Occupation and risk of lymphoma: a multicentre prospective cohort study (EPIC)

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ABSTRACT

Objectives Evidence suggests that certain occupations and related exposures may increase the risk of malignant lymphoma. Farming, printing and paper industry, wood processing, meat handling and processing, welding, shoe and leather manufacturing and teaching profession are among the categories that have been implicated in previous studies. The relationship between occupation and malignant lymphoma has been investigated in a large European prospective study.

Methods We investigated occupational risks for lymphomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). The mean follow-up time for 348 555 subjects was 9 years (SD: 2 years). The analysis was based on 866 and 48 newly diagnosed cases of non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). These were identified in the EPIC subcohorts with occupational data. Data on 52 occupations were collected through standardised questionnaires. Cox proportional hazard models were used to explore the association between occupation and risk of malignant lymphoma.

Results The following occupations were positively associated with malignant NHL after adjustment for study centre, age, sex, socioeconomic status (SES), smoking and alcohol: butchers (HR=1.53, 95% CI 1.05 to 2.48, including multiple myeloma/plasmacytoma; HR=1.30, 95% CI 1.00 to 2.66, excluding multiple myeloma/plasmacytoma) and car repair workers (HR=1.50, 95% CI 1.01 to 2.00, including multiple myeloma/plasmacytoma; HR=1.51, 95% CI 1.01 to 2.31, excluding multiple myeloma/plasmacytoma). HL was associated with gasoline station occupation (HR=4.59, 95% CI 1.08 to 19.6).

Conclusion The findings in this current study of a higher risk of NHL among car repair workers and butchers and a higher risk of HL among gasoline station workers suggest a possible role from occupationally related exposures, such as solvents and zoonotic viruses, as risk factors for malignant lymphoma.

What this paper adds

- Established risk factors for lymphomas are those associated with downregulation of immune function such as genetically determined or acquired immune deficiencies.
- Known risk factors explain only a small proportion of lymphomas. Evidence suggests other factors such as occupations and related exposures may increase risk of disease.
- This study found that certain occupations (butchers and car repair workers) were associated with non-Hodgkin's lymphoma. Gasoline station work was associated with Hodgkin's lymphoma.
- Our findings point to the role of occupationally related exposures (solvents and zoonotic viruses) as risk factors for malignant lymphoma.

INTRODUCTION

Lymphomas are a heterogeneous group of diseases caused by a proliferation of malignant lymphocytes that accumulate in lymph nodes. They are subdivided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), where HLs are B-cell malignancies distinguishable by the presence of Reed–Sternberg (RS) cells, and NHLs are of either T- or B-cell origin.[1] NHL accounts for 90% of all lymphomas and HL for the remaining 10%.

Lymphomas account for over 3% of cancers occurring worldwide.[1] The aetiology of these diseases remains largely unknown. The best established risk factors are those associated with downregulation of immune function such as genetically determined or acquired immune deficiencies, including HIV infection or iatrogenically induced immune suppression after transplantation.[2] Known risk factors explain only a small proportion of lymphomas. Evidence suggests that other factors such as certain occupations and related exposures may increase risk of disease.[3–12]

Very few studies examining occupation and lymphoma have used a prospective design.

Retrospective (case control) studies can be affected by recall bias and poor comparability of cases and controls. The present investigation evaluates the relationship between job title and lymphoma in a large prospective cohort (EPIC).

MATERIALS AND METHODS

Study population, outcomes and data collection

EPIC is a European multicentre prospective cohort study investigating the aetiology of cancers and other chronic diseases in relation to diet and lifestyle. Recruitment of subjects took place between 1992 and 2000 in 23 centres located in 10 European countries. The cohort includes participants of both genders, mostly in the age range of 35–70 at recruitment. Centres in France (n=61 996), Oxford (n=42 518), and Utrecht (n=15 174) did not collect job questionnaire information, therefore the current cohort size was 348 555 subjects (table 1). Recruitment was aimed at the general population or subgroups (such as blood donors or women attending breast cancer screening facilities). Identification of cancer cases was based on population cancer registries in seven of the participating countries (Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK). The other two countries (Germany and Greece) used a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next of kin. Information was updated in 2006 (end of follow-up).

Diagnosis of lymphoma cases in EPIC was based on the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). All lymphoma cases were subsequently reclassified according to the recently published WHO classification of haematopoietic and lymphoid tissues based on ICD-O-3. This was accomplished applying a conversion program available at the SEER webpage (http://seer.cancer.gov/tools/conversion/ICD02-3manual.pdf). NHL and multiple myeloma/plasmacytoma cases were grouped together (termed 'NHL'); HL cases were grouped separately (termed 'HL').[13] We further evaluated NHL excluding multiple myeloma/plasmacytoma.

Exposure information was collected via standardised dietary intake questionnaires and non-dietary questionnaires on lifestyle variables. Occupational status was self-reported and obtained using a standardised questionnaire in which participants were asked if they had ever worked in up to 52 jobs, selected a priori for being previously linked to risk of developing cancer. Data on educational attainment (a proxy for socioeconomic status), alcohol consumption and smoking status were obtained. Current smoker/drinker refers to status at baseline. Further details can be found elsewhere.[14]

Statistical analyses

All statistical analyses were performed using STATA 9 (Statacorp). Cox proportional hazard regression models were used to examine the association between job category and lymphoma. Time at entry was defined as age at recruitment and exit time was age when individuals were: diagnosed with lymphoma, died, or censored at end of follow-up, whichever came first. Analyses were stratified by centre to control for the differences in follow-up procedures and questionnaire design. Multivariate analyses were further adjusted for gender, education level (proxy for socioeconomic status), alcohol consumption (g/day) and smoking status at baseline.

RESULTS

Mean follow-up time for 348 555 subjects was 9 years (SD: 2 years). Unadjusted NHL and HL incidence rates were 27.7

Table 1 Characteristics of EPIC cohort population, NHL (including and excluding multiple myeloma/plasmacytoma (MM)) and HL separately

Descriptive data	Whole cohort (N=348555)	NHL (N=866)	NHL excluding MM (N=676)	HL (N=48)
Age at recruitment (%)				
Mean age, years (SD)	51.7 (9.7)	56.4 (8.4)	56.6 (7.8)	50.9 (11.2)
<35	16854 (4.9)	2 (0.2)	2 (0.3)	5 (10.4)
35–44	64930 (18.6)	70 (8.1)	56 (8.3)	8 (16.7)
45–54	133990 (38.4)	254 (29.3)	207 (30.6)	12 (25.0)
55–65	110837 (31.8)	413 (47.7)	309 (45.7)	19 (39.6)
65+	21944 (6.3)	127 (14.7)	102 (15.1)	4 (8.3)
Age*				
Mean age, years (SD)	60.6 (9.8)	61.5 (8.7)	61.7 (8.4)	55.6 (11.8)
Gender, n (%)				
Men	106813 (30.6)	427 (49.3)	330 (48.8)	29 (60.4)
Women	241742 (69.4)	439 (50.7)	346 (51.2)	19 (39.6)
School degree, n (%)				
None	18621 (5.3)	42 (4.8)	34 (5.0)	2 (4.1)
Primary	82940 (23.8)	270 (31.2)	197 (29.1)	18 (37.5)
Technical	75301 (21.6)	243 (28.1)	194 (28.7)	14 (29.2)
Secondary	80692 (23.2)	133 (15.4)	107 (15.8)	1 (2.1)
University	91001 (26.1)	178 (20.5)	144 (21.4)	13 (27.1)
Smoking habits, n (%)				
Never smoked	181384 (52.0)	372 (43.0)	290 (42.9)	12 (25.0)
Former smoker	92743 (26.6)	305 (35.2)	239 (35.4)	17 (35.4)
Current smoker	74428 (21.4)	189 (21.8)	147 (21.7)	19 (39.6)
Alcohol drinking history, n (%)				
Never drinkers	27406 (7.9)	48 (5.5)	37 (5.5)	2 (4.2)
Former drinkers	16733 (4.8)	62 (7.2)	50 (7.4)	3 (6.2)
Drinkers at recruitment only	36785 (10.5)	59 (6.8)	47 (6.9)	2 (4.2)
Lifetime drinkers	267631 (76.8)	697 (80.5)	542 (80.2)	41 (85.4)

*Age at exit from study based on: lymphoma diagnosis, death, or censoring at end of follow-up, whichever came first.
EPIC, European Prospective Investigation into Cancer and Nutrition; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma.

cases per 100 000 person-years (95% CI 25.9 to 29.6) and 1.5 cases per 100 000 person-years (95% CI 1.1 to 2.0), respectively, based on 866 and 48 newly diagnosed cases of NHL and HL. These incidence rates are comparable with other data sources.[15] After adjustment for centre, age, sex, educational status, smoking and alcohol consumption, butchers (including slaughterhouse and meat manufacturing workers) and car repair workers had significantly elevated risk of NHL (table 2) while gasoline station workers had elevated risk of HL. Excluding cases of multiple myeloma/plasmacytoma did not change our findings (apart from a significantly increased risk for chemical laboratory work: adjusted HR=3.21 (1.18–8.72)). This result and results from all 52 job categories can be found in the online supplementary table.

An analysis by NHL histological subtypes was attempted, but absolute numbers in most occupations were too small for subgroup analysis. Overall there were 117 diffuse large cell lymphomas, 117 follicular lymphomas, 187 chronic lymphocytic leukaemias, 190 multiple myelomas/plasmacytomas, 97 B-cell lymphomas NOS and 158 other specified non-Hodgkin's lymphomas.

DISCUSSION

We found that butchers, car repair and gasoline station workers were at increased risk of developing lymphoma compared with all other groups (findings consistent with previous studies). Car repair employees and gasoline station workers are known to be exposed to high levels of solvents such as benzene (and benzene-containing petroleum products),[16] and a growing body of evidence exists suggesting an association between occupational benzene exposure and lymphoma, especially NHL.[8 17 18] Milham analysed death certificates in Washington State and found that occupational groups with petrol or fuel exposure had excess risk of haematopoietic cancers, including lymphoma.[19] The main hypothesis concerning the mechanism of action of solvents in lymphomagenesis has been immunotoxicity. This mechanism has scientific plausibility since increased incidence of lymphoma (in particular, NHL) is well documented among subjects with

Table 2 Unadjusted and adjusted analysis (Cox proportional hazards model stratified by centre). HR and 95% CI by selected job category

Outcome and job title	Person-years	Cases, n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
NHL				
Butchers				
No	1678150	646 (97.4)	1.00 (-)	1.00 (-)
Yes	24356	17 (2.6)	1.81 (1.12 to 2.93)	1.53 (1.05 to 2.48)
Gasoline station workers				
No	1688100	652 (98.3)	1.00 (-)	1.00 (-)
Yes	14293	11 (1.7)	1.99 (1.10 to 3.62)	1.32 (0.73 to 2.41)
Car repair workers				
No	1427447	587 (95.4)	1.00 (-)	1.00 (-)
Yes	38997	28 (4.6)	1.74 (1.19 to 2.54)	1.50 (1.01 to 2.00)
NHL excluding MM/plasmacytoma				
Butchers				
No	1678150	509 (97.9)	1.00 (-)	1.00 (-)
Yes	24356	11 (2.1)	1.49 (1.02 to 2.89)	1.30 (1.00 to 2.66)
Gasoline station workers				
No	1688100	514 (98.8)	1.00 (-)	1.00 (-)
Yes	14293	6 (1.2)	1.38 (0.80 to 3.08)	1.19 (0.64 to 2.72)
Car repair workers				
No	1427447	462 (95.3)	1.00 (-)	1.00 (-)
Yes	38997	23 (4.7)	1.82 (1.20 to 2.77)	1.51 (1.01 to 2.31)
MM/plasmacytoma				
Butchers				
No	1678150	137	1.00 (-)	1.00 (-)
Yes	24356	6	3.02 (1.33 to 6.83)	2.34 (1.03 to 5.35)
Gasoline station workers				
No	1688100	138	1.00 (-)	1.00 (-)
Yes	14293	5	4.28 (1.77 to 10.55)	2.61 (1.06 to 6.43)
Car repair workers				
No	1427447	125	1.00 (-)	1.00 (-)
Yes	38997	5	1.46 (0.59 to 3.54)	0.93 (0.38 to 2.30)
HL				
Butchers				
No	1678150	37 (94.9)	1.00 (-)	1.00 (-)
Yes	24356	2 (5.1)	3.72 (0.90 to 15.4)	2.89 (0.68 to 12.2)
Gasoline station workers				
No	1688100	37 (94.9)	1.00 (-)	1.00 (-)
Yes	14293	2 (5.1)	6.38 (1.53 to 26.3)	4.59 (1.08 to 19.6)
Car repair workers				
No	1427447	35 (94.6)	1.00 (-)	1.00 (-)
Yes	38997	2 (5.4)	2.09 (0.51 to 8.80)	1.50 (0.35 to 6.37)

*Multivariate analysis stratified by centre and adjusted for gender, education level, alcohol consumption and smoking status at baseline.
HL, Hodgkin's lymphoma; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

primary immunodeficiency (eg, ataxia telangiectasia), acquired immunodeficiency (HIV), and autoimmune diseases (eg, rheumatoid arthritis, lupus erythematosus and Sjögren syndrome).[20] A recent literature review by the Agency for Toxic Substances and Diseases Registry[21] found sufficient consistent evidence to support an association between benzene exposure and adverse events related to functional immunity; in particular, benzene seems to determine an immunosuppressive response which is mediated by a depressive effect on T and B lymphocytes.[22 23] In a study of workers in the oil industry, Biro *et al*[24] also found that solvents such as benzene activate peripheral lymphocytes and cause changes to the prevalence of CD25+/CD4+ T lymphocytes. Lan *et al*[23] showed that benzene haematotoxicity effects were present even at very low exposure levels (<1 ppm). Such levels are consistent with those found in the car repair industry.[16]

The increased risk of lymphoma associated with butchers has been noted in some studies[5 9 10] but not others.[11 12] Since our study found no association with farming occupations, the results possibly implicate a role for exposures specifically related to meat handling and processing rather than rearing livestock. 't Mannetje *et al*[9] reported a twofold increase in risk among meat workers, consistent with elevated NHL risk in earlier New Zealand studies among abattoir workers. The increased risk may be due to zoonotic viruses or antigenic stimulation through chronic exposure to animal protein. Most attention has centred on animal oncogenic viruses such as bovine leukaemia virus (BLV).[25] However, to date, in vivo studies have not provided evidence that BLV increases NHL risk in humans,[26] though the possibility that other animal retroviruses may have an aetiological role cannot be ruled out entirely.

We found no consistent association between other job categories, for example, those with known solvent exposure such as painting, chemical and rubber industries, printing or leather industry. This could be for several reasons: the study has low case numbers to detect effects (particularly for HL); insufficient follow-up time for accrual of NHL or HL cases (latency between first exp1osure and cancer diagnosis can be much longer than 9 years for some environmental agents); exposure levels may be differentially lower in well-regulated industrial environments where levels of solvents are monitored compared to settings in which little or no monitoring takes place; job categories associated with solvent exposure will also inevitably have a wide range of exposure levels. The job categories where we found an effect (particularly car repair) are largely in the more unregulated environment, with known high levels of solvent exposure.[16] However, we had only limited job exposure information obtained from self-reported questionnaires and other job categories (such as painters) which might also be seen as less regulated in terms of exposure, showed no increased risk.

Our study is limited by small case numbers of lymphoma (particularly HL cases) and no available information on length of exposure which means that possible dose response effects were not assessed. EPIC also contains a higher proportion of women; effect estimates could be diluted as exposure levels may be lower in women compared with men for particular job categories. Multiple comparisons may give rise to 2–3 false positive significant associations for the analysis of up to 52 job categories, though our study is strengthened by having good a priori hypotheses and plausibility. In addition, the study design is prospective, with no recall bias, and has 100% follow-up. Overall, our findings should be corroborated by further research with more detailed exposure information.

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Competing interests None.

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Ethics approval This study was conducted with the approval of the IARC ethical committee and all the local IRBs.

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CORRECTION

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Neasham D, Sifi A, Nielsen KR, *et al*. Occupation and risk of lymphoma: a multicentre prospective cohort study (EPIC). *Occup Environ Med* 2011;**68**:77–81. The following sentence: "Centres in France (n=61 996), Oxford (n=42 518), and Utrecht (n=15 174) did not collect job questionnaire information, therefore the current cohort size is 348 555", should have been: "In Spain, Greece, Denmark, Germany, 4 Italian centers (Turin, Varese, Florence, Ragusa), and in 1 UK center (Cambridge), the lifestyle questionnaire included several questions on the occupational history of the participants, while other centres did not collect job questionnaire information. Therefore the current analytical cohort size, after exclusion of missing values, is 218 968 subjects". Table 1 below should replace the original table 1.

Since missing values were not included in the analyses, the Cox proportional hazards models and the corresponding HR in table 2 are correct.

Table 1 Characteristics of EPIC cohort population, NHL (including and excluding multiple myeloma/plasmacytoma (MM)) and HL separately

	Total Cohort		HL		NHL		NHL excl. MM	
	N (218 968)	%	N (40)	%	N (707)	%	N (550)	%
Age at recruitment								
Mean (SD)	53.22	9.04	54.39	9.56	57.79	8.03	57.60	8.03
<35	2892	1.32	1	2.50	0	0.00	0	0.00
35–44	41 232	18.83	6	15.00	55	7.78	43	7.82
45–54	79 638	36.37	10	25.00	195	27.58	160	29.09
55–64	78 200	35.71	19	47.50	341	48.23	258	46.91
≥65	17 026	7.78	4	10.00	116	16.41	89	16.18
Age at diagnosis/end of follow-up (mean, SD)	61.49	8.94	58.85	9.76	62.37	8.15	62.20	8.10
Sex								
Men	91 576	41.82	25	62.50	388	54.88	295	53.64
Women	127 392	58.18	15	37.50	319	45.12	255	46.36
Education								
None	18 386	8.40	3	7.50	40	5.66	32	5.82
Primary school completed	69 077	31.55	18	45.00	245	34.65	180	32.73
Technical/professional school	52 568	24.01	9	22.50	183	25.88	146	26.55
Secondary school	35 726	16.32	1	2.50	101	14.29	83	15.09
Longer education	36 679	16.75	8	20.00	109	15.42	87	15.82
Not specified	6532	2.98	1	2.50	29	4.10	22	4.00
Smoking status								
Never	99 106	45.26	9	22.50	273	38.61	212	38.55
Former	58 117	26.54	14	35.00	245	34.65	190	34.55
Current	56 735	25.91	15	37.50	174	24.61	137	24.91
Unknown	5010	2.29	2	5.00	15	2.12	11	2.00
Drinking status								
Never	19 712	9.00	3	7.50	40	5.66	29	5.27
Former	13 615	6.22	3	7.50	57	8.06	48	8.73
Drinkers only at recruitment	12 453	5.69	1	2.50	30	4.24	24	4.36
Lifetime drinkers	164 129	74.96	32	80.00	538	76.10	420	76.36
Unknown	9059	4.14	1	2.50	42	5.94	29	5.27