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Exposure to Phenoxyacetic Acids, Chlorophenols, or Organic Solvents in Relation to Histopathology, Stage, and Anatomical Localization of Non-Hodgkin's Lymphoma

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ABSTRACT

Results on 105 cases with histopathologically confirmed non-Hodgkin's lymphoma (NHL) and 335 controls from a previously published case-control study on malignant lymphoma are presented together with some extended analyses. No occupation was a risk factor for NHL. Exposure to phenoxyacetic acids yielded, in the univariate analysis, an odds ratio of 5.5 with a 95% confidence interval of 2.7–11. Most cases and controls were exposed to a commercial mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. Exposure to chlorophenols gave an odds ratio of 4.8 (2.7–8.8) with pentachlorophenol being the most common type. Exposure to organic solvents yielded an odds ratio of 2.4 (1.4–3.9). These results were not significantly changed in the multivariate analysis. Dichlorodiphenyltrichloroethane, asbestos, smoking, and oral snuff were not associated with an increased risk for NHL. The results regarding increased risk for NHL following exposure to phenoxyacetic acids, chlorophenols, or organic solvents were not affected by histopathological type, disease stage, or anatomical site of disease presentation. Median survival was somewhat longer in cases exposed to organic solvents than the rest. This was explained by more prevalent exposure to organic solvents in the group of cases with good prognosis NHL histopathology.

INTRODUCTION

In 1981, we reported a 6-fold risk of malignant lymphoma, both Hodgkin's disease and NHL,[2] among persons exposed to phenoxyacetic acids or chlorophenols as the result of a case-control study (1). An association was also found for exposure to organic solvents.

Since then, other studies have been performed within this field and an association between exposure to the phenoxy herbicide 2,4-D and NHL has been reported in studies from the United States (2, 3).

NHL is one of the malignant diseases with the most rapidly increasing incidence in the Western world. Pesticide exposure has been discussed as one contributing factor (4). This has prompted us to analyze and report data on NHL from our study (1), omitting Hodgkin's disease.

In this paper, we also present risk estimates for different histopathological subtypes, stage, and anatomical localization of NHL. The association between 2,4-D and NHL in a study from Eastern Nebraska did not appear to be specific to any subgroup, although the risk was somewhat higher in intermediate grade NHL (3). Exposure to organic solvents has been related to only supradiaphragmatic NHL in one study (5), whereas other studies have not provided information on tumor localization (6, 7).

Some studies in this field have used occupation as a surrogate for exposure to phenoxy herbicides without showing any association (8). In order to compare our results with the findings in such studies, we have calculated an OR for different occupations, including those with potential exposure to phenoxyacetic acids or chlorophenols, such as farmers, farm workers, afforestation workers, and lumberjacks.

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[2] The abbrevations used are: NHL, non-Hodgkin's lymphoma; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; OR, odds ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; DDT, dichlorodiphenyltrichloroethane.

MATERIALS AND METHODS

The study material consisted of all men aged 25–85 years who were admitted to the Department of Oncology in Umea between 1974 and 1978 with histopathologically verified NHL, 105 cases in total. The slides were previously reexamined and are presented here with the Rappaport classification, which was commonly used in Sweden during the 1970s. At the present time, the Kiel classification is usually used in Europe, and the Working Formulation is used in the United States. These three coding systems have been related to each other and are comparable (9).

The NHL cases in our study were classified according to the Ann Arbor staging system. In addition, the records were scrutinized in order to classify the disease at presentation as supradiaphragmatic, infradiaphragmatic, or generalized. To evaluate prognosis, the records of all 105 NHL cases were scrutinized.

As controls, all 335 control subjects who had inititally answered the questionnaire were used. They were matched for sex, age, place of residence, and vital status; deceased controls were also matched for year of death. The living controls were drawn from the National Population Registry and the deceased from the National Registry for Causes of Death. Details were presented in our previous publication (1).

Assessment of Exposure. A complete working history, various exposures, and leisure time activites covering the whole life were obtained by questionnaire. If necessary, the answers were completed over the phone. Protective equipment against the chemicals associated with NHL in this study was not commonly used, and information on such protection and how it was used is uncertain. Details have been published in the earlier report (1).

All occupations were now classified according to the Nordic Working Classification system (10). The results are presented only for occupations with at least 10 subjects. Since UV radiation has been suggested to be a factor to be considered in the etiology of NHL (11), occupations were also classified as outdoor, indoor, or mixed.

With regard to exposure to chlorophenols or organic solvents, exposure less than 1 week continously or less than 1 month in total was classified as low-grade and more than that as high-grade.

Overall survival was analyzed for the cases. Calculations were performed for exposed and unexposed cases separately.

Statistical Methods. The statistical analyses of the data were based on Mantel-Haenszel methods for calculation of OR by stratification by age and vital status (12). The 95% confidence intervals, given within parentheses, were calculated according to Cornfield as presented by Breslow and Day in 1980 (13). The analyses were performed with the Epilog Plus epidemiological software, both the univariate analyses and the multivariate logistic regression. Potential confounding between exposures of interest was evaluated in the multivariate analysis. The included variables are presented under results.

RESULTS

Occupations. No significantly increased or decreased risk for NHL was found in any occupation as presented in Table 1. Outdoor work yielded OR 0.9 (0.4–1.7), and for mixed outdoor/indoor work, OR = 0.9 (0.5–1.7) was obtained with indoor work used as a reference.

Phenoxyacetic Acids. Exposure to phenoxyacetic acids or chlorophenols gave OR 4.6 (2.7–7.8; Table 2). Exposure to all types of phenoxyacetic acids yielded OR 5.5 (2.7–11). No case was exposed to only 2,4,5-T, whereas one control reported 2,4,5-T as the only phenoxyacetic acid. Mostly, a combination of 2,4-D and 2,4,5-T had been used in both occupational and leisure time exposure. The combination

Table 1 *OR and 95% confidence interval in different occupations for non-Hodgkin lymphoma*

Occupation	Number exposed (Cases/controls)	OR	CI95[a]
Afforestation worker	7/30	0.7	0.3–1.7
Building worker	13/47	0.8	0.4–1.7
Carpenter	13/36	1.1	0.6–2.4
Driver	3/14	0.7	0.2–2.6
Farmer	20/74	0.7	0.4–1.4
Farm worker	4/19	0.6	0.2–2.1
Loader	2/9	0.7	0.1–3.5
Lumberjack	32/86	1.2	0.7–2.1
Mechanic	5/7	2.5	0.7–9.6
Motor mechanic	7/20	1.3	0.5–3.4
Miner	6/18	1.0	0.4–2.9
Officer	4/11	1.4	0.3–4.9
Office employee	1/11	0.3	0.1–2.1
Pulp industry worker	6/13	1.5	0.5–4.5
Salesman	2/13	0.4	0.1–2.2
Sawmill worker	13/29	1.5	0.7–3.2
Shop keeper	1/9	0.3	0.2–2.7
Smelting-house worker	4/6	2.3	0.5–9.5
Storeman	5/13	1.3	0.4–4.3
Truck driver	4/20	0.6	0.2–2.0

[a] CI95, 95% confidence interval.

Table 2 *OR and 95% confidence interval for exposure to different agents in the univariate analysis*

Agent	Number exposed (Cases/controls)	OR	CI95[a]
Phenoxyacetic acids or chlorophenols	47/51	4.6	2.7–7.8
Phenoxyacetic acids			
all	25/24	5.5	2.7–11
2,4,5-T including mixtures	18/23	4.1	1.9–8.6
2,4-D only	3/1	13	1.2–360
MCPA only	4/0		
Chlorophenols			
all	35/35	4.8	2.7–8.8
high grade	16/9	9.4	3.6–25
low grade	19/26	3.3	1.6–6.8
pentachlorophenol, high grade	15/9	8.8	3.4–24
Organic solvents			
all	45/88	2.4	1.4–3.9
high grade	31/50	2.9	1.6–5.6
low grade	14/38	1.8	0.8–3.8
benzine	3/1	28	1.8–730
thinner	11/14	3.4	1.4–10
trichloroethylene	4/4	7.2	1.3–42
turpentine	5/7	3.3	0.9–17
white spirit	12/20	3.2	1.3–8.3
degreaser	7/4	11	2.9–72
DDT	17/26	2.4	1.2–4.9
Asbestos	11/21	1.7	0.8–4.0
Smoking			
current	37/115	1.1	0.6–2.0
previous	25/80	1.0	0.5–2.0
Oral snuff	35/84	1.5	0.9–2.5

[a] CI95, 95% confidence interval; MCPA, 4-chloro-2-methylphenoxyacetic acid.

of 2,4-D and 2,4,5-T was the type of exposure in 17 cases and 22 controls. One case was exposed to both 2,4,5-T and 4-chloro-2-methylphenoxyacetic acid. Exposure to 2,4,5-T in any combination gave OR 4.1 (1.9–8.6).

Three cases and one control reported 2,4-D as the only phenoxyacetic acid producing OR 13 (1.2–357). With regard to 4-chloro-2-methylphenoxyacetic acid, four cases and no controls were exposed to that herbicide alone.

Dose-response for exposure to phenoxy herbicides was analyzed by dividing the number of exposed controls in three groups with equal numbers of exposed controls. Exposures of 1–17 days yielded OR = 6.5 (2.1–18); 18–43 days, OR = 3.3 (1.0–11); and >43 days, OR = 7.3 (2.2–23).

Median latency time period for cases exposed to phenoxyacetic acids was 18 years.

Chlorophenols. High grade exposure to chlorophenols yielded OR 9.4 (3.6–25), whereas low grade exposure gave OR 3.3 (1.6–6.8). Mostly pentachlorophenol has been used in Sweden, and high grade exposure produced OR 8.8 (3.4–24). One case with high grade chlorophenol exposure could not specify the type used. Median latency period was 21 years.

Organic Solvents. High grade exposure to organic solvents yielded OR 2.9 (1.6–5.6), whereas the risk for low grade exposure was lower, OR 1.8 (0.8–3.8). For different types of organic solvents, significantly increased risk was found for benzine, thinner, trichloroethylene, and white spirit. Exposure to degreasing agents gave OR 11 (2.9–72). The median latency period for exposure to organic solvents was 21 years.

Other Agents. In the univariate analysis, exposure to DDT was associated with NHL, OR 2.4 (1.2–4.9). Smoking, use of oral snuff, or exposure to asbestos yielded no significantly increased ORs.

Multivariate Analysis. In the multivariate analysis, exposure to phenoxy herbicides, high grade exposure to chlorophenols, and organic solvents gave signficantly increased ORs (Table 3). DDT exposure yielded OR 1.5 (0.6–3.6). As in the univariate analysis, low grade exposure to organic solvents and asbestos gave no signficantly increased risks for NHL.

Table 3 *OR and 95% confidence interval for exposure to different agents in the multivariate analysis*

Agent	OR	CI95[a]
Phenoxyacetic acids	5.2	1.6–17
Chlorophenols		
high grade	9.0	2.9–28
low grade	2.8	1.2–6.5
Organic solvents		
high grade	3.5	1.7–7.1
low grade	1.1	0.5–2.7
DDT	1.5	0.6–3.6
Asbestos	1.3	0.5–3.6

[a] CI95, 95% confidence interval, MCPA, 4-chloro-2-methylphenoxyacetic acid.

Table 4 *OR and 95% confidence interval for exposure to different agents related to different types of non-Hodgkin lymphoma according to the Rappaport classification.* Number (*n*) of cases in different subtypes given within parentheses.

Histopathology (*n*)	Phenoxyacetic acids	Chloro-phenols	Organic solvents
Lymphocytic, well-differentiated (32)	3.3 0.9–11	2.8 1.1–7.6	2.9 1.3–6.6
Diffuse lymphocytic, poorly differentiated (5)	10 1.0–120	4.4 0.2–76	
Diffuse mixed lymphocytic/histiocytic (4)	5.0 0.2–83	8.7 0.8–98	7.6 0.7–200
Diffuse histiocytic (44)	6.2 2.5–17	5.5 2.4–13	1.8 0.8–3.8
Nodular mixed lymphocytic/histiocytic (6)	2.3 0.1–28	2.0 0.1–25	2.2 0.2–17
Nodular lymphocytic, well-differentiated (3)	5.0 0.2–83		5.4 0.3–150
Nodular lymphocytic, poorly differentiated (7)	15 2.0–150	24 3.1–210	6.0 0.9–41
Nodular histiocytic (4)	52 0.6–990	22 2.1–670	3.5 0.3–34

Table 5 *OR and 95% confidence interval for exposure to different agents related to different stages of non-Hodgkin lymphoma.*
Number (*n*) of cases in different stages given within parentheses.

Stage (*n*)	Phenoxyacetic acids		Chlorophenols		Organic solvents	
	OR	CI95[a]	OR	CI95	OR	CI95
I (23)	4.3	1.4–16	3.2	1.0–11	2.5	0.9–6.9
A (21)	3.8	1.0–14	3.5	1.1–12	2.9	1.0–8.2
B (2)	8.9	0.5–990				
II (11)	16	2.8–110	4.6	0.8–25	0.3	0.1–2.5
A (8)	13	1.9–111	3.9	0.5–27	0.4	0.1–3.7
B (3)	53	0.6–990	7.1	0.2–300		
III (27)	5.3	1.7–19	7.2	3.0–20	2.5	1.0–5.9
A (21)	5.7	1.7–24	8.5	3.3–27	3.2	1.1–8.5
B (6)	4.3	0.2–68	2.9	0.1–39	1.0	0.1–7.1
IV (44)	5.3	1.9–15	4.6	2.0–11	3.1	1.5–6.5
A (26)	6.0	1.8–21	5.7	2.1–16	3.8	1.5–9.6
B (18)	4.1	0.7–20	3.4	0.9–12	2.1	0.7–6.5
I–IV						
A (76)	5.5	2.6–12	5.5	3.0–11	2.8	1.6–4.9
B (29)	5.5	1.5–20	3.2	1.0–9.5	1.4	0.5–3.5

[a] CI95, 95% confidence interval.

Table 6 *OR and 95% confidence interval for exposure to different agents related to anatomical site of non-Hodgkin lymphoma at diagnosis.*
Number (*n*) of cases given within parentheses.

Anatomical site (*n*)	Phenoxyacetic acids		Chlorophenols		Organic solvents	
	OR	CI95[a]	OR	CI95	OR	CI95
Supra-diaphragmatic (24)	5.7	1.8–18	3.2	1.0–9.5	1.4	0.5–3.9
Infra-diaphragmatic (21)	7.2	2.2–28	6.0	1.9–21	1.6	0.6–4.7
Generalized (60)	4.7	1.9–11	5.2	2.6–11	3.2	1.7–5.9

[a] CI95, 95% confidence interval.

Histopathology. ORs for exposure to phenoxyacetic acids, chlorophenols, or organic solvents for different types of NHL according to the Rappaport classification are given in Table 4. Increased risk was found for all subtypes. Due to the low number of cases with some of the subtypes, broad confidence intervals were obtained in these calculations.

Stage and Anatomical Site. Tables 5 and 6 present ORs and 95% confidence interval for different stages and anatomical sites of NHL at the clinical presentation. Increased risks for exposure to phenoxy herbicides, chlorophenols, or organic solvents were found, regardless of stage or site.

Prognosis. The median survival was 21 months in the unexposed cases, 27 months in cases exposed to phenoxyacetic acids or chlorophenols (both groups), and 36 months in patients exposed to organic solvents.

DISCUSSION

Exposures were self-reported and might have been influenced by recall bias. A similar questionnaire had been used in a previous case-control study on soft-tissue sarcoma in the same area (14). In a validation procedure, the exposure information in the questionnaires was verified by the employers in a high degree, *i.e.*, 97% for chlorophenols, and regarding phenoxyacetic acids, even higher OR was calculated in that study if data from employers were used. These results indicated that the validity of self-reported exposures was good and would also be applicable to the present study (14).

The influence of potential recall or observational bias in these studies has been previously evaluated and discussed (15). It was concluded that the results could not be explained by such bias.

In a review of the risk for NHL among farmers in 21 descriptive studies, the risk ratios ranged from 0.6 to 2.6 (16). The risk was significantly increased in three studies and significantly decreased in one study. In this investigation, OR for farmers was 0.7 and for farm workers 0.6. Jobs as afforestation workers or lumberjacks yielded OR 0.7 and 1.2, respectively. These results are in agreement with Swedish register studies where census data on occupations were linked with the Swedish Cancer Register (8, 17). Thus, it is necessary to obtain individual exposure data, and job title cannot be used as a surrogate for exposure.

Experimental studies indicate that UV radiation may cause systemic immunosuppression (18), and an increased risk for NHL has been found in immunosuppressed persons (19). Consequently, the risk might be increased in job categories classified as outdoor work. Such an association was not demonstrated in this study, nor was the risk increased in specific occupations of the outdoor type (Table 1).

Our data showed a significantly increased risk for NHL in persons exposed to phenoxyacetic acids or chlorophenols. In Sweden, mostly a combination of 2,4-D and 2,4,5-T was used within the forestry occupation in order to combat hard woods. 2,4,5-T was contaminated by the dioxin congener TCDD (20) and was banned in 1977. Most cases and controls had been exposed to that combination and thus also to TCDD. For 2,4-D exposure, the risk was especially high, although based on a few subjects with exposure to only 2,4-D. It is noteworthy that the studies done in the United States showed an association between 2,4-D and NHL (2, 3). Of interest is that dioxin contamination, occasionally including TCDD, has been found also in 2,4-D (21).

For chlorophenols, the risk increased with increasing exposure in number of days, whereas no dose-response was seen regarding exposure to phenoyxacetic acids.

The literature regarding the association between herbicides and cancer has been discussed elsewhere (4, 22). An association between

DDT exposure and NHL has been suggested (6). A significantly increased risk was found in our study in the univariate analysis, but the risk did not remain significant in the logistic regression. Exposure to asbestos yielded a nonsignificantly increased OR, which decreased in the multivariate analysis. Asbestos has been discussed as a risk factor for NHL of the gastrointestinal tract and oral cavity (23). This was not verified in our study (24).

Our finding of an increased risk for NHL following exposure to organic solvents is in agreement with other reports (5, 6, 25, 26). In contrast to a previous publication (5), the risk was not associated with any particular anatomical localization of NHL.

In this study, we showed that the increased risk associated with exposure to phenoxyacetic acids, chlorophenols, or organic solvents applied to all histopathological types of NHL. Exposure to 2,4-D was associated with an increased risk for all major types of NHL and for follicular large cell NHL in particular in one study (27). The follicular large cell NHL corresponds to the nodular histiocytic type in the Rappaport classification and yielded the highest OR for phenoxy herbicide exposure in this analysis. This finding was based on low numbers, however.

Use of tobacco products has been suggested as a risk factor for NHL (28). This was not confirmed in our study.

Median survival was somewhat shorter in unexposed cases than in those exposed. Exposure to phenoxy herbicides, chlorophenols, or organic solvents was more often reported in cases alive at the time of interviews as compared to deceased cases, which explains the finding. Cases exposed to organic solvents seemed to have a better prognosis than others, even if only cases alive at the time of assessment of exposure were considered. This seems to be explained by the fact that exposure to solvents was most common in the subtype of well-differentiated lymphocytic NHL, which belongs to the group of NHL of low malignancy with better prognosis than other types of NHL (29).

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