HIGH ORGANOCHLORINE BODY BURDEN IN BREAST CANCER WOMEN WITH ESTROGEN RECEPTORS

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In humans, few studies indicate a possible association between organochlorine (OC) exposure and breast cancer. Wasserman (1976)[1] reported that 9 women who died of breast cancer had higher concentrations of PCBs and o,p'-DDT in malignant tissue than in adjacent tissues of both cases and controls (n=5). Moreover, adipose tissue concentrations of o,p'-DDT and dieldrin were higher in cases than in controls.

In 1980[2], Unger and Olsen reported higher content of PCB and DDE in a lipid extract from breast cancer patients (n=16), compared with that of controls (n=22). However in 1984, Unger did not found any differences after controlling for fat percentage and age. Recently, Falck[3] found that mean concentrations of PCBs (Aroclor 1260) and p,p'-DDE were 50-60 % higher in mammary adipose tissue of 20 women with malignant breast disease compared with 20 women with benign breast disease. Finally Manz et al.[4] (1991) reported mortality data of workers exposed to dioxin (TCDD) and found a slight increase in breast cancer mortality among women (SMR= 2.15, CI= 0.98-4.09).

Some epidemiologic studies of breast cancer suggested that if ever having breast-fed is a protective factor for breast cancer, it might be seen more consistently in younger women. These studies indicated risk ratios ranging from 0.45 to 0.67 for women with more than 12 or 24 months of total life - duration of lactation compared with parous women who never breast-fed. This protective action could be due to the high excretion rate of these lipophilic chemicals through lactation, which would lower the OCs body concentration of women who had breast-fed in the past. However more recently, large prospective studies had reoriented epidemiologists towards the role of endogenous estrogens as a major risk factor[5].

Here we report on a preliminary study conducted in order to evaluate the possible role of environmental exposure to estrogen-like contaminants in breast cancer. Between November 1991 and May 1992, 41 women who had a diagnostic biopsy for a palpable breast mass volunteered to participate in the study. A consent form and a questionnaire on age, weight loss, gynecology, parity and breast-feeding history, was also administered. During biopsy, between 0.2 and 1 g of breast adipose tissue was also collected and analyzed for organochlorine determination. Fasting plasma were also obtained by venous puncture for the same chemical analyses. Breast samples were classified as mammary carcinoma in 20 cases (one case of in situ cancer was excluded) and benign diseases (adenoma, lipoma) for the remaining 20 women (controls). One case of severe dysplasia and one case of severe cell atypia were excluded from the control group. Estradiol receptors were measured a posteriori in the cytoplasm of breast cancer cells using the standard procedure. Fat and plasma samples were analyzed by high resolution gas chromatography using an electron capture detector for the following component: 10 PCB congeners (IUPAC No 99, 105, 118, 138, 153, 156, 170, 180, 183, 187) and 6 chlorinated compounds: p,p'-dichlorodiphenyl ethane (p,p'-DDE), βBHC, HCB, oxychlordane, transnonachlor and mirex. For fat samples, detection limit varied between 0.2 and 7 µg/kg depending of the amount of lipids available and the specific contaminant analyzed. For plasma samples, the detection limit was 0.05 µg/L. For "not detected" results, a value equal to half of the detection limit was used in statistical analyses, which were performed using the Statistical Analysis System (SAS Institute, NC, USA). The Wilcoxon rank sum test was used for non parametric comparisons of mean concentrations, when groups were stratified according to their estradiol receptor concentrations.

Cases (n= 20) and controls (n= 17) were similar for age (respectively 54 and 51 years). Mean blood concentrations of organochlorines were generally higher in cases than in controls. However, the only difference of statistical significance was for HCB concentration (316 and 225 ng/L for cases and controls respectively; p= 0.02). Mean concentration of p,p'-DDE were 5618 for cases and 3495 ng/L for controls, but this 38 % difference was not statistically significant. In adipose tissue, no statistically significant differences were observed, although mean p,p'-DDE concentration was 1274 µg/kg (lipid basis) for cases and 765 µg/kg for controls. Stratified analyses were performed among cases according to the concentration of estradiol receptor (ER) in the tumor cell cytosol. Women with an ER concentration less or equal to 10 fmol/mg proteins (the median concentration in the case group) were allocated to the ER- group, whereas those with an ER concentration

TABLE 1 Breast adipose tissue concentrations of organochlorines in control and breast cancer cases with or without estrogen receptors

	CONTROLS	BREAST CANCER CASES			
	(n= 17)	≤ 10 fmol/ng (n=9)		> 10 fmol/mg (n= 9)	
	X ± SD	X ± SD	p value	X ± SD	p value
DDE	765.3 ± 526.9	608.9 ± 338.9	0.63	2132.2 ±2049.9	0.01
HCB	33.4 ± 13.2	31.1 ± 11.5	0.53	41.7 ± 15.5	0.29
β-HCH	39.7 ± 23.4	34.7 ± 15.7	0.92	39.7 ± 11.5	0.77
Oxychlordane	31.1 ± 12.4	26.8 ± 7.4	0.59	38.9 ± 13.8	0.12
Transnonachlor	42.5 ± 17.8	34.8 ± 8.3	0.37	50.3 ± 11.1	0.07
Mirex	31.7 ± 28.1	13.2 ± 7.1	0.04	18.2 ± 15.5	0.20
PCB Cong.					
99	20.5 ± 11.7	14.6 ± 5.3	0.18	30.7 ± 17.0	0.05
105	6.0 ± 4.2	3.9 ± 1.8	0.26	7.3 ± 5.1	0.54
118	34.9 ± 20.1	19.1 ± 7.2	0.02	37.7 ± 20.0	0.91
138	70.1 ± 28.8	59.6 ± 15.0	0.47	78.1 ± 26.8	0.32
153	95.6 ± 36.3	82.2 ± 18.2	0.50	100.0 ± 30.7	0.59
156	17.9 ± 10.2	16.8 ± 5.3	0.68	15.7 ± 3.9	0.79
170	36.7 ± 18.3	28.2 ± 11.5	0.22	30.6 ± 11.1	0.61
180	86.2 ± 42.8	80.0 ± 25.3	1.00	74.6 ± 21.7	0.57
183	7.5 ± 2.0	6.8 ± 2.1	0.50	10.1 ± 4.6	0.12
187	20.4 ± 8.8	18.7 ± 7.3	0.57	19.4 ± 6.5	0.94
Σ PCBs	397.0 ± 161.5	331.5 ± 74.7	0.39	404.7 ± 130.7	0.79

higher than this value were classified in the ER+ group. Mean age and mean weight loss were similar for the two subgroups. No statistically significant differences were observed between mean concentrations of OCs in the breast adipose tissue of ER- cases and controls (Table 1). However, pp'-DDE concentration in the adipose tissue of ER+ women was three-fold greater than that of controls and cases ($P < 0.01$). Oxychlordane, transnonachlor, PCB congeners 99 and 118 concentrations were between 1.5 and 2 times greater in ER+ cases than in ER- cases ($P < 0.05$). No major differences were observed for the other organochlorines.

These results show that women with breast cancer have greater adipose tissue concentrations of organochlorine compounds than women with benign breast diseases, these differences being mainly due to high OC body burden in breast cancer women with estradiol receptors levels higher than 10 fmol/mg.

It is unlikely as discussed by Falck et al.[3] that these greater OCs concentrations in mammary adipose tissue could be attributable to a redistribution to the breast tissue during the disease process. First, differences in OCs concentrations were more important between ER+ cases and ER - cases than between all cases and controls. Secondly, the differences in mammary adipose tissue concentrations observed between cases and controls were also observed for plasma concentrations, which reflect total body burden. Mean DDE plasma concentrations were 3494 µg/L and 8533 µg/L for controls and ER+ cases, respectively (p= 0.05). Moreover, the linear correlation coefficients between adipose tissue concentrations and plasma concentrations (whole plasma) were highly significant: 0.95 for DDE and 0.60 to 0.88 for different PCB congeners ($P < 0.01$).
The role of organochlorines exposure as an environmental risk factor for breast cancer needs to be considered in further epidemiological studies. It could explain two classical but controversial risk factors: the fat composition of the diet and the protective effects of breast-feeding. Also, the temporal trends of breast cancer indicates an increasing incidence over the past half century that could correspond to the introduction of organochlorines in the environment in 1930. Because total exposure to estrogen may be a key indicator of breast cancer risk, the relation between the estrogenic properties of some organochlorine compounds and their carcinogen potency deserves further investigation.

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REFERENCES

1. Wasserman M, Nogueira DP, Tomatis L, Mirra AP, Shibata H, Arie G, Lucos S., Wasserman, D. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. *Bull Environ Contam Toxicol* 1976; 15:478-84.
2. Unger M, Olsen J. Organochlorine compounds in the adipose tissue of deceased people with and without cancer. *Environ Res* 1980; 23:257-63.
3. Falck F, Ricci A, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human beast lipids and their relation to breast cancer. *Arch Environ Health* 1992; 47:143-6.
4. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 1991; 338:959-64.
5. Harris JR, Lippman ME, Verenesi U, Willett W. Breast cancer: First part. *N Engl J Med* 1991; 327:319-27.