Malignant lymphomas and occupational exposures

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ABSTRACT The effects of potential risk factors for Hodgkin's disease (HD) and for non-Hodgkin lymphomas (NHL) were evaluated in a case-referent study encompassing 54 cases of HD, 106 cases of NHL, and 275 referents, all alive. Exposure information was obtained by questionnaires posted to the subjects. Crude rate ratios were increased for various occupational exposures including solvents, welding, wood preservatives, phenoxy acids, and fresh wood (sawmill workers, lumberjacks, paper pulp workers). After further analyses based on logistic regression occupational exposures to welding and creosote remained as significant risk factors for HD. For NHL, occupational exposures to solvents, phenoxy acids, and creosote but also work as carpenter or cabinet maker and contacts with pets (other than dogs, cats, and birds) were associated with significantly increased risks.

Malignant lymphomas (non-Hodgkin lymphoma (NHL) and Hodgkin's disease (HD)) have been subject to several epidemiological studies and found to be associated with various environmental exposures and a viral aetiology has been discussed in relation to HD.

An increased risk for HD has been reported among teachers and students exposed to patients with HD¹ and an excess risk has also been found among abattoir workers,² both findings suggesting an infectious aetiology. Occupational exposure to wood among carpenters or cabinet makers, as well as among workers in the paper pulp industry, may also be of aetiological importance for HD.³⁻⁵

Exposure to solvents such as carbon disulphide or carbon tetrachloride, trichlorethylene, and perchlorethylene has been associated with an increased risk for malignant lymphoma.^{6,7} A significant excess of deaths from lymphomas has also been reported in men employed in occupations where benzene or coal tar fractions, or both, were used.⁸

Several studies with non-specific exposure information have indicated an excess risk of HD and NHL among farmers.⁹ Different epidemiological studies have also shown that workers exposed to phenoxy acids and chlorophenols may run an increased risk of developing NHL and possibly also HD.^{7,10}

NHL is mainly of B-cell origin. In myeloma and chronic lymphatic leukaemia the tumour cells are also mainly of B-cell origin. Recent studies on myeloma and chronic lymphatic leukaemia indicate occu-

pational exposures to creosote and fresh wood (sawmill workers, lumberjacks, paper pulp workers), DDT, engine exhausts, and contact with horses to be associated with an increased risk with regard to these disorders.^{11,12} These exposures should therefore also attract interest in the context of aetiological studies of NHL. The aim of the present case-referent study was to examine whether or not an effect could be seen from the known or suggested potential risk factors and to study if any of the relations to specific occupational exposures noted for myeloma and chronic lymphatic leukaemia could be observed also for NHL and for HD, since some of these malignancies are morphologically related.

Materials and methods

CASES

Cases of malignant lymphoma, both HD and NHL, were obtained from the register of the Department of Oncology at Örebro Medical Centre Hospital, Sweden. The cases were diagnosed between 1964 and 1986 and still alive during the period of data acquisition in 1986. Some restrictions were applied—namely, that the cases should be at least 20 years old at the time of diagnosis and under 80 in 1986 and mentally capable of answering a questionnaire. Both sexes were included in the study population. Furthermore, the cases had to have been born in Sweden and to be living in the catchment area of the hospital at the time of diagnosis.

Altogether, 175 cases fulfilled the criteria. Six were either not willing to participate or impossible to

contact. Nine cases originally enrolled were excluded as representing particular subtypes (T-cell lymphomas) and other lymphomas (malignant histiocytosis), leaving a total of 160 cases for the study (54 cases of HD and 106 cases of NHL).

REFERENTS

Referents had originally been drawn from the population register for other studies^{11,12} and were also used in this study. In total 484 referents had originally been enrolled in these earlier studies, covering the catchment areas of several hospitals. Seventeen per cent of these had not been able or willing to reply and had therefore been replaced by other, similarly drawn subjects. In the present study only a subset of these referents could be used as representing the catchment area for the cases of this study—namely, 275 referents. The referents also fulfilled the criteria mentioned above with regard to the cases.

ASSESSMENT OF EXPOSURE

Information about various types of exposure among the cases was obtained by means of the questionnaire previously used for the referents. This questionnaire had nine pages and was preceded by an introductory letter and was posted to the subjects. The 17 main questions had further subdivisions: ten concerned occupational exposures, five were devoted to medical care, and there were also questions about exposures during leisure time. A minimum exposure time of one year was required and a latency time criterion was applied by considering only exposure within a time

window of five to 45 years before diagnosis and, for the referent, before the point in time of selection.

Information about exposure to solvents in qualitative terms was obtained directly from the questionnaires, whereas the quantitative classification was assigned to five categories of intensity on a judgmental basis, similar to a classification used in a study of glomerulonephritis.¹³ Furthermore, those who reported occupational use of herbicides in farming and forestry were considered exposed to phenoxy acids, since these are the main type of pesticides used in Sweden.

STATISTICAL METHODS

The rate ratios were either calculated crude or based on logistic regression by means of the EPILOG-package (Epicenter software) which also provided the confidence limits given in the tables.

Results

Of the 54 cases of HD, 35 were men and 19 women, whereas 66 men and 40 women had NHL. There were 157 male and 118 female referents. A reasonable correspondence with regard to age was obtained for cases and referents; the age range for cases of HD was 20–73, for NHL 22–79, and for referents 20–77. Several analyses were undertaken with regard to various exposures for orientation and identification of potential determinants that also might exert confounding among one another.

For HD, crude rate ratios were increased for those

Table 1 Crude odds ratios (OR) obtained for certain occupational exposures. Exposures associated with an increased risk (OR > 2) and with more than five subjects exposed along with some exposures of special interest are selected. In total there were 54 cases of Hodgkin's disease and 106 cases of non-Hodgkin lymphomas, both series compared with 275 referents

Exposure	Hodgkin's disease		Non-Hodgkin lymphomas	
	No of exposed cases/referents	OR	No of exposed cases/referents	OR
Solvents	18/50	2.3	33/50	2.0
Solvents, intensity category 2–5 V 0–1:	14/39	2.1	27/39	2.1
Thinner	9/16	3.2	15/16	2.7
White spirit	6/12	2.7	13/12	3.1
Trichloroethylene	7/14	2.8	8/14	1.5
Styrene	1/1	5.2	3/1	8.0
Painters	2/0	∞	3/0	∞
Plastic/rubber chemicals	4/10	2.1	9/10	2.5
Welding	9/10	5.3	7/10	1.9
Carpenter and cabinet makers	1/9	0.6	10/9	3.1
Fresh wood (sawmill workers, lumberjacks, paper pulp workers)	3/14	1.1	7/14	1.3
Lumberjacks	4/11	1.9	6/11	1.4
Farmers	6/30	1.0	7/30	0.6
Wood preservatives:	2/1	10.5	6/1	16.4
Creosote	2/1	10.5	5/1	13.6
Phenoxy acids	4/6	3.6	6/6	2.7
DDT	3/3	5.3	0/3	0
Other pesticides	3/5	3.2	1/5	0.5
Nursing	4/13	1.6	5/13	1.0
Hairdressers	1/2	2.6	1/2	1.3
Pets except dogs, cats, and birds (not occupational)	5/10	2.7	11/10	3.1

exposed to solvents and there was also a dose-response pattern when comparing higher exposure categories 2–5 to low exposure or no exposure (0–1) (table 1). When specific solvents were analysed—that is, regarding exposure to thinner, white spirit, trichloroethylene and styrene—increased risks were obtained also for work with painting (solvents with less than five exposed cases and referents taken together are not shown in the table). Welding and working with plastics and rubber chemicals were found to be associated with an increased risk for HD. Working as a farmer, carpenter, or cabinet maker was not connected with any increased risks but working with fresh wood at sawmills, in paper pulp industries, or as a lumberjack was associated with a slightly increased risk. Occupational exposures to wood preservatives, especially creosote, as well as phenoxy acids, DDT, and other pesticides were associated with increased risks. An increased risk for HD also appeared among hairdressers and a slightly increased risk among nursing personnel and lumberjacks. Contacts with various types of pets except dogs, cats, and birds, were associated with an increased risk. For NHL, exposure to solvents, particularly to white spirit, thinner, and styrene, and working with plastics and rubber chemicals, wood preservatives (creosote) or working as a carpenter, cabinet maker, or painter were associated with increased risks (table 1). Working with fresh wood, welding, or as a lumberjack or hairdresser was associated with only a slightly increased risk. No raised risks appeared among farmers or nursing personnel. Occupational exposure to phenoxy acids but not to DDT or other pesticides was associated with an increased risk. Contact with pets, except dogs, cats, and birds, was again associated with an increased risk.

Since the crude analyses might be affected by confounding effects, further analyses were undertaken, especially with regard to confounding in the data between the identified risk factors. Exposures

associated with at least a doubled risk for HD or NHL were included in a logistic regression with age at the time of diagnosis and sex and two determinants of special interest—namely, farming and exposure to fresh wood.

With regard to HD, increased logistic odds ratios were obtained for occupational exposures to solvents, welding, phenoxy acids, DDT, other pesticides, and creosote, and among farmers and hairdressers as well as for contact with pets other than dogs, cats, and birds (table 2). Only for welding and exposure to creosote, however, did the 90% confidence interval exceed unity.

For NHL also several exposures appeared as risk factors by logistic regression—namely, occupational exposure to solvents, phenoxy acids, and creosote. An increased risk was also seen for carpenters and cabinet makers and for contacts with other types of pets than dogs, cats, and birds (table 2). Farming as such appeared to be protective in connection with NHL. Exposure to plastic and rubber chemicals and work as a hairdresser showed increased risks but with the 90% confidence intervals including unity.

Discussion

Different exposures appear in this study as risk factors. Most are well known and have been reported before. In this study, however, welding attracts interest as a relatively new risk factor for HD, although an increased risk for HD among some welders has been reported from British Columbia.¹⁴ The causative agent in connection with welding is unclear, however. Welders are occupationally exposed to metal fumes and to electromagnetic fields and sometimes also to other agents. This finding regarding welders will require confirmation in other studies before any clear conclusions can be drawn.

Occupational exposure to creosote appeared as a

Table 2 Logistic odds ratios with regard to determinants of special interest or with a doubling of the risk for Hodgkin's disease or non-Hodgkin lymphomas

Exposure	Hodgkin's disease		Non-Hodgkin lymphomas	
	Logistic odds ratio	90% CI	Logistic odds ratio	90% CI
Solvents	1.7	0.8–3.5	1.9	1.1–3.2
Welding	5.4	2.0–15	1.0	0.3–2.7
Carpenters and cabinet makers	0.2	0.02–1.7	2.8	1.1–7.1
Fresh wood (sawmill workers, lumberjacks, paper pulp workers)	0.4	0.1–1.9	1.0	0.3–2.4
Plastic/rubber chemicals	0.8	0.2–3.1	2.2	0.9–5.2
Hairdressers	2.7	0.2–25	2.2	0.2–19
Farmers	1.2	0.4–3.5	0.3	0.1–0.7
Phenoxy acids	3.8	0.7–21	4.9	1.3–18
DDT	7.5	0.8–70	0	—
Other pesticides	2.0	0.3–12	0.4	0.04–3.0
Creosote	10.7	1.1–103	9.4	1.2–69
Pets except dogs, cats, and birds	2.1	0.7–5.9	3.4	1.4–7.9

risk factor for both HD and NHL; it appeared as a risk factor for multiple myeloma in a previous study¹¹ with which the referents are shared. There remains apparently the possibility that exposure to creosote for some reason has been underestimated among the referents in common. Creosote used as a wood preservative, however, consists of several distillation fractions of coal tar and contains mutagenic fractions of polyaromatic hydrocarbons.¹⁵ According to our knowledge, creosote has not been described before as a risk factor for lymphoma. Fencing work has been connected with an increased risk of NHL but creosote has only rarely been used for the poles according to the authors.¹⁶

Cases of HD reported exposure to pesticides likely to contain phenoxy acids more often than the referents. Five cases and four referents explicitly declared an exposure to phenoxy acid containing herbicides, which formally gives a rate ratio of 2.2, although based on small numbers. The effect of phenoxy acids appeared for both HD and NHL, although the risk estimate (logistic OR) is higher for NHL with the 90% confidence interval exceeding unity. This is in some agreement with the findings in a study from Kansas where NHL but not HD was associated with the use of phenoxyacids.¹⁰ Studies from New Zealand, however, have provided no clear support for any effect of phenoxy acids with regard to NHL¹⁶ but this study may have included cases under ICD code 202 which have been excluded here.

Interestingly, farming as such appeared to protect against NHL, implying negative confounding. This finding could perhaps be explained by recall bias leading to an increased risk among the exposed and a correspondingly decreased risk for other farmers,¹⁷ but if so the same phenomenon should have occurred also for HD. This protective effect may help to explain why no excess risk for NHL was seen on a relatively crude cohort basis when studying Swedish agricultural and forestry workers.¹⁸

In the present study carpenters and cabinet makers were found at an increased risk for NHL. The excess risk for HD among wood workers, however, does not appear in this study.³⁴ Contact with fresh wood as in sawmills, paper pulp factories, and among lumberjacks has been found to be associated with an increased risk for chronic lymphatic leukaemia. Although NHL is morphologically closely related to this type of leukaemia, no increased risk appeared for NHL in this study.

Exposure to some pets other than dogs, cats, and birds is connected to an increased risk for NHL. A clear biological explanation for this finding is hard to see, however, but, again, a viral aetiology might be considered.

Solvents have been associated with malignant lym-

phoma⁶⁻⁸ and a relation between exposure to organic solvents and supradiaphragmatic presentation of NHL has been suggested.¹⁹ In this study occupational exposure to solvents seems to be connected to NHL and possibly also to HD.

The oral administration of DDT has been reported to cause lymphomas, lung neoplasms, and benign and malignant liver neoplasms in mice.¹⁹ Association between DDT and malignant lymphomas⁷ and between DDT and chronic lymphatic leukaemia¹² have been noted before.

Hairdressers are exposed to various chemicals in hair dyes. Among these 2,4-diaminoanisole (sulphate) and 2,4-diaminotoluene are considered as possibly carcinogenic to man,²⁰ which may explain the excess of, especially, HD in this occupational group.

In summary, this study has to some extent confirmed earlier findings with regard to risk factors for Hodgkin's disease and non-Hodgkin lymphoma and some other aetiological possibilities have been indicated. Hence, exposure to welding and creosote have appeared as more or less new risk factors for HD. For NHL exposure to phenoxy acids and creosote appear as risk factors but also wood work and exposure to solvents may be of some importance. For welding, a good biological explanation of the effect seen is difficult to provide, whereas creosote is a known cause of skin cancer in man.²⁰

The study was supported by grants from the Swedish Cancer Fund and Örebro County Council. We thank Dr Gunnar Westman, Department of Oncology, Örebro Medical Centre Hospital, Örebro, for support and help.

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