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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Adult Acute Lymphocytic Leukemia: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

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Background Acute lymphoblastic leukemia/lymphoma (ALL) in adults is a rare malignancy with a poor clinical outcome, and few reported etiologic risk factors.

Methods We performed an exploratory pooled study of 152 ALL cases and 23 096 controls from 16 case–control studies to investigate the role of medical history, lifestyle, family history, and occupational risk factors and risk of ALL. Age-, race/ethnicity-, sex-, and study-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression.

Results An increased risk of ALL was found in those with a family history of a hematological malignancy (OR = 2.6, 95% CI = 1.22 to 5.54) and in leather (OR = 3.91, 95% CI = 1.35 to 11.35) and sewing/embroidery workers (OR = 2.92, 95% CI = 1.00 to 8.49). Consumers of alcohol had an increased risk of B-cell ALL (OR = 2.87, 95% CI = 1.18 to 6.95).

Conclusions The small number of statistically significant risk factors identified out of the 112 variables examined could be chance findings and will require further replication to assess their role in the etiology of adult ALL.

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Acute lymphoblastic leukemia/lymphoma (ALL) is a rare malignancy of B or T cells. However, unlike other hematological malignancies, the majority of ALL diagnoses are made in children under the age of 15 years with only 40% of cases diagnosed in adults 20 years or older in economically developed countries (1–3). Survival rates for childhood ALL have improved dramatically over the last 50 years, and several etiological risk factors have been identified including genetic susceptibility (4,5), high birth weight (6,7), and trisomy 21 (8), with maternal chemical exposures (9,10) and childhood immune response factors also thought to be important determinants of disease risk (11,12). However, the prognosis for adult ALL remains poor, with few reported risk factors except for those related to genetic susceptibility (13,14). To advance our understanding of the etiology of adult ALL, we investigated potential associations with lifestyle, medical history, family history, and occupational risk factors in a pooled analysis of 152 cases and 23 096 controls from 16 case–control studies from Europe, North America, and Australia as part of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma (NHL) Subtypes Project. We also sought to identify common risk factors for adult and childhood ALL.

Detailed methodology for the InterLymph NHL Subtypes Project is provided elsewhere in this issue. Studies eligible for inclusion in this pooled analysis fulfilled the following criteria: 1) case–control design with incident, histologically confirmed cases of ALL and 2) availability of individual-level data for at least several risk factors of interest by December 31, 2011. Contributing studies were approved by local ethics review committees, and all participants provided written informed consent before interview.

Cases were classified according to the World Health Organization classification (15,16) using guidelines from the InterLymph Pathology Working Group (17,18). Most studies had some form of centralized pathology review by at least one expert hematopathologist to confirm the ALL diagnoses. The pathology review procedures for each participating study were reviewed by an interdisciplinary team of pathologists and epidemiologists.

Each study collected data on putative NHL risk factors in a standardized, structured format by in-person or telephone interviews and/or self-reported questionnaires. Risk factors selected for inclusion were the available medical history, lifestyle, family history, and occupational risk factors with data from at least four studies. Details of the data harmonization rules are provided elsewhere in this issue (19).

Risk of ALL associated with each exposure variable was examined using logistic regression models in a basic model for age, race/ethnicity, sex, and study. We estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) for each association. The statistical significance of each relationship was evaluated by a likelihood ratio test comparing models with and without the exposure variable of interest, with P values less than .05 identifying putatively influential factors and P values greater than or equal to .05 to P values less than

.1 identifying suggestive risk factors. We also evaluated associations between exposures and ALL by cell type (B or T cell). To evaluate effect heterogeneity among the 16 studies, we performed a separate logistic regression within each study and then quantified the variability of the coefficients by the H statistic, adapting the definition of Higgins and Thompson to categorical variables (20).

Because controls for most original studies were chosen to frequency-match the age and sex of all NHL cases, rather than just ALL cases, we conducted sensitivity analyses using a subset of controls that were matched by age and sex to the ALL cases. The results of these sensitivity analyses were very similar to the results obtained using the full set of controls (results not shown); thus, we retained the full set of controls for our main analyses to increase statistical power.

Table 1. Characteristics of studies included in the InterLymph NHL Subtypes Project*

	Controls	Cases
	No. (%)	No. (%)
Total	23 096	152
Study		
New South Wales	694 (3.0)	5 (3.3)
Mayo Clinic	1314 (5.7)	1 (0.7)
British Columbia	845 (3.7)	6 (3.9)
Nebraska (newer)	533 (2.3)	1 (0.7)
United Kingdom	1139 (4.9)	0 (0.0)
NCI-SEER	1055 (4.6)	0 (0.0)
UCSF1	2402 (10.4)	12 (7.9)
EpiLymph	2460 (10.7)	46 (30.3)
Yale	717 (3.1)	3 (2.0)
SCALE	3187 (13.8)	15 (9.9)
Los Angeles	375 (1.6)	16 (10.5)
Italy multicenter	1771 (7.7)	12 (7.9)
Italy (Aviano-Milan)	1157 (5.0)	10 (6.6)
Italy (Aviano-Naples)	504 (2.2)	0 (0.0)
Iowa/Minnesota	1245 (5.4)	6 (3.9)
Kansas	948 (4.1)	1 (0.7)
Nebraska (older)	1432 (6.2)	3 (2.0)
Engela	722 (3.1)	8 (5.3)
UCSF2	457 (2.0)	7 (4.6)
University of Rochester	139 (0.6)	0 (0.0)
Region		
North America	11 462 (49.6)	56 (36.8)
Northern Europe	6542 (28.3)	59 (38.8)
Southern Europe	4398 (19.0)	32 (21.1)
Australia	694 (3.0)	5 (3.3)
Design		
Population based	17 846 (77.3)	104 (68.4)
Hospital based	5250 (22.7)	48 (31.6)
Total	23 096 (100.0)	152 (100.0)
Age		
<30	1360 (5.9)	38 (25.0)
30–39	2180 (9.4)	36 (23.7)
40–49	3159 (13.7)	16 (10.5)
50–59	4992 (21.6)	30 (19.7)
60–69	6380 (27.6)	24 (15.8)
70–79	4136 (17.9)	6 (3.9)
≥80	873 (3.8)	2 (1.3)
Missing	16 (0.1)	0 (0.0)
Sex		
Male	13 495 (58.4)	92 (60.5)
Female	9601 (41.6)	60 (39.5)
Race/ethnicity		
White, non-Hispanic	21 576 (93.4)	132 (86.8)
Black	351 (1.5)	1 (0.7)
Asian	321 (1.4)	7 (4.6)
Hispanic	360 (1.6)	6 (3.9)
Other/unknown/missing	488 (2.1)	6 (3.9)
SES		
Low	9335 (40.4)	51 (33.6)
Medium	6709 (29.0)	53 (34.9)
High	6642 (28.8)	48 (31.6)
Other/missing	410 (1.8)	0 (0.0)
NHL classification scheme		
World Health Organization	13 766 (59.6)	92 (60.5)
Working Formulation	9330 (40.4)	60 (39.5)
ALL cell type		
B cell	0 (0.0)	55 (36.2)
T cell	0 (0.0)	48 (31.6)
NOS	0 (0.0)	49 (32.2)
Missing	23 096 (100.0)	0 (0.0)

(Table continues)

Table 1 (Continued).

* ALL = acute lymphoblastic leukemia/lymphoma; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; SCALE = Scandinavian Lymphoma Etiology Study; SES = socioeconomic status; UCSF = University of California San Francisco.

This analysis included 152 cases of adult ALL (55 B cell, 48 T cell, and 49 not otherwise specified) and 23 096 controls from 16 studies. The median age of the cases at the time of diagnosis was 41 years (range, 18–91 years); 60 cases (39.5%) were women and 132 (87%) were of European decent (Table 1). The median age of the controls was 59 years (range, 16–98 years); 9608 controls (41.6%) were women and 21 572 (93.4%) were of European descent. Although the sample size was small, the sex and race/ethnicity distributions were fairly consistent across studies. The age distribution among the cases and controls was skewed, with cases being younger than controls.

Results with P values less than .05 and results approaching significance ($P \geq .05$ to $P < .1$), in an analyses adjusted for age, sex, and study, for associations with combined ALL, and B- or T-cell types, are presented in Table 2. All results, including null results with the exception where there were no cases with the exposure, are presented in Supplementary Table 1 (available online). A total of 112 variables were tested in all, though some variables within each risk factor category were correlated and thus did not represent independent exposures (19).

An increased risk of ALL was observed in those with a family history of a hematological malignancy (OR = 2.6, 95% CI = 1.22 to 5.54). This risk factor also approached significance for B-cell ALL (OR = 3.3, 95% CI = 1.10 to 9.91). An elevated OR also was seen for T-cell ALL, but the risk estimate was imprecise. These are novel findings for adult ALL but are consistent with previous reports of large population and case–control studies of other lymphoid cancers (21,22).

Although based on very small numbers, those who worked in the leather industry (four cases and 146 controls) had an increased risk of ALL (OR = 3.91, 95% CI = 1.35 to 11.35), and this risk was also evident for B-cell ALL (OR = 5.33, 95% CI = 1.17 to 24.2)

Table 2. Factors associated with acute lymphoblastic leukemia/lymphoma risk, overall and stratified by cell type*

	Total				B-Cell				T-Cell			
	Controls	Cases			Controls	Cases			Controls	Cases		
	No. (%)	No. (%)	OR (95% CI)†	*P*	No. (%)	No. (%)	OR (95% CI)†	*P*	No. (%)	No. (%)	OR (95% CI)†	*P*
First-degree family history												
Any hematologic malignancy												
No	11 705 (90.1)	93 (90.3)	1.00 (referent)	.027	4356 (86.6)	38 (90.5)	1.00 (referent)	.061	4364 (92.0)	19 (82.6)	1.00 (referent)	.175
Yes	614 (4.7)	8 (7.8)	2.60 (1.22 to 5.54)		236 (4.7)	4 (9.5)	3.30 (1.10 to 9.91)		200 (4.2)	2 (8.7)	3.33 (0.73 to 15.11)	
Any hematologic malignancy, male relative												
No	8940 (90.6)	78 (94.0)	1.00 (referent)	.204	3764 (87.4)	40 (97.6)	1.00 (referent)	.618	3760 (93.5)	13 (81.3)	1.00 (referent)	.222
Yes	256 (2.6)	3 (3.6)	2.38 (0.72 to 7.89)		107 (2.5)	1 (2.4)	1.75 (0.23 to 13.36)		83 (2.1)	1 (6.3)	4.88 (0.60 to 39.90)	
Any hematologic malignancy, female relative												
No	8961 (90.8)	77 (92.8)	1.00 (referent)	.057	3771 (87.6)	38 (92.7)	1.00 (referent)	.025	3759 (93.5)	14 (87.5)	1.00 (referent)	.487
Yes	235 (2.4)	4 (4.8)	3.30 (1.13 to 9.59)		100 (2.3)	3 (7.3)	5.87 (1.60 to 21.52)		84 (2.1)	0 (0.0)	—	
Occupation												
Leather worker												
No	8438 (94.9)	84 (94.4)	1.00 (referent)	.032	3818 (98.5)	41 (93.3)	1.00 (referent)	.073	6352 (97.8)	30 (93.8)	1.00 (referent)	.139
Yes	146 (1.6)	4 (4.5)	3.91 (1.35 to 11.35)		56 (1.3)	2 (4.4)	5.33 (1.17 to 24.21)		138 (1.9)	2 (5.7)	3.81 (0.85 to 17.02)	
Sewer and embroiderer												
No	9631 (94.9)	88 (94.6)	1.00 (referent)	.083	4278 (97.0)	40 (88.9)	1.00 (referent)	.027	7012 (97.3)	35 (100.0)	1.00 (referent)	.343
Yes	191 (1.9)	4 (4.3)	2.92 (1.00 to 8.49)		118 (2.7)	4 (8.9)	4.38 (1.41 to 13.62)		183 (2.5)	0 (0.0)	—	
Lifestyle												
History of alcohol consumption												
Nondrinker	3627 (27.7)	34 (29.6)	1.00 (referent)	.969	1134 (25.2)	8 (19.5)	1.00 (referent)	.015	1595 (28.1)	8 (28.6)	1.00 (referent)	.121
Drinker (at least one drink per month)	8558 (65.3)	64 (55.7)	1.01 (0.63 to 1.61)		2444 (54.4)	21 (51.2)	2.87 (1.18 to 6.95)		3331 (58.7)	15 (53.6)	0.46 (0.18 to 1.19)	
Alcohol consumption status as of ~2 y before diagnosis/interview												
Nondrinker	3627 (27.7)	34 (29.6)	1.00 (referent)	.357	1134 (25.2)	8 (19.5)	1.00 (referent)	.043	1595 (28.1)	8 (28.6)	1.00 (referent)	.285
Former drinker	520 (4.0)	6 (5.2)	2.39 (0.89 to 6.36)		437 (9.7)	5 (12.2)	5.87 (1.74 to 19.77)		252 (4.4)	1 (3.6)	1.22 (0.12 to 12.35)	
Current drinker	4147 (31.6)	28 (24.3)	0.95 (0.51 to 1.80)		2006 (44.6)	16 (39.0)	2.48 (0.99 to 6.19)		1744 (30.8)	8 (28.6)	0.75 (0.18 to 3.14)	
Drinker, status unknown	3891 (29.7)	30 (26.1)	0.93 (0.50 to 1.74)		1 (0.0)	0 (0.0)	—		1335 (23.5)	6 (21.4)	0.29 (0.08 to 1.00)	
Age at first alcohol consumption												
Nondrinker	3627 (27.7)	34 (29.6)	1.00 (referent)	.553	1134 (25.2)	8 (19.5)	1.00 (referent)	.005	1595 (28.1)	8 (28.6)	1.00 (referent)	.443
<21 y	2005 (15.3)	20 (17.4)	1.38 (0.70 to 2.73)		1268 (28.2)	15 (36.6)	4.36 (1.61 to 11.80)		1189 (21.0)	5 (17.9)	0.48 (0.14 to 1.63)	
≥21 y	3445 (26.3)	17 (14.8)	0.80 (0.39 to 1.64)		571 (12.7)	6 (14.6)	2.40 (0.77 to 7.52)		1487 (26.2)	4 (14.3)	0.37 (0.10 to 1.34)	
Drinker, age start unknown	3108 (23.7)	27 (23.5)	0.94 (0.47 to 1.89)		605 (13.5)	0 (0.0)	—		655 (11.6)	6 (21.4)	0.61 (0.11 to 3.39)	
Duration of alcohol consumption												
Nondrinker	3627 (27.7)	34 (29.6)	1.00 (referent)	.462	1134 (25.2)	8 (19.5)	1.00 (referent)	.010	1595 (28.1)	8 (28.6)	1.00 (referent)	.428
1–20 y	1195 (9.1)	22 (19.1)	1.47 (0.73 to 2.96)		331 (7.4)	12 (29.3)	3.56 (1.22 to 10.40)		375 (6.6)	1 (3.6)	0.72 (0.06 to 8.91)	
≥21 y	3837 (29.3)	16 (13.9)	1.25 (0.59 to 2.68)		1507 (33.5)	9 (22.0)	3.29 (1.05 to 10.36)		1016 (17.9)	2 (7.1)	0.78 (0.10 to 5.88)	
Drinker, duration unknown	3526 (26.9)	26 (22.6)	0.71 (0.37 to 1.35)		606 (13.5)	0 (0.0)	—		1940 (34.2)	12 (42.9)	0.39 (0.14 to 1.13)	
Blood transfusion												
No	8448 (74.7)	95 (91.3)	1.00 (referent)	.027	4551 (79.5)	45 (97.8)	1.00 (referent)	.022	4461 (82.0)	23 (95.8)	1.00 (referent)	.327
Yes	1616 (14.3)	4 (3.8)	0.4 (0.14 to 1.03)		896 (15.7)	1 (2.2)	0.2 (0.02 to 1.29)		862 (15.9)	1 (4.2)	0.4 (0.06 to 3.12)	

* CI = confidence interval; OR = odds ratio.

† Adjusted for age, sex, race/ethnicity, and study.

and approached statistical significance for T-cell ALL (OR = 3.81, 95% CI = 0.85 to 17.0). An elevated risk of ALL also was observed in textile workers in the sewing and embroidery industry (OR = 2.92, 95% CI = 1.00 to 8.49). Despite the small numbers (four cases and 191 controls), this association was observed for B-cell ALL (OR = 4.38, 95% CI = 1.41 to 13.6), but not for T-cell ALL. Previous studies have also reported an increased risk of NHL in workers in textile-related occupations (23–25) and of acute myeloid leukemia in those in shoe or other leather goods industries (26). However, there have been no previous reports linking textile and sewing/embroidery occupations with risk of adult ALL. There are also no reports of parental occupations in the textile or leather industries and risk of childhood ALL.

We also observed an increased risk of B-cell ALL in ever versus never consumers of alcohol (OR = 2.87, 95% CI = 1.18 to 6.95), whether they were former (OR = 5.87, 95% CI = 1.74 to 19.8) or current drinkers (OR = 2.48, 95% CI = 0.99 to 6.19), and in those who started drinking before 21 years (OR = 4.36, 95% CI = 1.61 to 11.8). No evidence of associations were observed between any alcohol variables and T-cell ALL. Based on a meta-analysis of 21 childhood leukemia case–control studies, maternal alcohol consumption during pregnancy was associated with a significantly increased risk of childhood acute myeloid leukemia, but not ALL (27), suggesting potentially different modes of action related to alcohol exposure in the pathogenesis of adult and childhood acute leukemia.

A suggestive inverse association with ALL risk was found for individuals who had ever received a blood transfusion compared with those who were never transfused, though this analysis was based on only four cases (OR = 0.4, 95% CI = 0.14 to 1.03). This finding is consistent with InterLymph reports for other lymphomas, as described elsewhere in this issue, but inconsistent with previous reports of positive associations with blood transfusions (28). If real, the mechanism of action for this protective effect in transfused individuals remains to be elucidated.

Previous childhood ALL studies have reported positive associations with exposures to herbicides (9), benzene (10), and maternal hair dyes (29). We did not find evidence of associations for adult ALL with any farming variables linked to herbicide exposure (Supplementary Table 1, available online). Moreover, no evidence of an association was found in petroleum workers, painters, or engine mechanics as surrogates for benzene exposure or with exposure to hair dyes. Overall, no evidence of associations was found with other lifestyle, medical history, family history, or occupational risk factors (Supplementary Table 1, available online). However, because of the relatively small numbers of cases, this study may be underpowered to detect differences in these other exposures under study.

In summary, we performed exploratory analyses investigating a variety of potential risk factors for ALL. Statistically significant or suggestive increased risks of ALL were observed in those with a family history of hematological malignancy, working in the leather or textile industries, and alcohol consumption, whereas having one or more blood transfusions was protective. Small sample size limited our power to truly test differences between B- and T-cell ALL. Although the results of this pooled analysis indicate some novel risk factors for adult ALL, multiple testing was not adjusted for and larger studies will be needed to further investigate these associations and rule out explanations other than a direct causal relationship, such as reverse causality, and selection or recall bias. Ideally, these studies will include prospective studies to address potential issues of temporality and misclassification as well as the inclusion of inherited variants in multivariate models.

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