Do we have to consider chemotherapy in the analysis of association between OCs in breast adipose tissue and the risk of female breast cancer?

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Introduction

Controversies about the role of persistent environmental organochlorine contaminants (OCs) in disrupting human endocrine system are justifying new investigations. It has been hypothesized that these compounds may play a role in the etiology of mammary gland neoplasms *via* mimicking or interfering with the functions of the hormone system and induce mixed-function P-450 enzymes, which are also closely associated with the metabolism of steroid hormones [1-4]. A growing number of epidemiological studies have investigated body burdens of these compounds in association with increasing risk of breast cancer but the data has yielded inconsistent results [5-11].

In majority of such studies, where case and control groups' findings have been compared, no information was given about chemotherapy status of the cases. It means that when the blood/serum has been analyzed, it was usually not stated whether the pre- or posttreatment samples have been collected, and in case of breast adipose tissue samples there is nothing known if the women had undergone any kind of chemotherapy before surgery operation.

It is still unknown whether treatment affects body burdens of organochlorines. If yes, the assessed exposure would be misclassified and findings distorted. Several groups of drugs are used in chemotherapy, including alkylating agents, nitrosoureas, antimetabolites, antitumour antibiotics, mitotic inhibitors, hormones, plant alkaloids, and others. As their mechanisms of action differ, usually the combination chemotherapy is administered. Such therapy may significantly affect the metabolism of both, endogenous and exogenous substances, present in human body. It may concern, among others, the metabolism rate and turnover times of organochlorine compounds stored mainly in adipose tissue or simply body weight change and release of the compounds from the tissue deposits to the blood. Such effect, if exists, would justify elimination of samples derived from breast cancer women after chemotherapy from the case group in case-control studies on contribution of OCs in female breast cancer risk.

Methods and materials

The purpose of this study was to investigate whether adipose tissue levels of selected persistent organochlorine pollutants might be associated with chemotherapy in women with breast

cancer. A total of 165 samples, of mammary gland's adipose tissue taken from breast cancer women, obtained from Maria Sklodowska-Curie Institute of Oncology in Warsaw, were assayed. The donors had been divided into two subgroups – first, treated shortly before mastectomy with preoperative induction chemotherapy (used in case of locally advanced, primary inoperable breast cancers) and neoadjuvant chemotherapy (given to prevent metastases or spread the disease beyond the primary tumour), consisting of 29 patients, and second, including 136 untreated patients.

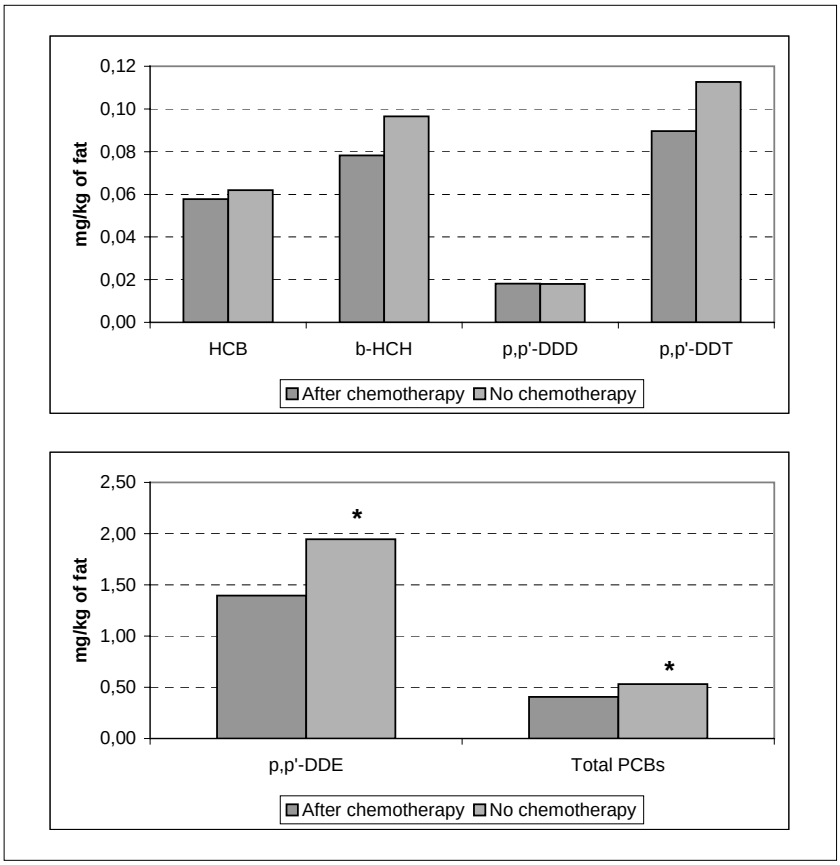
The identification and quantification of compounds analyzed: HCB, β-HCH, p,p'-DDT, p,p'-DDD, p,p'-DDE, and ΣPCBs (calculated as Aroclor 1254) in adipose tissue samples was performed in the Department of Environmental Toxicology of the National Institute of Hygiene in Warsaw. The analytical procedure included analyte extraction with n-hexane, and clean-up with concentrated sulfuric acid. Finally, the analysis was carried out by gas chromatography with electron capture detector with ion-trap mass spectrometric confirmation.

To assure the quality of the results, the laboratory simultaneously used the same method in the international proficiency testing scheme (UK FAPAS). In addition, certified reference materials and own fortified samples were routinely analyzed as a part of internal quality assurance system.

Results and discussion

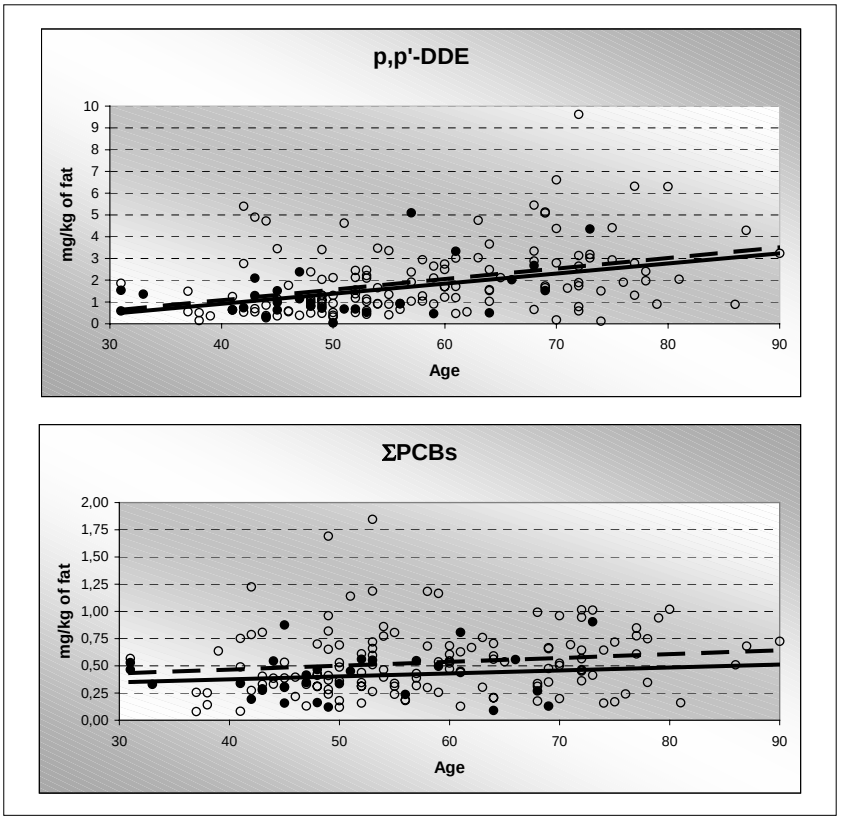
All women had measurable levels of HCB, β-HCH, p,p'-DDT, p,p'-DDE and total PCBs, while p,p'-DDD, has been found in the 75% of the samples. p,p'-DDE, as expected, was found to be dominant analyte. The mean concentration of all compounds, except p,p'-DDD, has been slightly lower in women who have undergone chemotherapy as compared to non treated patients (see Figure 1). The differences were statistically significant for p,p'-DDE and total PCBs and at the borderline of statistical significance for β-HCH.

Figure 1. Comparison of mean concentrations of HCB, β-HCH, p,p'-DDT, p,p'-DDE and total PCBs in adipose breast tissue of breast cancer women who did and did not undergone chemotherapy (* - statistically significant at $p \leq 0,05$).



This, however, could result from the differences in mean age of donors in both groups – women after chemotherapy (mean age 50,4±10,9) were significantly younger ($p<0,05$) than the non-treated ones (mean age 57,8±12,3). It is widely known that there is a positive association between age and organochlorine compounds levels [12-14]. The relationships between age and concentration of p,p'-DDE and total PCBs in our studies displayed a similar pattern in both subgroups and are shown on Figure 2.

Figure 2. Relationship between p,p'-DDE and 3PCBs levels and age of donors. White circles represent non-treated breast cancer patients, and black circles represent subjects who undergone chemotherapy. Broken and solid lines represent trends for non-treated and treated subjects, respectively.



To check if there were significant differences in levels of ΣPCB and p,p'-DDE in women who had undergone chemotherapy and those without such a treatment we have performed covariance analysis in which chemotherapy was a risk factor and age was a covariate. The results show that

after controlling for age differences in levels of both the substances were not statistically significant ($p > 0.1$). Adjusted for age (age = 56.5 in the model) mean values (and 95% confidence intervals) of total PCBs in the group without chemotherapy and with chemotherapy were 0.526 (0.476 – 0.576) and 0.427 (0.318 – 0.536) respectively. As for p,p'-DDE the respective values were 1.882 (1.642 – 2.123) and 1.690 (1.159 – 2.220).

The results of small scale pilot studies of Gammon et al.[15] has shown that posttreatment blood samples drawn within 3 months of pretreatment samples, provide similar measures of DDE body burden levels among breast cancer cases. However, the use of blood samples collected after treatment, rather than before treatment, for characterizing PCB levels may lead to misclassification of exposure. In the second available study, serum levels of p,p'-DDE and PCBs (total, and 3 congeners) have significantly decreased between initiation and completion of chemotherapy, with the time difference between pre- and posttreatment sample ranged from 15 to 27 months [16].

To the Authors' knowledge no attempts have been made earlier to look at the potential impact of chemotherapy on OCs level in adipose tissue. Presented results suggest that the use of adipose tissue samples taken from patients who have undergone chemotherapy shortly before mastectomy does not bias exposure assessment. Thus, it seems justified to use such results in an analysis of OCs levels and the risk of breast cancer however, more studies are needed to confirm our observation.

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