

Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study

M Nordström¹, L Hardell¹, A Magnuson², H Hagberg³ and A Rask-Andersen⁴

¹Department of Oncology, Örebro Medical Centre, S-701 85 Örebro; ²Department of Occupational and Environmental Medicine, University Hospital, S-581 85 Linköping; Departments of ³Oncology and ⁴Occupational and Environmental Medicine, University Hospital, S-751 85 Uppsala

Summary To evaluate occupational exposures as risk factors for hairy cell leukaemia (HCL), a population-based case-control study on 121 male HCL patients and 484 controls matched for age and sex was conducted. Elevated odds ratio (OR) was found for exposure to farm animals in general: OR 2.0, 95% confidence interval (CI) 1.2–3.2. The ORs were elevated for exposure to cattle, horse, hog, poultry and sheep. Exposure to herbicides (OR 2.9, CI 1.4–5.9), insecticides (OR 2.0, CI 1.1–3.5), fungicides (OR 3.8, CI 1.4–9.9) and impregnating agents (OR 2.4, CI 1.3–4.6) also showed increased risk. Certain findings suggested that recall bias may have affected the results for farm animals, herbicides and insecticides. Exposure to organic solvents yielded elevated risk (OR 1.5, CI 0.99–2.3), as did exposure to exhaust fumes (OR 2.1, CI 1.3–3.3). In an additional multivariate model, the ORs remained elevated for all these exposures with the exception of insecticides. We found a reduced risk for smokers with OR 0.6 (CI 0.4–1.1) because of an effect among non-farmers.

Keywords: case-control study; hairy cell leukaemia; occupational exposure; animal exposure; smoking

Hairy cell leukaemia (HCL), first described in 1958, is regarded as a subgroup of non-Hodgkin lymphomas (NHL) in modern classifications. The malignant cells are circulating lymphocytes of B-cell type with characteristic cytoplasmic projections (Bouroncle, 1958), characterized by a specific CD antigen pattern and, in most cases, the presence of tartrate-resistant acid phosphatase.

The introduction of new cytotoxic agents over the last 10 years has led to an improved response rate. HCL is more common in men, with a reported male to female ratio of about 4:1. The number of incident cases reported yearly to the Swedish Cancer Registry varied between 21 and 39 men and between one and 17 women during the period 1987–92 (Anon, 1958–92).

The pathogenesis of HCL is unknown, although several aetiological factors have been investigated. A correlation with farming and various occupational factors associated with farming has been suggested (Oleske et al, 1985; Clavel et al, 1995, 1996a). In a pilot study, we reported that 39% of male patients with HCL at a single Swedish institution (Hagberg et al, 1995) worked in farming or gardening.

Farming can involve exposure to many different chemicals, in contrast to other industries in which workers are exposed to a limited number of chemicals.

Exposure to pesticides has been associated with increased risk for NHLs, as a whole, in previous studies (Hardell et al, 1981, 1994; Hoar et al, 1986; Zahm et al, 1990). In various types of lymphoid malignancies, exposure to farm animals has been suggested as a risk factor. Thus, in a study on multiple myeloma (another malignancy of B-cell phenotype), a correlation to several

species of farm animals was found (Eriksson and Karlsson, 1992). A UK study found an OR of 1.69 for exposure to farm animals (CI 0.61–4.70), although the number of exposed cases was few (Staines and Cartwright, 1993). In a French study (Clavel et al, 1995), breeding of both bovine and ovine farm stock showed increased ORs of 1.9 (CI 1.1–3.1) and 1.8 (0.9–3.6), respectively, among men. In a small case-control study from the UK (McKinney et al, 1988), an elevated OR of 3.56 (CI not shown) for exposure to dead animals was found. Increased mortality from NHL has been described among abattoir workers, possibly because of zoonotic viruses (Pearce et al, 1988). Forage growing was in one study associated with an increased risk for HCL (Clavel et al, 1996a), although in a study from Iowa and Minnesota no correlation between the risk for NHL overall and different crops was found (Cantor et al, 1992).

Exposure to known leukaemic agents has been investigated. Benzene has in some small studies been described to yield increased risk for HCL (Flandrin and Collado, 1987; McKinney et al, 1988; Staines and Cartwright, 1993), but in a recent larger study no increased OR was found (Clavel et al, 1996b).

NHL has been associated with exposure to other organic solvents (Hardell et al, 1981, 1994; Olsson and Brandt, 1981). As for HCL, in studies from France and the UK, exposure to organic solvents gave OR values between 1.2 (CI 0.8–1.7) (Clavel et al, 1995) and 1.45 (CI 0.58–3.66) (Staines and Cartwright, 1993), but in another small study from the UK, no increased OR was found (McKinney et al, 1988). In addition, exposure to exhausts has shown an increased OR for HCL (Clavel et al, 1995).

Interestingly, in two earlier studies, smoking gave a clear reduction in OR for HCL (Staines and Cartwright, 1993; Clavel et al, 1995). However, with respect to NHL in general, a Swedish case-control study found an OR for ex-smokers of 2.2 (CI 1.2–3.8) (Persson et al, 1993), and in a study from the USA the OR was 1.4 (CI not given) (Brown et al, 1992). In another Swedish

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Correspondence to: M Nordström

Table 1 OR and number of exposed cases and controls for farm animals (exposure divided according to median time in years)

	Number exposed (cases/controls)	OR	95% CI
Cattle			
≤ Median time 16 years	15/46	1.5	0.7–3.0
> Median time 16 years	18/41	2.1	1.0–4.0
Total	33/88 ^a	1.8	1.1–2.9
Horse			
≤ Median time 17 years	18/44	2.0	1.0–3.8
> Median time 17 years	15/41	1.8	0.9–3.5
Total	33/85	1.9	1.1–3.2
Hog			
≤ Median time 17 years	13/41	1.5	0.7–3.1
> Median time 17 years	14/34	2.0	0.9–4.1
Total	28/75 ^a	1.8	1.0–3.1
Poultry			
≤ Median time 15 years	10/34	1.4	0.6–3.2
> Median time 15 years	17/25	3.4	1.6–6.9
Total	28/60 ^b	2.3	1.3–4.1
Sheep			
≤ Median time 13 years	5/7	3.5	1.0–12
> Median time 13 years	4/8	2.4	0.6–8.2
Total	9/15	2.9	1.1–7.1
All	43/104	2.0	1.2–3.2

^aInformation on exposure time missing for one individual. ^bInformation on exposure time missing for two individuals.

Table 2 OR and number of exposed cases and controls for herbicides, insecticides, fungicides and impregnating agents

	Number exposed (cases/controls)	OR	95% CI
All herbicides	16/22	2.9	1.4–5.9
Phenoxyacetic acids	13/19	2.7	1.3–5.7
MCPA ^a	9/12	3.0	1.2–7.3
2,4-D	2/5	1.6	0.3–8.3
2,4-D+2,4,5-T	5/7	2.9	0.9–9.3
Glyphosate	4/5	3.1	0.8–12
TCA	4/3	5.2	1.2–24
Chlorosulphuran	3/5	2.3	0.5–9.9
Other herbicides (excluding phenoxyacids)	7/11	2.5	0.9–6.6
All insecticides	22/45	2.0	1.1–3.5
DDT	11/31	1.4	0.7–2.9
Mercury	3/8	1.5	0.4–6.0
Fungicides	9/9	3.8	1.5–9.9
All impregnating agents	19/31	2.4	1.3–4.6
Pentachlorophenols	9/14	2.6	1.1–6.2
Creosote	7/9	3.1	1.1–8.6

^aMCPA, 4-chloro-2-methylphenoxyacetic acid

study on NHL, the OR was close to unity for both current and previous smokers (Hardell et al, 1994).

Exposure to UV light has recently been debated as an aetiological factor in NHL in several studies (Cartwright et al, 1994; Adami et al, 1995; Melbye et al, 1996), and in an earlier report we found data suggestive of an association between occupational

exposure to UV light and the risk for HCL among farmers but not for other occupations (Nordström et al, 1997). The aim of the present study was to further evaluate occupational risk factors for HCL in a case-control study.

PATIENTS AND METHODS

This population-based study consisted of 121 male patients with HCL reported to the Swedish Cancer Registry between 1987 and 1992. One case later turned out to have been diagnosed in 1993, but was still included in the analysis. Four controls for each case (484 in total) were drawn from the National Population Registry, matched for age and county. Thereby, the two persons before and after the index case in birth order were used. A complete working history and information about various exposures and leisure time activities were obtained from an extensive questionnaire mailed to the participants. Two written reminders were sent to those who did not return the first questionnaire. No additional controls were drawn if an answer was not obtained. The study was approved by the local ethical committee. To obtain an as uniform assessment of exposures as possible, all persons were carefully questioned if data was missing in the questionnaire. These supplementary questions were made over the phone by a trained interviewer, using written instructions. The total numbers of days of exposure to various agents were estimated. A minimum exposure of 1 working day (8 h) and an induction period of at least 1 year were used in the coding of exposures to chemicals. Some exposures (e.g. organic solvents) that may occur both in leisure time activities and occupationally were calculated together in the coding process. All interviews and all coding were made blinded with respect to the persons case or control status. The aim of the study was not disclosed to the subjects, and the questions dealt with a broad range of exposures, without focusing on any one in particular.

Statistical methods

The material was analysed by logistic regression, controlling for age. All of the calculations were performed using the EGRET program (Epidemiological Graphics Estimation and Testing package, Seattle, WA, USA). OR and 95% CI were calculated for the different exposures.

RESULTS

The primary questionnaire was answered by 111 (91%) of the cases and 400 (83%) of the controls. Ten cases and 84 controls refused to participate. For medical reasons, three cases and five controls were not capable of answering the questionnaire themselves. Proxy answers were used for these subjects. Additionally, one case died after the questionnaire was sent out, and his wife answered the questions. We thus report the results for the remaining 111 cases and 400 controls. The mean age of the individuals included in the final analysis was 57.9 years among cases and 58.6 among controls (range 28–86 years).

Active smokers had a reduction in OR to 0.6 (CI 0.4–1.1). Ex-smoking yielded an OR of 0.6 (CI 0.4–1.0). Interestingly, in a further analysis, smoking farmers had an OR of 1.4 (CI 0.5–4.1), while smoking non-farmers had an OR of 0.5 (CI 0.3–0.98). Of the farmers, 16% were active smokers compared with 28% among non-farmers.

Exposure to farm animals overall showed an increased OR of 2.0 (CI 1.2–3.2). The results for different species of farm animals are shown in Table 1. If time of exposure was taken into consideration, there was a tendency towards higher ORs with increasing exposure to cattle, hog and poultry. Farmers keeping only one species of animals were too few to permit a multivariate analysis of these results. A further analysis using a 5-year latency period showed no marked difference compared with 1-year latency, and the results are therefore not shown separately.

Exposure to herbicides showed a increased OR of 2.9 (CI 1.4–5.9) in the univariate analysis. ORs for insecticides, fungicides and impregnating agents were 2.0 (CI 1.1–3.5), 3.8 (CI 1.5–9.9) and 2.4 (CI 1.3–4.6) respectively (see Table 2). In a univariate analysis, exposure to organic solvents showed an OR of 1.5 (0.99–2.3), and in Table 3 ORs for different solvents are shown.

In a further multivariate analysis to control for possible confounding (see Table 4), the risk remained elevated for exposure to herbicides, fungicides, impregnating agents and organic solvents, while the OR for insecticides decreased. We could identify a strong correlation between exposure to herbicides and insecticides.

UV light was investigated as a risk factor for HCL in this study. We found an increased risk for subjects with the highest score for exposure (Nordström et al, 1997), however this was only among farmers. If UV exposure according to the highest score > 50 points was added to the multivariate model presented in Table 4, an OR of 0.9 (CI 0.4–1.6) was obtained. No major changes in the results presented in Table 4 were seen in this additional analysis.

The OR for exposure to all exhausts was 2.1 (CI 1.3–3.3), and the OR for tractor drivers was 2.2 (CI 1.3–3.8), which remained after a further multivariate analysis (OR 2.1, CI 1.0–4.1). Exposure to diesel exhausts yielded an OR of 2.0 (CI 1.0–4.0), which decreased to 1.5 (CI 0.7–3.2) after multivariate analysis. Drivers of cars and trucks had an OR of 2.2 (CI 1.0–3.3); the OR changed to 1.5 (CI 0.7–3.2) after further multivariate analysis. Only minor changes were observed (data not shown) in an analysis using a 5-year latency period regarding exposure to impregnating agents, organic solvents and exhaust fumes. A further analysis of dose–response is shown in Table 5. An increase in OR with an increased number of exposure days was shown for fungicides and impregnating agents. In Table 6, ORs for exposures to various other chemicals are shown. Work at a display unit yielded an OR of 0.8 (CI 0.5–1.5). Having ever worked in the paper pulp industry yielded for sulphate pulp OR 5.5 (CI 0.9–33) and sulphite pulp OR 1.8 (CI 0.3–10), although the number of exposed cases and controls were few. Exposure to chlorine yielded OR 2.5 (0.7–8.8). The risk was further increased if chlorine exposure in the pulp industry was considered.

DISCUSSION

The compulsory notification to the Swedish Cancer Registry makes it plausible that most cases of HCL were identified. In a study from the county of Uppsala in Sweden, it was concluded that only 6.7% of cases of lymphomas were not reported to this registry (Martinsson et al, 1992). It is, however, a possibility that patients with HCL might be misdiagnosed and treated under other diagnoses.

To minimize recall bias, only living cases were included. In the present study, age and county-matched male controls from the general population were used. The matching was dissolved in the analysis to use all information obtained. By dissolving the matching,

Table 3 OR and number of exposed cases and controls for solvents

	Number exposed (cases/controls)	OR	95% CI
All solvents	51/143	1.5	0.99–2.3
White spirit	33/69	2.0	1.2–3.4
Paint	11/11	4.3	1.8–10.3
Turpentine	5/11	2.0	0.7–5.9
Acetone	3/11	1.2	0.3–4.3
Petrol	6/23	1.1	0.4–2.9
Aviation fuel	2/4	2.1	0.4–12
Thinner	14/44	1.4	0.7–2.6
Trichloroethylene	9/26	1.5	0.7–3.3
Lacquer	6/18	1.4	0.5–3.8
Methylated spirit	2/12	0.7	0.2–3.3
Degreaser			
Car	4/25	0.7	0.2–2.0
Other	3/9	1.4	0.4–5.4
Other solvents	5/9	2.4	0.8–7.4

Table 4 Univariate and multivariate analysis controlled for age

	Number exposed (cases/controls)	Univariate		Multivariate	
		OR	95% CI	OR	95% CI
Animals (all)	43/104	2.0	1.2–3.2	1.4	0.8–2.5
Herbicides	16/22	2.9	1.4–5.9	1.8	0.7–4.6
Insecticides	22/45	2.0	1.1–3.5	0.7	0.3–1.7
Fungicides	9/9	3.8	1.4–9.9	2.1	0.6–6.5
Impregnating agents	19/31	2.4	1.3–4.6	2.0	1.0–3.9
Organic solvents	51/143	1.5	0.99–2.3	1.4	0.8–2.2
Exhausts	60/143	2.1	1.3–3.3	1.5	0.9–2.6

Table 5 Dose–response univariately controlled for age. Time of exposure divided according to median time of exposure in days for cases and controls together

	Time of exposure (days)	Number exposed (cases/controls)	OR	95% CI
Solvents ^a	1–139	25/69	1.5	0.8–2.7
	140–7860	25/68	1.6	0.9–2.7
Herbicides	2–46	9/10	3.6	1.4–9.3
	47–370	7/12	2.3	0.8–6.2
Fungicides ^b	1–37	3/6	1.9	0.4–7.7
	38–1650	5/3	6.5	1.5–28
Impregnating agents ^c	1–24	7/18	1.6	0.6–3.9
	25–2700	12/12	4.0	1.7–9.2
All exhausts ^d	1–1562	29/65	2.2	1.3–3.9
	1563–10700	28/66	2.2	1.2–3.8

^aTime of exposure missing for one case and six controls. ^bTime of exposure missing for one case. ^cTime of exposure missing for one control. ^dTime of exposure missing for three cases and 12 controls.

theoretically, bias may have been introduced by not controlling for county. In a further analysis, the data regarding exposure to animals, pesticides, solvents, exhausts and smoking was reanalysed in a matched analysis using conditional logistic regression. This analysis lead to the exclusion of 33 controls, who had no corresponding case. Examples of the OR values obtained for various exposures are as follows: animals, OR 2.2 (CI 1.3–3.6); herbicides, 3.1 (CI 1.4–6.3); insecticides, 2.1 (CI 1.1–3.9); fungicides, 4.2 (CI 1.4–13); and

Table 6 OR and number of exposed cases and controls for different exposures

	Number exposed (cases/controls)	OR	95% CI
Wood gas	4/13	1.1	0.4–3.6
Chlorine	4/6	2.5	0.7–8.8
Oils	4/14	1.0	0.3–3.2
Hydrochloric acid	3/8	1.4	0.4–5.3
Epoxy compound	2/9	0.8	0.2–3.7
Glue	5/14	1.3	0.5–3.7
Asbestos	33/86	1.5	0.9–2.5
Cutting oils (manufacturing industry)	8/42	0.6	0.3–1.4
Pulp industry	5/6	3.0	0.9–10.2
Sulphur compounds	3/8	1.4	0.4–5.2
Chlorine bleaching			
Employment	4/3	4.9	1.1–22
Chlorine exposure	3/1	11	1.1–107
All insect repellants	9/51	0.6	0.3–1.3
Glass wool	15/44	1.3	0.7–2.4
Mineral wool (construction worker)	12/34	1.3	0.6–2.6
Mould dust	8/14	1.8	0.7–4.2
Formic acid (farming)	8/15	2.0	0.8–4.9

impregnating agents 2.7 (CI 1.4–5.3). This reanalysis resulted in only minor changes, with generally slightly higher ORs, and we conclude that county was not an important confounding factor in this study setting.

To minimize bias, only men were included in the study. One advantage in using controls from the general population is that selection of hospital patients may introduce bias, as it can not be excluded that the possible aetiological factors, for example immunological disturbances, might be correlated to the disease under study and the conditions causing the hospitalization. Thus, in this respect, hospital controls may not be representative for the population under study. Using the unique ten-digit identification number of all Swedish citizens, we were able to verify the number of cases of malignant diseases among the controls. In all, 21 incident cases of malignant diseases were diagnosed before the interview and were reported to the Cancer Registry. Among these 21 cases, there was one case of Hodgkin's disease but no other haematopoietic or lymphatic malignancies were found. However, among these 21 individuals, exposure to solvents and impregnating agents was less common than among the other controls. Of all controls, 25.8% reported exposure to farm animals, compared with 42.9% of the controls with a diagnosed malignant disease other than HCL. Exposure to herbicides or insecticides was reported among 5.5% and 11.3% of all controls compared with 14.3% and 14.3%, respectively, among those controls with a malignant disease. Regarding exposure to herbicides, insecticides and farm animals, the possibility of recall bias can not be completely excluded. No such effect was observed for the other major exposure categories that showed elevated ORs. The proportion of controls with malignant diseases exposed to fungicides and

solvents was, respectively, 0% compared with 2.3% and 35.8% in controls without a malignant disease. Increased OR for HCL associated with exposure to farm animals has been reported from France and the UK (Staines and Cartwright, 1993; Clavel et al, 1995). Our results show modestly increased ORs for exposure to cattle, horse, hog, poultry and sheep. Similar results have also been shown in studies regarding NHL (Persson et al, 1993). For cattle, hog and poultry, an increased risk over time for exposure is suggested in our data. A correlation to zoonotic viruses, mainly bovine leukaemia virus (BLV), which is related to HTLV-1, has been hypothesized (Pearce and Bethwaite, 1992). An increased risk for NHL in abattoir workers was found in a review of studies from New Zealand and the USA (Pearce et al, 1988).

As in other studies, we were able to show a clear negative correlation between smoking and HCL (Staines and Cartwright, 1993; Clavel et al, 1995). In the present study, no dose–response relation was found (data not shown). In our study, the risk was only decreased for non-farmers, and a confounding effect can not be excluded. The reason for this effect of exposure to smoking on the risk of HCL is unclear and biologically difficult to explain. However, it is known that non-smokers have a higher risk of other diseases that are correlated to the immune system, such as allergic alveolitis and sarcoidosis (Warren, 1977; Valeyre et al, 1988). There is no reason to believe that smoking habits of the controls differ from that of the population in general. In the Lutheran brotherhood cohort study, an increased risk of HCL among smokers was found, and a dose–response effect was noted (Linet et al, 1992). In a Swedish study on NHL, the OR was close to unity for both current and previous smokers (Hardell et al, 1994). In a hospital-based case–control study from Italy, the RR was 1.5 (CI 1.0–2.3) for both current smokers and ex-smokers compared with those who had never smoked (Franceschi et al, 1989). A recent combined analysis of data from three population-based case–control studies showed no association between NHL and tobacco use in men (Zahm et al, 1997).

Exposure to herbicides has been debated as a risk factor for HCL. In addition, in several studies since the 1980s, exposure to herbicides has been investigated as a risk factor for NHL in general (Hardell et al, 1981, 1994; Hoar et al, 1986; Persson et al, 1989; Zahm et al, 1990). Our results show an increased risk for all herbicides including phenoxyacetic acids, with the highest OR for exposure to MCPA. In addition, ORs for fungicides and insecticides were increased, as was the case for impregnating agents. These results are in accordance with previously published results. In a recent report, significantly increased ORs for HCL were found for insecticides, fungicides and herbicides (Clavel et al, 1996a). In a multivariate analysis, the authors found an OR of 7.5 (0.9–61.1) for non-smokers exposed to organophosphorus insecticides. No other increased OR remained after multivariate analysis. The authors concluded that there was no association to phenoxyacetic acids, triazines or organochlorine insecticides. In a further multivariate analysis, we could confirm elevated ORs for herbicides, fungicides and impregnating agents but not for insecticides. There was a strong correlation between herbicides and insecticides; 31 of 38 individuals with exposure to herbicides also reported exposure to insecticides. Such strong correlations make multivariate analyses difficult. Regarding insecticides, the OR changed from 2.0 (CI 1.1–3.5) to 0.7 (CI 0.3–1.7) in the multivariate analysis. This does not necessarily show that exposure to insecticide is not correlated to increased risk for HCL but might reflect the difficulties in separating the effects of insecticides from other effects.

As previously discussed, an association between occupational UV exposure and HCL has been suggested for farmers but not for other occupations (Nordström et al, 1997). If the highest UV score, > 50 points, was added to our multivariate analysis presented in Table 4, UV exposure did not increase the risk for HCL [OR 0.9 (CI 0.4–1.6)]. Thus, other exposures, for example to pesticides, might have operated as confounders and explain the increased risk for UV exposure in farmers.

Other chemicals, for example organic solvents, have in previous studies showed an increased OR for HCL with ORs of 1.2 (CI 0.8–1.7) (Clavel et al, 1995) and 1.45 (CI 0.58–3.66) (Staines and Cartwright, 1993). In our study we found an increased risk associated with an overall exposure to solvents. There was an increase in OR with exposure to exhaust fumes, as in certain other studies. As in a French study (Clavel et al, 1995), we also found increased OR for HCL correlated to occupational exposure to exhaust fumes. These results remained in a multivariate analysis that also included car, truck and tractor drivers. A study from the UK combining registry data on occupation and data from the national cancer registry found slightly elevated RR for lymphomas among drivers of buses and coaches (Balarajan, 1983).

In conclusion, this study seems to support an association of HCL and exposure to solvents, herbicides, fungicides, impregnating agents and exhaust fumes. There was a clear negative association between HCL and smoking for non-farmers. Exposure to farm animals also seemed to be associated with an increased risk for HCL.

As many of these occupational exposures might be correlated, the effects of confounding can not be excluded. The results must also be interpreted with caution, as many comparisons were made and some correlations may occur by chance; there is a possibility that the odds ratios are, to some extent, elevated by recall bias.

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