Reviewer’s report

Title: Effect of organochlorines cancer on breast cancer risk and survival according to estrogen receptor status: a Danish cohort-nested case-control study

Authors:

Annette P Hoyer (aph@post8.tele.dk)
Torben Jorgensen (tojo@glostruphosp.kbhamt.dk)
Fritz Rank (rh02869@rh.dk)
Philippe A Grandjean (pgrand@health.sdu.dk)

Version: 1 Date: 13 Jun 2001

Reviewer: Pierre Ayotte

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after revision, which I do not need to see

Major comments

This work is a sequel to the cohort-nested case-control study conducted by the same group on breast cancer risk and organochlorine exposure. The authors already reported an association between the risk of breast cancer and plasma concentration of dieldrin. More recently, this group also reported an association between dieldrin and breast cancer survival. The present study focuses on the expression of the estrogen receptor in breast tumors and investigate how organochlorines may modulate breast cancer risk and survival differently in estrogen receptor positive (ERP) and estrogen receptor negative (ERN) cases. Results show an association between dieldrin and ERN, not ERP tumors. Some associations are also reported with survival that are based on a relatively small number of cases, especially for ERN tumours.

1. My first comments concern the biological plausibility of the associations reported in this work. The hypothesis is that organochlorine compounds exhibiting estrogenic properties can modulate breast cancer risk and survival through binding to the ER receptor. The authors identified associations between the risk of breast cancer with ERN tumors and dieldrin plasma levels, which is hard to reconcile with their original hypothesis.

Perhaps the biggest difficulty is to understand why dieldrin, a weak estrogenic compound exhibiting estrogenic activity in in vitro cell assays only at micromolar concentrations, could be involved in the disease process. The more so considering that dieldrin is only a minor compound among all organochlorines usually found in plasma lipid extracts from human biological samples. Why would dieldrin, and not another weak estrogenic compound such
as p,p\textasciitilde-DDE that is present at much higher levels in the plasma of women in this study, be associated with breast cancer risk?

Along the same line, organochlorine compounds found in human biological samples share a number of common properties including solubility in lipids, persistence and fatty foods as the main source of exposure (except for direct exposure during agricultural use in few cases). For example, Pearson \textasciitilde's correlation coefficient between concentrations of p,p\textasciitilde-DDE and dieldrin in plasma samples from 325 adults from the Inuit population of Northern Quebec was 0.70 (Dewailly et al., personal communication). I gather from results presented in Table 5 of the manuscript that p,p\textasciitilde-DDE and dieldrin plasma levels are probably not strongly correlated in their database, since the association of ERN tumours with p,p\textasciitilde-DDE was not statistically significant. Was there a unique source of exposure to dieldrin in Denmark other than food? In the absence of an explanation for this result, my interpretation is that it is either a spurious association, or that dieldrin plasma levels are associated with a yet unidentified factor that modulates dieldrin plasma concentration (biotransformation enzyme activity?) and breast cancer risk. It is noteworthy that a recent study conducted in Norway failed to find an association between dieldrin and breast cancer risk (Ward EM, et al. Cancer Epidemiol Biomarkers Prev. 2000 Dec;9(12):1357-67).

2. The authors adjusted for metastatic lymph nodes and tumor size in the analysis of survival. Is this appropriate considering that organochlorines may be related to the aggressiveness of the disease? We previously reported that the risk of breast cancer with a large tumor and lymph node involvement increased with exposure to several organochlorines (ref. 23 of the manuscript). Was this the case in the present study?

3. As previously stated, the number of women in the survival analysis is small and the relative risks are unstable. Perhaps it would be more appropriate to use tertiles instead of quartiles in this analysis.

Minor comments

1. Abstract, results: ?With the exception of dieldrin, the risk of dying was higher among ERP than ERN tumors?. This sentence is not clear and should be modified to reflect more adequately the results presented in Table 5.

1. The limit of detection (LOD) for dieldrin should be provided. Also, the percentage of samples with concentration above the LOD should also be given and quartiles limits should be presented for all organochlorines. It is important to provide the reader with sufficient information on the distribution of plasma organochlorine levels in this population.

2. Percent recoveries, precision and accuracy data for organochlorine analyses should be presented in the method section.

3. Why adjust for weight instead of body mass index, which is usually
included in these analyses?

4. p.6, lines 12-13: ?Only covariates that altered risk estimates materially...? What was the criteria used? In the same paragraph, it is also mentioned that the modifying effects of other organochlorines was tested. What happened to the relative risks when DDE was included together with dieldrin in the models? What is the correlation between DDE and dieldrin plasma levels?

**Competing interests:**

None declared.