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Full Length Article

Comparison of questionnaire data and analyzed dioxin concentrations as a measure of exposure in soft-tissue sarcoma studies

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HIGHLIGHTS

- Self-reported exposure to chemicals contaminated by dioxins suggested high odds ratios for soft- tissue sarcoma in a case-control study.
- Chemical analysis of dioxins in the same patients and controls indicated no risk.
- The results suggest that recall bias has confounded previous soft-tissue sarcoma studies.
- The role of the main chemical (chlorophenols or phenoxy acids) is not fully ruled out.

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ABSTRACT

Soft-tissue sarcoma is one of the few specific tumors thought to be caused by polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) and specifically TCDD. Evidence is, however, based on questionnaire-based case-control studies, and on very few cancer cases in cohort studies at high occupational exposures to chlorophenols or chlorophenoxy acid herbicides with dioxin impurities. Recall bias has been suspected to influence the reporting of exposure, but this possibility has never been adequately put to test. In the present study 87 cancer patients and 308 controls answered a questionnaire asking their exposure to wood preservatives, fungicides and herbicides, and insecticides, and their PCDD/F concentrations were also measured. After matching for age and area 67–69 sarcoma patients and 153–156 controls were available for the study depending on the chemical group, 1–3 controls for each sarcoma patient. Sarcoma patients reported exposure to these chemicals significantly more often than controls did, odds ratios were 6.7 for wood preservatives ($p = 0.02$), 16 for fungicides and herbicides ($p = 0.01$), and 4.9 for insecticides ($p = 0.06$). There was no association, when the analysis was based on measured PCDD/F concentrations (odds ratios close to 1). Although it is not possible to exclude the role of the main chemical as the cause with certainty, the results indicate that recall bias is very likely in previous studies. Thus the causality between contaminant PCDD/Fs and soft tissue sarcoma cannot be considered proven.

1. Introduction

Dioxins (polychlorinated dibenzo-*p*-dioxins and dibenzofurans, PCDD/Fs), chlorophenols, and chlorophenoxy acid herbicides have been implicated in the etiology of soft tissue sarcoma as one of the few specific cancers identified (Hardell and Sandström, 1979; Kogevinas et al., 1997; IARC, 2012 Kogevinas et al., 1997; IARC, 2012); otherwise dioxins have been suggested to slightly increase the risk of all cancer combined (Kogevinas et al., 1997; Steenland et al., 1999; IARC, 1997, 2012). The carcinogenicity of chlorophenols

Abbreviations: CI, confidence interval; OR, odds ratio; PCBs, polychlorinated biphenyls; PCDD/Fs, polychlorinated dibenzo-*p*-dioxins and dibenzofurans; TCDD, 2,3,7,8-tetrachlorodibenzo -*p*-dioxin; WHO, World Health Organization; WHO-TEQ, toxic equivalencies according to WHO.

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and phenoxy acids was attributed to PCDD/F contaminants (IARC, 1997). The evidence on soft tissue sarcoma has been based largely on case-control studies using questionnaires to assess exposure (Cole et al., 2003) and on occupational cohort studies with very few cases of soft tissue sarcoma (Kogevinas et al., 1997; Steenland et al., 1999). No increased risk of soft-tissue sarcoma has been noted after accidents with high exposures to PCDD/Fs (Onozuka et al., 2009; Pesatori et al., 2009).

From the beginning of 1980s it has been suspected that there is a major possibility of recall bias in using questionnaire information in exposure assessment (Hardell, 1981), and no differences in PCDD/F concentrations were found between the exposed persons and controls (Nygren et al., 1986). However, as yet there has been no attempt to clarify this matter by comparing questionnaire data and actual dioxin analysis by investigating the same group of patients within the same study.

Scientifically sound and correct cancer risk estimates are preferable to ill-founded precautionary estimates, because these may lead to wrong priorities. Extreme control measures by authorities can also be directly harmful, e.g. by discouraging breast feeding (WHO, 2000) and decreasing fish consumption (Tuomisto et al., 2004b). Health benefits of these have been calculated greater than even pessimistically assessed risks of dioxins (Tuomisto, 2005).

We have previously published a large case-control study on the association between soft tissue sarcoma and PCDD/Fs indicating no increased risk associated with WHO-TEQ or individual congeners, e.g. TCDD (Tuomisto et al., 2004a). This study was not recognized by the IARC working group (IARC, 2012). In this study, subcutaneous fat samples were collected from 954 patients with soft tissue sarcomas or controls undergoing appendicitis operation, and PCDD/Fs were analyzed. Because of the long half-lives of PCDD/Fs, the analysis reflects the exposure over most of the lifetime. Patients also filled in a questionnaire asking a number of variables, including their dietary habits, weight history, and chemical exposure. This study material allows us to assess the magnitude of the recall bias that may exist, by studying in detail whether the observed associations between PCDD/F exposure and soft tissue sarcoma are similar regardless of whether the exposure is measured based on questionnaire data or the actual concentrations of PCDD/Fs in fat.

Three of the questions dealt with exposure to wood preservatives, agricultural fungicides and herbicides, and insecticides. The most common group of wood preservatives in past was chlorophenols which contain various PCDD/Fs as synthesis byproducts (Vartiainen et al., 1995a). Chlorophenols were implicated in soft-tissue sarcoma in several case-control studies (Hardell and Sandström, 1979; Eriksson et al., 1981 Eriksson et al., 1981). Pesticides are more diverse group of chemicals, among them PCDD/F impurities are found in chlorophenoxy acid herbicides (IARC, 1997) which were also implicated in soft tissue sarcoma in case-control studies (Hardell and Sandström, 1979; Hardell and Eriksson, 1988Hardell and Sandström, 1979; Hardell and Eriksson, 1988). Subsequently these authors assumed that the associations were possibly due to PCDD/F impurities (Hardell and Eriksson, 1988). The initial odds ratios were five to six (Hardell and Sandström, 1979), and in later studies around two to three (Hardell and Eriksson, 1988; Hardell et al., 1995 Hardell et al., 1995). Several other groups did not find an elevated risk (cf. IARC, 1997).

In the present study we compare the odds ratios based on positive answers on exposure to these groups of chemicals with the odds ratios based on dioxin concentrations in the patients and controls.

2. Material and methods

2.1. Soft tissue sarcoma patients and referents

A detailed description of sample collection and PCDD/F analysis has been given in the previous papers (Tuomisto et al., 2004a; Kiviranta et al., 2005).

Briefly, sarcoma patients attended the University hospitals of Helsinki, Kuopio, Turku and Tampere. All patients over 15 years of age operated for soft tissue sarcoma between June 1997 and December 1999 were eligible as cases. Patients over 15 years of age and operated due to appendicitis in any study hospital from the same catchment area were eligible as controls. Informed consent was obtained from all patients in writing before the operation, and the study was duly approved by the ethics committees. The total number of patients recruited was 972, and after exclusion of some patients for technical reasons (e.g. too small sample volume, see Tuomisto et al., 2004a), data on 954 patients (148 cases and 806 controls) were available.

A subcutaneous fat sample obtained during an appendectomy or sarcoma operation was analyzed for 17 PCDD/F congeners using gas chromatography – mass spectrometry (Vartiainen et al., 1997) at the Laboratory of Chemistry of the National Public Health Institute of Finland (currently Chemicals and Health Unit of the

Table 1
Number of patients reporting exposure to pesticides and wood preservatives against soft-tissue sarcoma status (case/control) available for matched analyses.

Reported exposure		Numbers of soft-tissue sarcoma cases and controls in differently exposed groups	
		Case	Control
Wood preservatives	Yes	8	2
	No	61	152
	Total	69	154
Fungicides and herbicides	Yes	7	4
	No	60	151
	Total	67	155
Insecticides	Yes	6	2
	No	61	151
	Total	67	153
Any of the three chemical groups	Yes	15	7
	No	54	149
	Total	69	156