Occupation and lymphoid neoplasms

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Summary The relationship between occupation and exposure to a number of occupational agents and lymphoid neoplasms was investigated in a case–control study of 69 cases of Hodgkin's disease, 153 non-Hodgkin's lymphomas, 110 multiple myelomas and 396 controls admitted for acute diseases to a network of teaching and general hospitals in the greater Milan area. Among the cases, there was a significant excess of individuals ever occupied in agriculture and food processing: the multivariate relative risks (RR) were 2.1 (95% confidence interval, CI = 1.0–3.8) for Hodgkin's disease, 1.9 (95% CI = 1.2–3.0) for non-Hodgkin's lymphomas and 2.0 (95% CI = 1.1–3.5) for multiple myeloma. Significant trends for duration of exposure to herbicides were observed for lymphomas, but the association was stronger for overall occupation in agriculture than with the specific question of herbicide use. History of occupation in the chemical industry was more frequent among Hodgkin's disease (RR = 4.3, 95% CI = 1.4–10.2), and a significant trend in risk was observed between duration of exposure to benzene and other solvents and multiple myeloma. No significant relation was found between any of the lymphoid neoplasms considered and rubber, dye, painting, printing, tanning leather, photography, pharmaceuticals, wood, coal/gas and nuclear industries.

A number of studies have suggested that certain occupational exposures are related to neoplasms of the lymphoid system. Among the groups of occupations considered, agriculture and food processing have been associated in several studies with elevated risk of multiple myeloma (Burmeister et al., 1983; Cuzick & De Stavola, 1988; Gallagher et al., 1983; Levi et al., 1988; Morris et al., 1986; Nandakumar et al., 1986; Steineck & Wiklund, 1986), Hodgkin's and non-Hodgkin's lymphomas (Brownson & Reif, 1988; Cantor, 1982; Giles et al., 1984; Hardell & Bengtsson, 1983; Hardell et al., 1981; Levi et al., 1988; Linos et al., 1986; Lynge, 1985; Pearce & Howard, 1986; Pearce et al., 1985; Reif et al., 1989). The evidence was inconsistent in other investigations (Friedman, 1986; Hoar et al., 1986; Linet et al., 1987; Tollerud et al., 1985; Vagero & Persson, 1986), and the specific agents or exposures which may be responsible for this association are far from defined (Council of Scientific Affairs, 1988). Other agents that have emerged are occupational exposures to radiation for myeloma (Cuzick, 1981), oil and various chemicals and toxic substances including arsenic, cutting oils, heavy metals, asbestos, plastic manufacture, wood dust, electromagnetic fields or, in consideration of the possible viral origin of these neoplasms, professional groups such as teachers, physicians or drivers of buses or coaches (Balarajan, 1983; Cartwright et al., 1988; Cuzick & De Stavola, 1988; Garland et al., 1987; Grufferman & Delzell, 1984; Milham, 1988; Tollerud et al., 1985).

There are, however, substantial uncertainties in the epidemiological definition of occupational correlates of lymphoid neoplasms. In order to provide further information in the topic, this paper presents further data on occupational histories and the risk of lymphomas and myeloma, derived from a case–control study conducted in Northern Italy.

Subjects and methods

The data were derived from an ongoing case–control study of lymphoid neoplasms being conducted in the greater Milan area since June 1983. Trained interviewers identified and questioned patients aged 15–74 with histologically confirmed diagnosis of Hodgkin's disease, non-Hodgkin's lymphomas and multiple myeloma, and hospital controls admitted to a network including major teaching and general hospitals in

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the area under surveillance. Participation rate was almost complete, since less than 3% of cases and controls refused to be interviewed. The present report is based on data collected before October, 1988.

The cases were 69 incident cases of Hodgkin's disease (44 males and 25 women, median age 41 years), 153 non-Hodgkin's lymphomas (93 males and 60 females, median age 58 years) and 110 multiple myelomas (56 males and 54 females, median age 63 years), diagnosed within the year before interview.

The control group comprised 396 subjects (269 males, 127 females, median age 57 years) admitted for acute conditions to the same network of hospitals where cases had been identified. Of these, 28% were admitted for traumatic conditions, 15% had non-traumatic orthopaedic diseases, 25% acute surgical conditions and 32% other miscellaneous disorders, such as skin, ear, nose and throat or dental ailments. Controls were not individually matched with cases, and the same pool of controls was used for all the neoplasms considered. Table I gives the distribution of cases of various lymphoid neoplasms and of the comparison group according to age. The catchment area of cases and controls was well comparable: overall, 86% of the cases and 89% of the controls came from the same region, Lombardy, and in large proportion from the highly industrialised area of greater Milan, which includes about 50% of the total population of the region; 94% of the cases and 95% of the controls came from Northern Italy.

The structured questionnaire comprised information on socio-demographic characteristics, family size and order, lifestyle habits, including smoking, alcohol, coffee and other methylxanthine consumption; a few selected indicator foods; a problem-oriented medical history, including questions on specific infections and auto-immune diseases, and immunisation history; menstrual and reproductive factors (for women); and history of occupations and occupational exposures. Information was collected on date of starting and stopping for 16 industries or occupations, on the role in the industry in terms of direct involvement in production aspects, and on exposure to 13 selected occupational agents or groups of agents.

Data analysis

For each cancer site, the number of observed occupational exposures was compared with the expected one based on the distribution of controls adjusted for sex and decade of age. In relation to the exposures for which a significant excess

Table I   Distribution of cases of lymphoid neoplasms and controls according to sex and age, Milan, Italy, 1983–88

Age group	Hodgkin's disease (9th ICD = 201)		Non-Hodgkin's lymphomas (9th ICD = 200–202)		Multiple myeloma (9th ICD = 203)		Controls	
	Males	Females	Males	Females	Males	Females	Males	Females
15–34	10	13	7	3	–	–	20	12
35–44	12	3	5	10	3	5	49	21
45–54	8	4	23	8	12	12	59	18
55–64	10	4	32	17	17	10	64	22
65–74	4	1	26	22	24	27	77	54

Table II   Percentages of cases of lymphoid neoplasms and controls ever occupied in selected industries or occupations (numbers in parentheses give the percentage employed in production aspects),[a] Milan, Italy, 1983–88

Occupation/industry	Hodgkin's disease (n = 69)		Non-Hodgkin's lymphomas (n = 153)		Multiple myeloma (n = 110)		Controls (n = 396)	
Agriculture/food processing	21.7[b]	(20.3)[b]	24.8[c]	(23.5)[c]	22.7[b]	(22.7)[c]	14.1	(13.6)
Chemical	10.1[c]	(7.4)[c]	2.0	(2.0)	3.6	(1.8)	1.5	(1.0)
Rubber	1.4	(1.4)	0.7	(0.7)	1.8	(0.9) ·	1.3	(1.0)
Dye	1.4	(–)	1.3	(1.3)	2.7	(1.8)	1.0	(1.0)
Painting (incl. spray)	4.3	(2.9)	4.0	(4.0)	4.5	(3.6)	5.1	(2.0)
Printing	1.4	(1.4)	–	(–)	0.9	(0.9)	2.0	(1.5)
Furniture/upholstery	5.8	(5.8)	2.0	(2.0)	1.8	(1.8)	5.6	(5.3)
Coal/gas	1.4	(1.4)	0.7	(–)	0.9	(0.9)	1.0	(1.0)

[a]Other would be office or service workers; [b]$P<0.05$; [c]$P<0.01$.

was observed among the cases, relative risks (RR) and the corresponding 95% approximate confidence intervals (CI) were first computed, adjusted for age and sex, by the Mantel–Haenszel procedure (Mantel & Haenszel, 1959). Likewise, sex and age-adjusted tests for trend in risk were based on the test described by Mantel (1963). Unconditional multiple logistic regression (Breslow & Day, 1980) fitted by the method of maximum likelihood (Baker & Nelder, 1978) was used to obtain relative risks simultaneously adjusted for age, sex, area of residence and smoking.

Results

Table II gives the proportions of cases of various lymphoid neoplasms and controls employed in selected industries or occupations. Significant excesses were observed for Hodgkin's, non-Hodgkin's lymphomas and myelomas for agriculture or food processing (22–25% among the cases vs 14% in the controls). A larger proportion of Hodgkin's disease cases were ever employed in the chemical industry, too (10.1% vs 1.5% in the controls), but there was no difference for non-Hodgkin's lymphomas and myelomas.

Likewise, no significant association was found between any of the lymphoid neoplasms considered and rubber, dye, printing, painting, wood and coal/gas industries, or other industries (including tanning leather, photography, petroleum, pharmaceuticals and nuclear) not shown in the table because of the low prevalence of exposure.

Table III gives the corresponding relative risks in relation to significant associations; these were around 2 for the three neoplasms considered among subjects ever employed in agriculture, and 4.3 (with 95% CI from 1.4 to 10.2) for Hodgkin's disease among subjects ever employed in the chemical industry.

In Table IV the proportions of cases and controls exposed to selected groups of occupational agents are reported, with a measure of duration of exposure. Significant direct trends of risk were observed for herbicides with Hodgkin's and non-Hodgkin's lymphomas, chemicals with Hodgkin's disease or multiple myeloma, and solvents/benzene with multiple myeloma. No significant association was observed for any of the other agents listed in Table IV (including gases, metals, plastic, oil, dyes, wood, asbestos, electricity/radar and coal), or for radiation (only one Hodgkin's disease and two controls exposed).

Discussion

The most consistent finding of this study was the two-fold elevated risk of both Hodgkin's and non-Hodgkin's lymphomas and multiple myeloma among subjects ever employed in agriculture. Further, an association between history of employment in the chemical industry and Hodgkin's disease was observed.

These results should be taken with due caution, in consideration of the limits of the study. In particular, information on occupation was restricted to a selected series of broad items and, consequently, does not allow any precise inference on specific occupational agents. It is unlikely, on the other hand, that these findings are substantially affected by bias, since there is no obvious reason to suppose a differential recall between cases and controls for these broad occupational categories. Cases and controls came from well comparable catchment areas and, in the aetiology of the neoplasms, there is no known confounding factor which could account for the associations observed.

The association with farming is consistent with most (Barnes *et al.*, 1987; Brownson & Reif, 1988; Burmesiter *et al.*, 1983; Cantor, 1982; Cuzick & De Stavola, 1988; Gallagher *et al.*, 1983; Giles *et al.*, 1984; Levi *et al.*, 1988; Linos *et al.*, 1986; Lynge, 1985; Morris *et al.*, 1986; Nandakumar *et al.*, 1986; Pearce & Howard, 1986; Pearce *et al.*, 1985; Reif *et al.*, 1989; Steineck & Wicklund, 1986), though not all (Bernard *et al.*, 1987; Friedman, 1986; Hoar *et al.*, 1986; Tollerud *et al.*, 1985; Vagero & Persson, 1986), previous studies of leukaemias, lymphomas and myelomas, and with a Swedish case–control study of Hodgkin's lymphoma (Hardell & Bengtsson, 1983; Hardell *et al.*, 1981), and could be related either to the use of pesticides, or to exposure to viruses or antigens. In this study, the association was stronger for overall occupation in agriculture than with the specific question of herbicide use, although the figures are clearly too small to permit meaningful distinction between the two items. Cereal growing (rice, wheat and corn) are major agricultural activities in this area, together with grapes and other fruits, and bovine and poultry livestock farming.

Consideration of the time trends in mortality for these neoplasms would support a possible association with herbicides, since mortality rates in Italy have been stable (or possibly upwards) over the more recent decades (La Vecchia & Decarli, 1985), while the proportion of the population

Table III Relative risk estimates of lymphoid neoplasms for selected occupations, Milan, Italy, 1983–88

Type of disease	Occupation	Relative risk (95% CI) (a)	(b)
Hodgkin's disease	Agriculture	2.0 (1.0–3.7)	2.1 (1.0–3.8)
Non-Hodgkin's lymphomas	Agriculture	2.1 (1.3–3.4)	1.9 (1.2–3.0)
Multiple myeloma	Agriculture	1.9 (1.1–3.2)	2.0 (1.1–3.5)
Hodgkin's disease	Chemical industry	5.1 (1.9–13.7)	4.3 (1.4–10.2)

[a]Mantel–Haenszel estimates adjusted for age and sex; [b]Estimates from multiple logistic regression equations including terms for age, sex, area of residence and smoking.

Table IV Percentage of cases of lymphoid neoplasms and controls exposed to selected occupational agents by duration of exposure, Milan, Italy, 1983–88

Agents	Hodgkin's disease 1–10 years	>10 years	Non-Hodgkin's lymphomas 1–10 years	>10 years	Multiple myeloma 1–10 years	>10 years	Controls 1–10 years	>10 years
Herbicides	1.4	8.7[a]	2.6	5.2[a]	1.8	1.8	1.5	2.5
Chemicals	7.2	8.7[a]	2.6	5.9	3.6	7.3	2.3	4.5
Plastic resins/glues	5.8	4.3	1.3	–	1.8	0.9	1.8	2.0
Solvents/benzene	2.9	1.4	1.3	2.6	2.7	5.5[a]	2.5	3.0
Gases/fumes	1.4	1.4	2.0	1.3	1.8	0.9	1.8	1.5
Metals/metal dusts	4.3	7.2	3.3	6.5	4.5	4.5	3.5	6.6
Oil	1.4	–	2.0	2.6	1.8	2.7	1.0	2.5
Dyes/paints	5.8	–	2.6	1.3	2.7	0.9	1.5	4.5
Wood dust	4.3	1.4	0.7	2.6	–	1.8	3.0	3.0
Asbestos	–	–	0.7	–	0.9	0.9	–	0.3
Electricity/radar	–	–	0.7	0.7	–	0.9	–	0.5
Coal/gas	1.4	–	0.7	1.3	–	–	1.0	1.0

[a]$P < 0.05$ (for linear trend).

occupied in agriculture has steadily declined. If these time trends are not substantially influenced by changes in diagnostic or certification accuracy, they would suggest that the exposure to chemical or viral carcinogens in agriculture has increased over recent decades. Likewise, the positive association between occupation in the chemical industry or exposure to chemicals and Hodgkin's disease in this study (as well as the positive trend in risk between chemical – specifically benzene – exposure and multiple myeloma) are in agreement with previous studies from the United States (Garland et al., 1987; Linet et al., 1987; Vianna & Polan, 1979), Sweden (Olin & Ahlbom, 1980; Olsson & Brandt, 1979) and Britain (Cuzick & De Stavola, 1988), although there have been negative or inconsistent results too (Benn et al., 1979; Morris et al., 1986; Grufferman & Delzell, 1984). It is difficult, however, to find a plausible aetiopathogenic interpretation of this association and identify specific chemical agents to account for such epidemiological observations.

Some of the negative findings of this study should be considered, too. For instance, there was no relation between woodworking and Hodgkin's disease (RR = 1.0) (Grufferman & Delzell, 1984; Tollerud et al., 1985) or other lymphomas

(Cartwright et al., 1988), although, with this sample size, it was possible to exclude only a relative risk of 3, at the usual 95% confidence interval.

In conclusion this study, the major strength of which lies in the fact that it provides an opportunity for obtaining an overall pattern of risk for various lymphoid neoplasms, confirmed that the risk of lymphomas and multiple myeloma was approximately double among individuals who had worked in agriculture and food processing, and further suggested that occupational exposure to chemicals may be related to the risk of Hodgkin's disease or multiple myeloma.

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