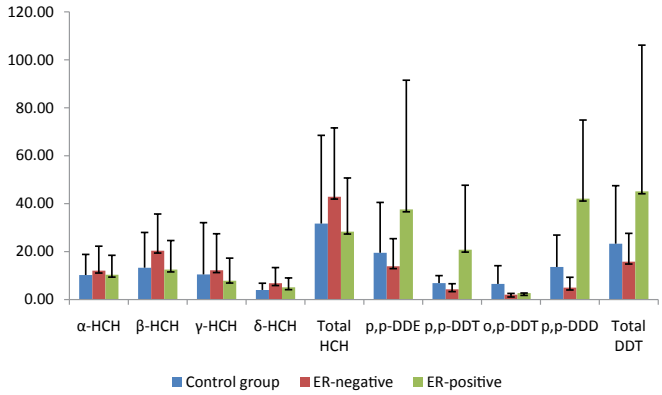
Discussion

Investigation of environmental contributions to breast cancer risk offers the potential to reveal more about the etiology of this complex disease and may provide opportunities for prevention of the most common cancer among women in India.

Only a handful of studies investigated whether ER status of breast tumors is related to body burdens of DDT or DDE and breast cancer risk [16] compared the concentrations of DDE in the breast adipose tissue of 9 women with ER-positive breast tumors, 9 women with ER-negative tumors, and 17 controls with benign breast disease (BBD). The mean concentrations of DDE in breast adipose tissue were substantially higher in the women with ER-positive breast tumors (2132.2 ± 2049 μg/kg) compared with levels in women with ER-negative breast tumors (608 ± 338.9 μg/kg) or controls (765.3 ± 526.9 μg/kg). Other case–control and nested case–control studies have not find any relationship between ER-positive status and levels of DDE in blood or adipose tissue [23,24,29-31]. For example, Zheng et al. [31] reported very similar mean serum DDE levels for the 163 cases with ER-positive tumors (435.5 ppb) and the 140 cases with ER-negative tumors (453.9 ppb). Another study conducted by Wolff and colleagues [34], the geometric mean serum DDE levels were not higher, but were lower in cases with ER-positive tumors (950 ± 2.41 ng/g lipid) compared to cases with ER-negative breast tumors (1300 ± 1.79 ng/g lipid). Studies published to date have not confirmed the observation originally made by Dewailly et al. [16] of a relationship between ER-positive receptor status of breast tumors and tissue levels of DDE.

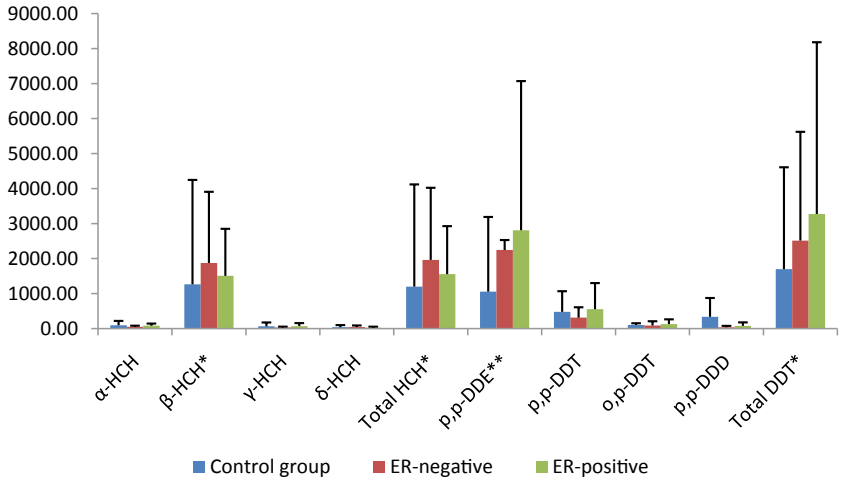
In this study subjects were categorized into rural or urban categories depending on the majority of time of stay in the past 30 years. With agriculture being the main site of application of pesticides, it was expected that the rural subjects would have higher pesticide levels than the urban subjects. However, our pilot study has shown that isomers of HCH are higher in urban subjects than in rural subjects. In the present study, there are only two cases of rural in the control group, 2 cases in ER-negative group and 4 cases in ER-positive group (Table 1) and is not likely to influence the results. When we looked at the pesticide residue levels in blood of the estrogen receptor positive group, DDT and its metabolites were found higher in ER-positive group, blood levels of HCH and its isomers were found higher in ER-negative cases than in their controls. In addition, there were no statistically significant differences in organochlorine pesticide levels between ER-positive and ER–negative cases. Tumor tissue levels of p,p-DDE and total DDT were significantly elevated ($p<0.001$ and $p<0.05$ respectively) in ER-positive cases. However, in case of β-HCH and total HCH, the levels were found significantly higher ($p<0.05$ each) in ER-negative cases. Our results are well supported by the findings of Dewailly et al. [16], who also found higher level of DDE in ER-positive tumors, same as our results.

In our study adipose tissues, p,p-DDE and total DDT ($p<0.05$ each) was found significantly higher in ER-negative cases. These results are not in the same line as Dewailly, reported higher mean levels of DDE in breast adipose tissue samples of women with ER-positive breast tumors (2132.2 ± 2049 μg/kg) compared with levels in women with ER-negative breast tumors (608 ± 338.9 μg/kg) and controls (765.3 ± 526.9 μg/kg). However, other studies did not find any relationship between ER-positive status and levels of DDE in blood [29,35,36] or adipose tissue [28,35]. An adverse effect of organochlorine pesticides on women



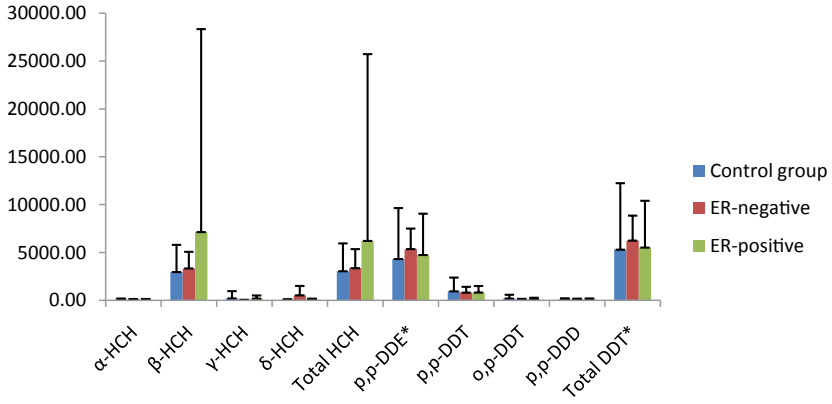
* Results are in ppb
Values represented as mean ± SD.

Figure 1: Blood concentration of organochlorine pesticides in women with benign breast disease (control subjects) and breast cancer with or without estrogen receptors.



Results are in ppb
Values represented as mean ± SD.

Figure 2: Tumor concentration of organochlorine pesticides in women with benign breast disease (control subjects) and breast cancer with or without estrogen receptors.



Results are in ppb
Values represented as mean ± SD.

Figure 3: Adipose concentration of organochlorine pesticides in women with benign breast disease (control subjects) and breast cancer with or without estrogen receptors.

with ER-positive tumors could be anticipated, as this compound is able to stimulate the growth of human estrogen-sensitive cells [36]. Another non-hormonal mechanism must lie behind the poorer prognosis of women with ER-negative tumors. Possibly, exposure to organochlorine pesticides may lead to development of breast tumor. In some studies beta-HCH has estrogenic properties with the failure to demonstrate binding of beta-HCH to ER [37,38].

A plausible mechanism in which organochlorine compounds could act as an etiological factor for breast cancer lies in their ability to act as xenoestrogens [8]. This is related to their estrogen receptor agonist activity, and to the fact that they are metabolized in a manner similar to the primary endogenous estrogen i.e. estradiol. Estradiol is metabolized via one of two pathways that produce products with different estrogenicity. The first pathway yields a product known as 2-hydroxyestrone, a compound with minimal estrogenic activity thought to be an inactive and benign metabolite. The second metabolic route yields 16-α-hydroxyestrone, a potent estrogen. It has been postulated that by Telang et al. [39] that either inhibiting the second pathway, ultimately reducing the amount of 16-α-hydroxyestrone, or by enhancing the first pathway of estrogen, which produces the benign metabolite.

These compounds could displace endogenous estrogen from its receptor thereby altering the stimulating / inhibiting effects of estrogen at the level of the cell or tissue. They could also dominate the metabolic pathways of catabolism resulting in production of alternative compounds, which could also be estrogenic. The xenoestrogens may also alter the predominant metabolism of endogenous compounds resulting in increased usage of alternative pathways, and production of metabolic products with varying degrees of estrogenic activity. Xenoestrogens which affect the relative functioning of the two previously described pathways could be responsible for shifting the overall estrogenic balance and hence modifying the risk of breast cancer.

It has been postulated that ER positive and ER negative breast cancers represent different entities of the disease [22]. If this hypothesis is correct the risk factor profiles may differ between the two types of breast cancer, especially for hormone related factors as parity, hormone replacement therapy and body weight. The present study's results on these breast cancer risk factors according to ER are in accordance with previous epidemiological studies, which do not provide consistent evidence to conclude that development of ER positive breast cancer is associated with exposure to estrogen related factors [17,40-45].

The present study support the hypothesis that estrogen related risk factors or potential estrogenic organochlorines (HCH) increase the risk of developing ER negative tumors, whereas DDT increases the risk of developing ER positive tumors. However, this finding should be interpreted with caution due to the limited number of ER negative cases, so whether exposure to estrogenic organochlorine compounds affect the risk and prognosis of a hormone-responsive breast cancer needs to be clarified. It now seems likely that whatever environmental exposures contribute to the risk of breast cancer, exposure to organochlorine cannot be ruled out, it should be taken into consideration in future studies that seek to understand environmental risk factors for breast cancer with large number of samples.

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