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Organochlorine concentrations in adipose tissue and survival in postmenopausal, Danish breast cancer patients

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ABSTRACT

Background: Several studies have investigated an association between organochlorine-concentrations and breast cancer incidence, whereas few have investigated an association with breast cancer mortality.
Methods: We used Cox Proportional Hazards Models to estimate the association between adipose organochlorine-concentrations and mortality after breast cancer in a survivor-cohort of 399 postmenopausal women. During a median follow-up of 16.1 years, 177 women died; 119 from breast cancer.
Results: There was a general inverse association with PCB-concentration (e.g. ΣPCBs: Mortality Rate Ratio (MRR) 0.79, 95% confidence interval (CI) (0.64–0.98) per inter-quartile range (IQR)), and for all pesticides, except β-Hexachlorocyclohexane, which was not associated with mortality (MRR 1.02(0.87–1.18) per IQR), and dieldrin, which was associated with a significantly increased risk of death (MRR 1.22(1.05–1.41) per IQR). We found an interaction with prognostic factors for all PCBs, confining the inverse association to those with adverse prognostic factors. Results for pesticides suggested a similar, but mostly non-significant interaction. Dieldrin diverged from the general picture by being associated with increased mortality across all strata.
Conclusion: A higher concentration of PCBs and several organochlorine pesticides may be inversely associated with breast cancer mortality among women with adverse prognostic factors. Further studies are required to investigate if this is a causal association. Dieldrin was associated with a higher mortality, regardless of prognostic factors.
Impact: This is the first study to investigate an association between organochlorine concentrations in adipose tissue and breast cancer mortality. A prominent finding is a strong interaction with prognostic factors. The unexpected direction of association for most organochlorines encourages further studies of the role of individual metabolism of the organochlorines and a potentially stronger effect of the metabolites on mortality.

1. Introduction

Breast cancer is the most frequent cancer in women, in Denmark as well as worldwide, and the number of breast cancer survivors has increased steadily over the last decades (World Cancer Research Fund, 2014; Engholm et al., 2016), as a result of an increasing disease incidence and improved diagnostic tools, combined with improved treatment, which prolongs survival (World Cancer Research Fund, 2014, 2007). This has sparked growing interest in lifestyle and environmental factors affecting survival.

Organochlorines have previously had widespread use as pesticides, fungicides, insecticides, and industrial chemicals since the first half of the 20th century. Despite the fact that many organochlorines have now been banned for decades, they are still ubiquitously present in the environment due to their persistent nature (Li et al., 2006), and humans are primarily exposed through ingestion of contaminated foods, as organochlorines bioaccumulate in the food chain (Vaclavik et al., 2006). Some of the most persistent organochlorines have been found to have half-lives of several decades in human tissue (Wolff et al., 2000; Bu et al., 2015). In 2013, the International Agency for Research on Cancer (IARC) classified polychlorinated biphenyls (PCBs) as carcinogenic to humans (Group 1), based on sufficient evidence from both human and animal studies (IARC, 2013). They have also assessed the carcinogenity of several pesticides (International Agency for Research on Cancer Monograph Working Group, 1991; Loomis et al., 2015; Guyton et al., 2015), and e.g. DDT was classified as a probable carcinogen (Group 2A)

Abbreviations: CI, Confidence interval; DBCG, Danish Breast Cancer Cooperative Group; DCH, Diet, Cancer and Health cohort; ER, Estrogen receptor; IARC, International Agency for Research on Cancer; IQR, Inter-quartile range; MRR, Mortality rate ratio; PCB, Polychlorinated biphenyls

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in 2015 (Loomis et al., 2015).

The accumulation of organochlorines in human breast tissue (Ellsworth et al., 2015), combined with the known estrogenic and anti-estrogenic properties of the compounds (Bonefeld-Jørgensen et al., 2001; Kelce et al., 1995; Wade et al., 1997), suggest that they may affect breast cancer initiation and progression. However, their role may differ with their different biological properties, as also found in some of the several human studies, which have investigated the association between organochlorines and breast cancer incidence: A 2015 meta-analysis of 25 studies, which measured PCB concentrations in biological samples found an increased disease risk with group II (potentially anti-estrogenic) and III PCBs (phenobarbital, CYP1A and CYP2B inducers, biologically persistent), but not group I (potentially estrogenic) or total PCB exposure (Zhang et al., 2015). A systematic literature review found no convincing association between persistent organic pollutants and risk for breast cancer, including hexachlorocyclohexane, hexachlorobenzene, chlordane, and total organochlorine compounds. They did, however, point out that most studies examined exposure around or after breast cancer diagnosis and may possibly have overlooked earlier critical windows of vulnerability (Mouly and Toms, 2016). In the Diet, Cancer and Health cohort, in which the present study is conducted, we have previously investigated the association between organochlorines and breast cancer incidence, finding no overall association with any PCB or pesticide, whereas for estrogen receptor negative tumors, there was an inverse association (Raaschou-Nielsen et al., 2005).

In contrast, studies on measured organochlorine concentrations and breast cancer survival are scarce: Høyer et al. (2000) investigated serum concentrations of organochlorines in 195 breast cancer patients nested in the Copenhagen City Heart Study and found a strong association with dieldrin. In updates of the study, the authors considered also estrogen receptor (ER) status and p53-mutations, and found suggestions of increased mortality in association with dieldrin and ΣPCBs for ER+ but not ER- tumors (Høyer et al., 2001), and a significant dose-response association between dieldrin and tumors with wild-type, but not mutant p53 (Høyer et al., 2002). A study investigating blood concentrations of organochlorines (Parada et al., 2016a) and PCBs (Parada et al., 2016b), in 633 and 627 American women, respectively, found a significant association with DDT in relation to mortality, and an inverse association with DDE (Parada et al., 2016a). When examining PCBs, there was an association with PCB174 and PCB177, and an inverse association between ΣGroup 2A congeners and PCB118 and mortality (Parada et al., 2016b). Further studies on organochlorines and breast cancer survival are needed.

The study aim was to investigate the association between organochlorine concentrations in adipose tissue and survival after a breast cancer diagnosis, in a population of postmenopausal, Danish women.

2. Material and methods

2.1. Study population

A detailed description of the Diet, Cancer and Health (DCH) cohort is published previously (Tjønneland et al., 2007). Briefly; 160,725 Danes were invited to participate from 1993–97. Inclusion criteria were residence in the greater Copenhagen or Aarhus area, 50–64 years of age, and no previous cancer diagnosis in the Danish Cancer Registry. In total, 57,053 participants (29,875 women) accepted. At baseline they filled in lifestyle and food frequency questionnaires, were subjected to anthropometrical measurements, and provided blood and urine samples. Furthermore, an adipose tissue biopsy was taken from the buttock, using a luer-lock system (Terumo, Terumo Co, Tokyo, Japan) consisting of a needle, a venobject multisampler luer adaptor, and an evacuated blood tube, according to the method of Beynen and Katan (Beynen and Katan, 1985) yielding an average of 40 mg (range, 1–108 mg) tissue. Within 2 h of collection, samples were frozen at −20 °C and within 8 h put in liquid nitrogen vapor (max. −150 °C) for long-term storage.

Participants have been followed in Danish registries since baseline, and between baseline and December 31st, 2000, 425 known postmenopausal women were diagnosed with breast cancer as their first cancer in the Danish Cancer Registry (Storm et al., 1997).

2.2. Organochlorine analyses

The analysis methods are described in detail in Raaschou-Nielsen et al. (2005). Briefly, we measured 18 PCB congeners (International Union of Pure and Applied Chemistry nos. 28, 52, 54, 99, 101, 104, 105, 118, 128, 138, 153, 155, 156, 170, 180, 183, 187, and 201), and p,pV-DDT, p,pV-DDE, h-hexachlorocyclohexane, a-chlordane, g-chlordane, oxychlordane, cis-nonachlor, trans-nonachlor, aldrin, dieldrin, endrin, heptachlorepoxide, hexachlorobenzene, and mirex. Samples were analyzed at Le Centre de Toxicologie, Institut national de santé publique du Quebec.

PCBs and organochlorinated pesticides were extracted from adipose tissue using dichloromethane (Patterson et al., 1986; Ryan, 2004). A fraction of this extract was used to determine the lipid content of the sample. The other fraction was used for determination of PCBs and pesticides: first it was treated by gel permeation chromatography to remove fatty residues and subsequently it was further cleaned on a Florisil column before high resolution gas chromatography-mass spectrometry analysis. The total lipid content was determined on the designated extract using a gravimetric method (Ryan, 1991). Two hundred microliters were precisely weighed on an analytic balance and the solvent evaporated at room temperature in a desiccator. The resulting lipid weight was adjusted to the initial sample weight, and the percentage of lipid content was calculated. Organochlorine concentrations were expressed in microgram/kilogram of lipids. For each of the analytes, the detection limit was determined by first estimating the concentration equivalent to a signal to noise ratio of 3. We then measured 10 replicates of a sample with the analytes at a concentration from 4 to 10 times the estimated detection limit. The calculated detection limit became the value equivalent to thrice the SD of those 10 replicates.

In the laboratory analyses, the organochlorines could be divided into three groups by detection limit: Group I included PCB congeners 52, 54, 104, and 155; group II included PCB congeners 28, 99, 101, and 105, p,pV-DDE, p,pV-DDT, h-hexachlorocyclohexane, oxychlordane, aldrin, dieldrin, heptachloroepoxide, and mirex; and group III included the remaining compounds. For each sample, the detection limit was adjusted regarding the sample weight and the lipid content, providing different detection limits for the different samples. The median (5th, 95th percentiles) detection limits for all samples were 28.4 (14.9, 139.2) Ag/kg lipids for group I, 8.5 (4.5, 41.8) Ag/kg lipids for group II, and 2.8 (1.5, 13.9) Ag/kg lipids for group III.

2.3. Outcomes

We investigated overall mortality after breast cancer diagnosis. Information regarding vital status was collected by linkage to the Danish Civil Registration System (Pedersen, 2011). As a supplementary analysis we investigated breast-cancer specific mortality. Information on cause of death was collected from the Cause of Death Registry (Helweg-Larsen, 2011).

2.4. Covariates

Dietary and lifestyle information were available from questionnaires, and anthropometric measures were collected by trained personnel. Information on prognostic factors (tumor size, ER-status, and lymph node involvement) was available from time of diagnosis through linkage with the database of the Danish Breast Cancer Cooperative Group (DBCG) (Møller et al., 2008).

Selection of covariates was done based on existing literature, biological plausibility, and availability of data. We included lifestyle