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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Sporadic Burkitt Lymphoma/Leukemia: The Interlymph Non-Hodgkin Lymphoma Subtypes Project

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Background The etiologic role of medical history, lifestyle, family history, and occupational risk factors in sporadic Burkitt lymphoma (BL) is unknown, but epidemiologic and clinical evidence suggests that risk factors may vary by age.

Methods We investigated risk factors for sporadic BL in 295 cases compared with 21 818 controls in a pooled analysis of 18 case–control studies in the International Lymphoma Epidemiology Consortium (InterLymph). Cases were defined to include typical BL or Burkitt-like lymphoma. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations were calculated separately for younger (<50 years) and older (≥50 years) BL using multivariate logistic regression.

Results Cases included 133 younger BL and 159 older BL (age was missing for three cases) and they were evenly split between typical BL (n = 147) and Burkitt-like lymphoma (n = 148). BL in younger participants was inversely associated with a history of allergy (OR = 0.58; 95% CI = 0.32 to 1.05), and positively associated with a history of eczema among individuals without other atopic conditions (OR = 2.54; 95% CI = 1.20 to 5.40), taller height (OR = 2.17; 95% CI = 1.08 to 4.36), and employment as a cleaner (OR = 3.49; 95% CI = 1.13 to 10.7). BL in older participants was associated with a history of hepatitis C virus seropositivity (OR = 4.19; 95% CI = 1.05 to 16.6) based on three exposed cases. Regardless of age, BL was inversely associated with alcohol consumption and positively associated with height.

Conclusions Our data suggest that BL in younger and older adults may be etiologically distinct.

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Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma (NHL) that occurs as three histologically indistinguishable subtypes: sporadic, endemic, and immunodeficiency-associated BL (1,2). Sporadic BL occurs in developed countries, accounting for about 30% of all lymphoid malignancies in children and 1%–5% of NHL in adults (3,4). Endemic BL occurs in equatorial Africa and Papua New Guinea as the most common childhood cancer and is associated with Epstein–Barr virus and *Plasmodium falciparum* infections (5). Immunodeficiency-associated BL is seen in those with HIV infection (6) or a history of solid organ transplantation (7).

In contrast, risk factors for sporadic BL are unknown because no analytical epidemiological studies have examined risk factors other than infectious agents (8,9). Descriptive epidemiological and clinical studies conducted in developed countries point to age-related differences in BL. These include distinct age-specific incidence peaks of BL, one during childhood and the other at 60 years of age, in a study conducted in the Netherlands (10), as well as distinct peaks in adults in two studies conducted in the United States (6,11), and one study conducted using BL data from four continents excluding Africa (12). Clinical studies indicate a superior treatment outcome in pediatric BL patients compared with older BL patients (13). As with other cancers (14,15), the bimodality of BL and the different clinical outcomes by age suggest distinct etiologies of BL diagnosed at different ages.

We investigated the associations between BL and medical history, lifestyle, family history, and occupational risk factors using pooled data from 18 case–control studies conducted in Europe, North America, and Australia as part of the International Lymphoma Epidemiology Consortium (InterLymph) NHL Subtypes Project. Our study is the first analytic epidemiological study to evaluate a broad range of risk factors for BL. The main aim of the study was to identify risk factors for sporadic BL in younger versus older participants (ie, <50 vs ≥50 years old).

Methods

Detailed methods for the InterLymph NHL Subtypes Project are reported elsewhere in this issue. Briefly, de-identified individual-level

data from 18 case–control studies were included in this pooled analysis based on the following criteria: 1) case–control design with incident, histologically confirmed cases of BL and 2) availability of individual-level data for several risk factors of interest by December 31, 2011. Participants with serologically confirmed HIV infection or a history of solid organ transplantation were excluded. Because none of the cases was enrolled from equatorial Africa or Papua New Guinea, all cases in this analysis were considered to be sporadic BL. Ethics review committees at the participating institutions approved the studies and participants were enrolled after providing written informed consent.

NHL Subtype Ascertainment and Harmonization

Cases were diagnosed as BL, including a diagnosis of Burkitt-like lymphoma (BLL), according to the Working Formulation (16,17) or the 2001 World Health Organization (WHO) classification for hematologic malignancies (18). The histologic definition of BL is based on observing a diffuse and starry-sky pattern at low magnification under the microscope, a homogenous population of medium-sized lymphoid cells with round nuclei, open chromatin, multiple distinct nucleoli, moderate amounts of basophilic cytoplasm and frequent mitotic figures at high magnification, typical immunohistochemistry (positive for CD10, CD20, and Bcl-6 and negative for Bcl-2, and with high Ki-67 proliferation index), and a simple cytogenetic profile involving *c-MYC* gene translocation. Cases suggestive of BL but showing a more pleomorphic cytology of the tumor cells were diagnosed as BLL. Not all studies retained tissue samples, so centralized pathology review of the diagnoses was not possible. An interdisciplinary team of pathologists and epidemiologists reviewed the pathology reports from the original studies to ensure that the NHL subtype classification was as accurate and specific as possible using guidelines from the InterLymph Pathology Working Group (19,20).

Risk Factor Ascertainment and Harmonization

Self-reported medical, family, lifestyle, and occupational histories were elicited using a standardized, structured in-person or telephone interview and/or written questionnaire, as reported elsewhere in this issue. The questionnaire data obtained from the contributing studies was harmonized centrally with each individual variable in the dataset reviewed and checked for consistency with related exposure variables.

Statistical Analysis

As the main study objective was to investigate risk factors for BL in younger and older participants, stratified analyses were conducted with cases and controls categorized as younger participants (<50 years) or older participants (≥50 years), based on the median age at BL diagnosis. Demographic and socioeconomic factors were analyzed. Associations of age-specific BL in younger and older participants with risk factors were estimated by calculating pooled odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure category relative to the stated referent group, as well as the appropriate *P* values, using fixed-effects logistic regression models that adjusted for study, age, sex, and race/ethnicity (ie, the basic adjusted model). Because the controls from most of the studies were frequency matched by age and sex to all cases (ie, all NHL subtypes) in the study rather than just BL, we conducted all analyses using all controls. Sensitivity analyses using a subset of controls from each study that were individually matched by age and sex to BL cases gave essentially similar results (not shown). Associations with nominal multilevel exposures were evaluated by testing for statistical heterogeneity across the variable categories, whereas associations with ordinal multilevel exposures were evaluated by testing for a monotonic statistical trend in the OR per change in variable category using the likelihood ratio test. A two-sided *P* value less than .05 without adjustment for multiple comparisons indicated a statistically significant association. Individuals with missing data for the exposure variable of interest were excluded from the model when estimating the association. Interstudy heterogeneity among the 18 studies was evaluated using separate logistic regression models performed within each study and the variability of the study-specific coefficients was quantified by the H statistic as described elsewhere in this issue.

The independent association of age-specific BL with variables identified in the basic adjusted model was evaluated by constructing a final logistic regression model including all significantly associated variables and running a forward stepwise multivariate logistic regression until only variables that were statistically significant at *P* less than .05 were retained (the final model). In contrast to analyses in the basic adjusted model, individuals with missing variable categories were retained in the final model by including a code for the missing category in the variable. We also conducted histology-specific analyses (typical BL or BLL) and with younger and older cases combined for comparison with the age-specific results. Results were reported only when based on data from six or more studies.

Results

We studied 295 cases (147 typical BL and 148 BLL) and 21818 controls (Table 1). Most came from population-based studies (83.7% of cases and 76.6% of controls) and from studies conducted in North America (62.4% of cases and 51.9% of controls). The median age of all patients with BL was 52 years (interquartile range: 36–63 years) and was similar for typical BL and BLL (data not shown). No differences were noted between the cases and controls with respect to white, non-Hispanic ethnicity (84.4% vs 93.1%) or socioeconomic class distribution (Table 1). The age-stratified analyses were performed by rounding the median age to a more intuitive cut point of 50 years.

The results from the basic adjusted model showed that BL in younger participants was inversely associated with a history of allergy (OR = 0.52; 95% CI = 0.30 to 0.90) or asthma (OR = 0.35; 95% CI = 0.13 to 0.95; based on four exposed cases). A non-significant inverse association with BL in younger participants was also observed for a history of atopy (OR = 0.68; 95% CI = 0.45 to 1.02), hay fever (OR = 0.60; 95% CI = 0.35 to 1.05), or food allergy (OR = 0.50; 95% CI = 0.17 to 1.50; based on four exposed cases). A history of eczema was unrelated to BL in younger participants. However, when eczema alone without other atopic conditions was

Table 1. Demographical characteristics of cases of sporadic Burkitt lymphoma and controls in the InterLymph NHL Subtypes Project*

	Controls	Cases
	No. (%)†	No. (%)†
All subjects	21 818 (100)	295 (100)
Age, y		
<30	1267 (5.8)	41 (13.9)
30–39	2001 (9.2)	45 (15.3)
40–49	2926 (13.4)	47 (15.9)
50–59	4508 (20.7)	64 (21.7)
60–69	6104 (28.0)	65 (22.0)
70–79	4127 (18.9)	27 (9.2)
≥80	860 (3.9)	3 (1.0)
Sex		
Male	12 809 (58.7)	207 (70.2)
Female	9009 (41.3)	88 (29.8)
Race/ethnicity		
White, non-Hispanic	20 318 (93.1)	249 (84.4)
Black	342 (1.6)	3 (1.0)
Asian	320 (1.5)	15 (5.1)
Hispanic	356 (1.6)	21 (7.1)
Other/unknown/missing	482 (2.2)	7 (2.4)
Socioeconomic status		
Low	8900 (40.8)	117 (39.7)
Medium	6280 (28.8)	80 (27.1)
High	6233 (28.6)	94 (31.9)
Other/missing	405 (1.9)	4 (1.4)
NHL classification		
World Health Organization	12 488 (57.2)	159 (53.9)
Working Formulation	9330 (42.8)	136 (46.1)
Histological diagnosis		
Burkitt lymphoma	—	147 (49.8)
Burkitt-like lymphoma	—	148 (50.2)
BL anatomic site		
Nodal	—	120 (40.7)
Extranodal	—	73 (24.7)
Systemic	—	21 (7.1)
Not collected	—	81 (27.5)
Study region		
North America	11 323 (51.9)	184 (62.4)
Northern Europe	5403 (24.8)	58 (19.7)
Southern Europe	4398 (20.2)	49 (16.6)
Australia	694 (3.2)	4 (1.4)
Study design		
Population-based	16 707 (76.6)	247 (83.7)
Hospital-based	5111 (23.4)	48 (16.3)

* BL = Burkitt lymphoma; NHL = non-Hodgkin lymphoma.

† The counts do not add up to the total number of cases/controls due to data missing by design or report.

considered, it was associated with elevated BL risk (OR = 2.8; 95% CI = 1.35 to 5.86) (Table 2). In contrast to BL in younger participants, a history of allergy, asthma, atopy, hay fever, or eczema was not associated with BL in older participants.

We observed an elevated risk of BL among older participants who reported of a history of hepatitis C virus (HCV) seropositivity (OR = 4.1; 95% CI = 1.10 to 15.4), based on three exposed cases in the six studies that reported HCV serostatus (Table 2). The relationship between BL and HCV seropositivity in younger participants was indeterminate because none of the 31 younger cases reported a seropositive history. A history of prior blood transfusion (yes vs no) was unrelated to BL in younger participants but was inversely associated with BL risk in older participants. Younger participants who reported receiving three or more transfusions had an elevated risk of BL in (OR = 6.46; 95% CI = 1.75 to 23.8), but this result was based on only three exposed cases and the risk was not increased in the older participants with higher numbers of transfusions (Table 2). Peptic ulcer and hormone use were not associated with BL in younger or older participants (data not shown). The risk of BL in younger or older participants was not associated with a history of NHL or leukemia among first-degree relatives, but the number of cases was small in both groups (Table 2).

With respect to anthropometric factors, the risk of BL doubled in the tallest participants (quartile 4) compared with the shortest ones (quartile 1), both in the younger (OR = 2.14; 95% CI = 1.07 to 4.25) and the older (OR = 1.79; 95% CI = 0.92 to 3.49) age groups (Table 3). BL was not associated with usual weight or body mass index in younger participants, but a non-significant inverse association was observed between BL and body mass index in older participants (P_{trend} = .07). With respect to lifestyle factors, the risks for both younger and older BL were inversely associated with alcohol consumption (Table 3), particularly among older participants. A history of cigarette smoking was not associated with BL in either younger or older participants (Table 3). We observed a non-significantly elevated risk of BL among younger participants who reported the use of light-colored hair dye compared with never use (OR = 3.0; 95% CI = 0.91 to 9.9), but the association with BL among older participants was indeterminate because only one older case was exposed. BL among older participants was not associated with the use of dark hair dyes (OR = 1.29; 95% CI = 0.46 to 3.63) based on nine exposed cases, and among younger participants, only two cases were exposed. BL was not associated with recreational sun exposure in either younger or older participants (Table 3).

Among 31 occupations evaluated, we observed an increased risk of BL among younger participants who reported employment as a cleaner (OR = 2.6; 95% CI = 1.01 to 6.83), especially a char worker cleaner (OR = 3.8; 95% CI = 1.26 to 11.3) based on four exposed cases (Table 4). A char worker cleaner is a person employed to clean and maintain the interiors of buildings. Occupation as a cleaner was not associated with BL among older participants nor was any other occupation associated with BL in younger or older participants (data not shown).

In the final model, BL in younger participants was associated with a history of allergy (OR = 0.58; 95% CI = 0.32 to 1.05), eczema without other atopic conditions (OR = 2.54; 95% CI = 1.20 to 5.40), taller height (OR = 2.17; 95% CI = 1.08 to 4.36), the use of light-colored hair dye (OR = 2.89; 95% CI = 0.84 to 9.94), and working in a cleaning occupation (OR = 3.49; 95% CI = 1.13 to 10.7) (Table 5). BL in older participants was independently associated with a history of HCV infection (OR = 4.19; 95% CI = 1.05 to 16.6), usual adult body mass index (P_{trend} = .049), and consumption of at least one drink of alcohol per month (OR = 0.63; 95% CI = 0.40 to 0.98).

The associations with BL found in the age-specific analyses were attenuated or became statistically non-significant when the histological subtypes of BL and BLL were analyzed individually or with the younger and older cases combined (data not shown). There was

Table 2. Association of medical and family history with sporadic Burkitt lymphoma in the InterLymph NHL Subtypes Project from the basic model, stratified by age*

	<50 years				≥50 years			
	Controls	Cases			Controls	Cases		
	No. (%)†	No. (%)†	OR (95% CI)‡	*P*	No. (%)†	No. (%)†	OR (95% CI)†	*P*
Medical history								
Any atopic disorder§								
No	3763 (65.4)	89 (67.4)	1.00 (referent)	.058	10156 (70.3)	114 (72.2)	1.00 (referent)	.736
Yes	1878 (32.6)	40 (30.3)	0.68 (0.45 to 1.02)		3977 (27.5)	43 (27.2)	0.94 (0.64 to 1.37)	
Allergy‖								
No	2490 (64.9)	64 (70.3)	1.00 (referent)	.016	7082 (71.3)	64 (68.8)	1.00 (referent)	.760
Yes	1093 (28.5)	21 (23.1)	0.52 (0.30 to 0.90)		2231 (22.5)	23 (24.7)	1.09 (0.64 to 1.85)	
Food allergy								
No	3146 (82.0)	70 (76.9)	1.00 (referent)	.176	7140 (81.7)	57 (71.3)	1.00 (referent)	.989
Yes	274 (7.1)	4 (4.4)	0.50 (0.17 to 1.50)		586 (6.7)	5 (6.3)	0.99 (0.38 to 2.59)	
Asthma								
No	4865 (84.6)	109 (82.6)	1.00 (referent)	.015	12296 (85.1)	136 (86.1)	1.00 (referent)	.745
Yes	461 (8.0)	4 (3.0)	0.35 (0.13 to 0.95)		1061 (7.3)	13 (8.2)	1.11 (0.61 to 2.00)	
Hay fever								
No	2646 (62.9)	68 (62.4)	1.00 (referent)	.062	8543 (71.6)	98 (72.6)	1.00 (referent)	.228
Yes	909 (21.6)	23 (21.1)	0.60 (0.35 to 1.05)		1769 (14.8)	20 (14.8)	0.71 (0.41 to 1.25)	
Eczema								
No	3583 (83.7)	91 (84.3)	1.00 (referent)	.649	9868 (86.9)	122 (92.4)	1.00 (referent)	.684
Yes¶	516 (12.0)	12 (11.1)	1.16 (0.62 to 2.19)		912 (8.0)	8 (6.1)	0.86 (0.41 to 1.80)	
Eczema without other atopic conditions								
No eczema	3583 (83.7)	91 (84.3)	1.00 (referent)	.008	9868 (86.9)	122 (92.4)	1.00 (referent)	.805
Eczema without other atopic conditions#	176 (4.1)	9 (8.3)	2.82 (1.35 to 5.86)		402 (3.5)	4 (3.0)	1.06 (0.38 to 2.93)	
Eczema with other atopic conditions	340 (7.9)	3 (2.8)	0.41 (0.13 to 1.32)		510 (4.5)	4 (3.0)	0.723 (0.26 to 2.02)	
History of hepatitis C virus infection								
No	1891 (59.3)	31 (56.4)	1.00 (referent)	.430	4453 (69.7)	30 (62.5)	1.00 (referent)	.066
Yes	42 (1.3)	0 (0.0)	—		109 (1.7)	3 (6.3)	4.10 (1.10 to 15.4)	
Blood transfusion								
No	3062 (89.8)	71 (86.6)	1.00 (referent)	.228	6091 (70.6)	78 (75.7)	1.00 (referent)	.054
Yes	232 (6.8)	8 (9.8)	1.64 (0.77 to 3.50)		1514 (17.5)	10 (9.7)	0.54 (0.27 to 1.06)	
Total number of blood transfusions								
No transfusion	3062 (89.8)	71 (86.6)	1.00 (referent)	.201	6091 (70.6)	78 (75.7)	1.00 (referent)	.267
1 transfusion	163 (4.8)	4 (4.9)	1.09 (0.39 to 3.08)		973 (11.3)	6 (5.8)	0.48 (0.21 to 1.13)	
2 transfusions	39 (1.1)	1 (1.2)	1.61 (0.21 to 12.2)		292 (3.4)	2 (1.9)	0.74 (0.18 to 3.10)	
≥3 transfusions	23 (0.7)	3 (3.7)	6.46 (1.75 to 23.81)		189 (2.2)	2 (1.9)	0.79 (0.19 to 3.40)	
Number of years from first blood transfusion								
No transfusion	3062 (89.8)	71 (86.6)	1.00 (referent)	.194	6091 (70.6)	78 (75.7)	1.00 (referent)	.101
<20 years	134 (3.9)	6 (7.3)	2.22 (0.92 to 5.34)		657 (7.6)	3 (2.9)	0.36 (0.11 to 1.16)	
20–39 years	85 (2.5)	1 (1.2)	0.51 (0.07 to 3.74)		557 (6.5)	6 (5.8)	0.92 (0.39 to 2.17)	
Blood transfusion before 1990								
No transfusion	3062 (89.8)	71 (86.6)	1.00 (referent)	.117	6091 (70.6)	78 (75.7)	1.00 (referent)	.068
Transfusion before 1990	158 (4.6)	7 (8.5)	2.22 (0.98 to 5.04)		1118 (13.0)	10 (9.7)	0.65 (0.33 to 1.28)	
Transfusion year unknown	11 (0.3)	1 (1.2)	1.97 (0.21 to 18.0)		94 (1.1)	0 (0.0)	—	
Family history of non-Hodgkin lymphoma								
No	3057 (91.3)	68 (77.3)	1.00 (referent)	.517	9501 (91.8)	111 (91.0)	1.00 (referent)	.272
Yes	40 (1.2)	2 (2.3)	1.71 (0.37 to 7.91)		229 (2.2)	1 (0.8)	0.38 (0.05 to 2.83)	
Family history of leukemia								
No	3451 (91.6)	74 (80.4)	1.00 (referent)	.088	9409 (90.9)	107 (87.7)	1.00 (referent)	.644
Yes	65 (1.7)	0 (0.0)	—		321 (3.1)	5 (4.1)	1.26 (0.49 to 3.21)	

* CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.
† The counts do not add up to the total number of cases/controls due to data missing by design or report.
‡ Adjusted for age, sex, race/ethnicity, and study.
§ Atopic disorders include asthma, eczema, hay fever, or other allergies, excluding drug allergies.
‖ History of allergy included plant, food, animal, dust, insect, or mold allergy.
¶ Eczema, with or without other atopic conditions.
# Eczema alone, excluding participants who reported eczema and other atopic conditions.

Table 3. Association of anthropometry and lifestyle factors with sporadic Burkitt lymphoma in the InterLymph NHL Subtypes Project from the basic model, stratified by age*

	<50 years				≥50 years			
	Controls	Cases			Controls	Cases		
	N (%)†	N (%)†	OR (95% CI)‡	*P*	N (%)†	N (%)†	OR (95% CI)‡	*P*
Usual adult height§								
Quartile 1 (low)	816 (17.1)	12 (12.0)	1.00 (referent)	.029	3039 (26.7)	19 (20.9)	1.00 (referent)	.301
Quartile 2	979 (20.5)	14 (14.0)	1.03 (0.46 to 2.28)		2693 (23.7)	22 (24.2)	1.57 (0.83 to 2.97)	
Quartile 3	1174 (24.6)	21 (21.0)	1.27 (0.60 to 2.70)		2703 (23.8)	24 (26.4)	1.66 (0.87 to 3.15)	
Quartile 4 (high)	1612 (33.8)	47 (47.0)	2.14 (1.07 to 4.25)		2528 (22.2)	24 (26.4)	1.79 (0.92 to 3.49)	
Usual adult weight‖								
Quartile 1 (low)	1342 (28.2)	22 (22.0)	1.00 (referent)	.294	2452 (21.6)	24 (26.4)	1.00 (referent)	.636
Quartile 2	1122 (23.6)	23 (23.0)	1.26 (0.68 to 2.33)		2555 (22.5)	22 (24.2)	0.93 (0.51 to 1.68)	
Quartile 3	1102 (23.1)	29 (29.0)	1.67 (0.93 to 3.00)		3032 (26.7)	19 (20.9)	0.68 (0.37 to 1.27)	
Quartile 4 (high)	1015 (21.3)	20 (20.0)	1.05 (0.54 to 2.02)		2924 (25.7)	24 (26.4)	0.80 (0.43 to 1.46)	
Usual adult body mass index (kg/m^2)								
15–<18.5	105 (2.2)	1 (1.0)	0.49 (0.07 to 3.77)		146 (1.3)	3 (3.3)	1.94 (0.55 to 6.89)	
18.5–<22.5	1320 (27.7)	24 (24.0)	1.00 (referent)	.71	1879 (16.5)	19 (20.9)	1.00 (referent)	.07
22.5–<25	1250 (26.2)	31 (31.0)	1.31 (0.75 to 2.29)		2724 (24.0)	20 (22.0)	0.68 (0.36 to 1.29)	
25–<30	1434 (30.1)	27 (27.0)	0.91 (0.50 to 1.65)		4415 (38.8)	28 (30.8)	0.52 (0.28 to 0.96)	
30–<35	345 (7.2)	9 (9.0)	1.11 (0.49 to 2.56)		1344 (11.8)	17 (18.7)	1.08 (0.54 to 2.14)	
35–50	127 (2.7)	2 (2.0)	0.73 (0.16 to 3.24)		455 (4.0)	2 (2.2)	0.37 (0.08 to 1.66)	
Alcohol consumption status 2 years prior to diagnosis/interview								
Non-drinker	1065 (23.4)	32 (29.9)	1.00 (referent)	.211	3103 (23.4)	54 (36.0)	1.00 (referent)	.05
Former drinker	96 (2.1)	0 (0.0)	—		468 (3.5)	2 (1.3)	0.48 (0.10 to 2.25)	
Current drinker	1394 (30.7)	22 (20.6)	0.75 (0.36 to 1.57)		3335 (25.1)	21 (14.0)	0.44 (0.21 to 0.91)	
Drinker, status unknown	1480 (32.6)	38 (35.5)	0.68 (0.39 to 1.20)		3240 (24.4)	53 (35.3)	0.65 (0.41 to 1.03)	
Age at first alcohol consumption								
Non-drinker	1065 (23.4)	32 (29.9)	1.00 (referent)	.192	3103 (23.4)	54 (36.0)	1.00 (referent)	.07
<20 years	662 (14.6)	13 (12.1)	1.26 (0.51 to 3.12)		1478 (11.1)	7 (4.7)	0.38 (0.15 to 0.98)	
20–29 years	1045 (23.0)	11 (10.3)	0.48 (0.19 to 1.19)		1801 (13.6)	15 (10.0)	0.58 (0.28 to 1.19)	
≥30 years	102 (2.2)	2 (1.9)	1.10 (0.24 to 5.14)		654 (4.9)	3 (2.0)	0.36 (0.10 to 1.23)	
Drinker, age start unknown	1161 (25.6)	34 (31.8)	0.63 (0.35 to 1.16)		3110 (23.4)	51 (34.0)	0.65 (0.41 to 1.05)	
Duration of alcohol consumption¶	6048 (100.0)	133 (100.0)	0.98 (0.94 to 1.02)	.353	15086 (100.0)	159 (100.0)	0.98 (0.96 to 1.00)	.047
Ethanol per week as an adult, consumed from any type of alcoholic beverage#								
Non-drinker	1065 (23.4)	32 (29.9)	1.00 (referent)	.409	3103 (23.4)	54 (36.0)	1.00 (referent)	.043
Q1 (low)	730 (16.1)	22 (20.6)	0.81 (0.45 to 1.45)		1508 (11.4)	24 (16.0)	0.75 (0.45 to 1.27)	
Q2	676 (14.9)	17 (15.9)	0.83 (0.44 to 1.58)		1532 (11.5)	13 (8.7)	0.42 (0.22 to 0.80)	
Q3	670 (14.8)	10 (9.3)	0.56 (0.26 to 1.18)		1548 (11.7)	21 (14.0)	0.69 (0.40 to 1.20)	
Q4 (high)	683 (15.0)	10 (9.3)	0.57 (0.26 to 1.25)		1682 (12.7)	17 (11.3)	0.51 (0.27 to 0.94)	
Drinker, grams unknown	211 (4.6)	1 (0.9)	0.19 (0.02 to 2.42)		773 (5.8)	1 (0.7)	0.16 (0.01 to 2.26)	
Lifetime alcohol consumed								
Non-drinker	1065 (23.4)	32 (29.9)	1.00 (referent)	.604	3103 (23.4)	54 (36.0)	1.00 (referent)	.025
1–100 kg	581 (12.8)	10 (9.3)	1.02 (0.40 to 2.55)		765 (5.8)	8 (5.3)	0.90 (0.36 to 2.24)	
101–200 kg	226 (5.0)	2 (1.9)	0.56 (0.12 to 2.68)		404 (3.0)	2 (1.3)	0.37 (0.08 to 1.67)	
201–400 kg	150 (3.3)	2 (1.9)	0.83 (0.17 to 4.01)		497 (3.7)	2 (1.3)	0.23 (0.05 to 1.06)	
>400 kg	116 (2.6)	2 (1.9)	1.10 (0.23 to 5.28)		640 (4.8)	3 (2.0)	0.22 (0.06 to 0.86)	
Drinker, consumption unknown	1897 (41.8)	44 (41.1)	0.63 (0.37 to 1.06)		4737 (35.7)	61 (40.7)	0.63 (0.40 to 0.98)	
Cigarette smoking status 2 years prior to diagnosis/interview								
Non-smoker	2511 (43.2)	68 (53.1)	1.00 (referent)	.552	5760 (39.8)	58 (37.7)	1.00 (referent)	.912
Former smoker	1075 (18.5)	19 (14.8)	0.85 (0.5 to 1.47)		4777 (33.0)	55 (35.7)	0.92 (0.62 to 1.34)	
Current smoker	1774 (30.5)	29 (22.7)	0.72 (0.45 to 1.14)		2645 (18.3)	29 (18.8)	0.88 (0.54 to 1.42)	
Smoker, status unknown	125 (2.2)	2 (1.6)	0.73 (0.16 to 3.37)		399 (2.8)	5 (3.2)	1.21 (0.41 to 3.56)	
Color of hair dye used								
Never hair dye	426 (13.3)	6 (9.7)	1.00 (referent)	.007	1318 (17.5)	7 (12.7)	1.00 (referent)	.291
Light	189 (5.9)	8 (12.9)	2.99 (0.91 to 9.88)		690 (9.2)	1 (1.8)	0.26 (0.03 to 2.16)	
Dark	407 (12.7)	2 (3.2)	0.35 (0.06 to 1.92)		1319 (17.5)	9 (16.4)	1.29 (0.46 to 3.63)	
Ever hair dye, color unknown	116 (3.6)	1 (1.6)	0.15 (0.01 to 1.89)		310 (4.1)	2 (3.6)	0.57 (0.07 to 4.98)	
Male**	1995 (62.1)	44 (71.0)	—		3716 (49.4)	35 (63.6)	—	

(Table continues)

Table 3. (Continued).

	<50 years				≥50 years			
	Controls	Cases			Controls	Cases		
	N (%)†	N (%)†	OR (95% CI)‡	*P*	N (%)†	N (%)†	OR (95% CI)‡	*P*
Recreational sun exposure††								
Quartile 1 (low)	409 (16.1)	7 (13.7)	1.00 (referent)	.930	1425 (22.0)	12 (28.6)	1.00 (referent)	.725
Quartile 2	654 (25.7)	13 (25.5)	1.16 (0.44 to 3.00)		1324 (20.5)	7 (16.7)	0.61 (0.24 to 1.56)	
Quartile 3	445 (17.5)	10 (19.6)	1.17 (0.43 to 3.19)		1190 (18.4)	8 (19)	0.80 (0.32 to 2.00)	
Quartile 4 (high)	726 (28.5)	13 (25.5)	0.92 (0.36 to 2.39)		1729 (26.7)	10 (23.8)	0.66 (0.28 to 1.57)	

* CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.

† The counts do not add up to the total number of cases/controls due to data missing by design or report.

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

§ Height quartile cutoffs are: 172, 177.8, and 182 cm for Q1-2, Q2-3, and Q3-4, respectively, for males, and 159, 163.0, and 168 cm, respectively, for females.

‖ Weight quartile cutoffs are: 72.6, 80, and 89 kg for Q1-2, Q2-3, and Q3-4, respectively, for males, and 58.1, 65, and 74.8, respectively, for females.

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

Alcohol quartile cutoff points: 44.4, 110.7, and 252 g, respectively, for Q1-2, Q2-3, and Q3-4, respectively.

** Males were not included in the analysis of use of hair dye.

†† Recreational sun exposure (hours per week, study-specific quartiles available upon request).

Table 4. Association of cleaning-related occupations with sporadic Burkitt lymphoma in the InterLymph NHL Subtypes Project from the basic model, stratified by age*

	<50 years				≥50 years			
	Controls	Cases			Controls	Cases		
	N (%)†	N (%)†	OR (95% CI)‡	*P*	N (%)†	N (%)†	OR (95% CI)‡	*P*
Cleaners								
No	3026 (88.5)	59 (85.5)	1.00 (referent)	.077	6721 (94.5)	54 (96.4)	1.00 (referent)	.863
Yes	137 (4.0)	5 (7.2)	2.62 (1.01 to 6.83)		337 (4.7)	2 (3.6)	0.88 (0.21 to 3.70)	
Duration of employment as cleaner								
Never	3026 (88.5)	59 (85.5)	1.00 (referent)	.158	6721 (94.5)	54 (96.4)	1.00 (referent)	.051
1–10 years	109 (3.2)	5 (7.2)	3.27 (1.24 to 8.60)		188 (2.6)	0 (0.0)	—	
>10 years	23 (0.7)	0 (0.0)	—		143 (2.0)	1 (1.8)	1.14 (0.15 to 8.48)	
Yes, missing duration	5 (0.1)	0 (0.0)	—		6 (0.1)	1 (1.8)	– (3.69 to infinity)	
Charworker cleaner or related work§								
No	3071 (89.8)	60 (87.0)	1.00 (referent)	.040	6473 (96.2)	52 (100.0)	1.00 (referent)	.124
Yes	86 (2.5)	4 (5.8)	3.76 (1.26 to 11.3)		203 (3.0)	0 (0.0)	—	
Duration of employment as charworker cleaner								
Never	3071 (89.8)	60 (87.0)	1.00 (referent)	.095	6473 (96.2)	52 (100.0)	1.00 (referent)	.500
1–10 years	64 (1.9)	4 (5.8)	5.00 (1.65 to 15.21)		103 (1.5)	0 (0.0)	—	
>10 years	18 (0.5)	0 (0.0)	—		99 (1.5)	0 (0.0)	—	
Yes, missing duration	4 (0.1)	0 (0.0)	—		1 (0.0)	0 (0.0)	—	

* CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.

† The counts do not add up to the total number of cases/controls due to data missing by design or report.

‡ OR (95% CI): adjusted for age, sex, race/ethnicity, and study.

§ Charworker cleaner is a person who is employed to clean and maintain the interiors of buildings.

no evidence of significant interstudy heterogeneity across the studies for the associations found in this study (data not shown).

Discussion

Our study, which is the first to evaluate a broad range of noninfectious risk factors for BL, showed some differences and similarities between BL in younger and older participants. Specifically, we observed significant inverse associations between BL in younger participants and a history of allergy, and significant positive associations with a history of eczema alone and working in a cleaning occupation, especially as a char worker cleaner. Conversely, among older participants, we observed a positive association with a history of HCV infection based on three exposed cases. Among both younger and older participants, BL was positively associated with height and inversely associated with alcohol consumption. These associations were attenuated or not statistically significant when the histological subtypes of typical BL and BLL were analyzed individually or when younger and older cases were combined. Our results provide epidemiological support for the hypothesis that younger and older adult sporadic BL may be distinct biologically or etiologically (11,12).

Table 5. Independent risk factors for younger and older sporadic Burkitt lymphoma in the InterLymph NHL Subtypes Project from the final model*

	OR (95% CI)	*P*
<50 years		
Allergy†		
No	1.00 (referent)	.065
Yes	0.58 (0.32 to 10.5)	
Eczema without other atopic conditions		
No eczema	1.00	
Eczema with no other atopic conditions	2.54 (1.20 to 5.40)	
Eczema with other atopic conditions	0.51 (0.15 to 1.74)	.041
Usual adult height‡		
Quartile 1 (low)	1.00 (referent)	.028
Quartile 2	1.03 (0.46 to 2.30)	
Quartile 3	1.31 (0.62 to 2.80)	
Quartile 4	2.17 (1.08 to 4.36)	
Color of hair dye used		
Never hair dye	1.00 (referent)	.014
Light	2.89 (0.84 to 9.94)	
Dark	0.37 (0.06 to 2.06)	
Charworker cleaner or related work§		
No	1.00 (referent)	.054
Yes	3.49 (1.13 to 10.7)	
≥50 years		
Hepatitis C virus infection		
Negative	1.00 (referent)	.070
Positive	4.19 (1.05 to 16.61)	
Usual adult body mass index (kg/m^2)		
15–<18.5	1.00 (referent)	.049
18.5–<22.5	0.55 (0.15 to 1.97)	
22.5–<25	0.37 (0.10 to 1.32)	
25–<30	0.27 (0.08 to 0.98)	
30–<35	0.56 (0.15 to 2.08)	
35–50	0.16 (0.02 to 1.05)	
History of alcohol consumption		
Non-drinker	1.00 (referent)	.001
Drinker (at least 1 drink per month)	0.63 (0.40 to 0.98)	

* Table reports results from the final stepwise regression analysis models. CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.

† History of allergy includes participants who reported eczema plus other atopic conditions.

‡ Height quartile cutoffs are: 172, 177.8, and 182 cm for Q1-2, Q2-3, and Q3-4, respectively, for males, and 159, 163.0, and 168 cm, respectively, for females.

§ Charworker cleaner is a person who is employed to clean and maintain the interior of buildings.

Our results agree with recent epidemiologic and clinical studies that reported multiple incidence peaks and different outcomes by age (6,10–13,15,21), all suggesting the possibility of etiologically and clinically distinct BL entities at different ages. Because no single parameter is a gold standard for BL diagnosis, and because the diagnosis of BL may be difficult, particularly in older patients (22), diagnostic uncertainty may be a factor in our results. Expert hematopathologists agree on the diagnosis of BL in 80%–90% of pediatric cases, but in only 26%–48% of adult cases (22), in part because the classification of older adult BL has been in some flux during the period of the study (1). Thus, some cases previously diagnosed as BLL might now be reclassified as BL or as a gray-zone lymphoma with features intermediate between BL and diffuse large B-cell lymphoma (4). Gray-zone lymphoma, which is characterized by a pleomorphic tumor cell morphology and complex cytogenetics, sometimes including a combination of *c-MYC* and *BCL2* or *BCL6* gene rearrangements (referred to as "double hit" lymphoma) (23), is overrepresented in older patients and has an extremely poor prognosis with standard treatment (24). Further studies are needed to confirm the age-related BL entities and to elucidate their molecular abnormalities.

The significant inverse association between younger BL and a history of allergy mirrors the associations that have been reported for diffuse large B-cell lymphoma and follicular lymphoma (25). Allergic diseases appear to be protective against certain NHL subtypes, but the mechanism is unknown. Assuming these results are valid, protective effects could be mediated via immunological hypersensitivity (26) or antitumor cytotoxicity (27). We found a significant positive association between a history of HCV infection and BL only in older participants, based on three cases of BL with HCV infection. This result agrees with the fivefold risk for BL reported among elderly patients in US Medicare data who had two or more insurance claims for HCV infection (28). Although HCV and HIV coinfection are common, particularly in intravenous drug users, coinfection with HIV is unlikely to explain our results because serologically confirmed HIV-positive cases were excluded in the cases in our study. Because HCV infection may increase risk for some NHL subtypes (29), perhaps by inducing chronic immune activation (30), further studies are needed to investigate the potential role of HCV infection in older adult BL.

BL in both younger and older participants was positively associated with height. This association has also been reported for other cancers (31,32) and might be indicative of the role of early-life exposures that influence height and also impact risk for cancer, such as insulin-like growth factors. Insulin-like growth factors are correlated with adult height and are thought to modulate cell proliferation and/or turnover (33,34). Our finding that the risk for BL was decreased in both younger and older participants who consumed alcohol is in accord with a previous report using much of the same data (35), but it is unexplained. In contrast to the previous reports of a positive association between use of dark hair dye and NHL risk (36–40), we found a positive association between the use of light-colored hair dye and BL only in younger participants. These results are conflicting and highlight the difficulty of evaluating hair dye use in rare cancers such as BL. A history of working in cleaning occupations, especially as a char worker cleaner, was positively associated with BL in younger participants. This result is similar to the associations reported for all NHL (41) and may point to a role for chemicals that are found in products used for cleaning.

The strengths of our pooled analysis include having relatively large case numbers from geographically diverse areas and centrally harmonized data classification and analysis procedures. Because up to one-third of BL cases may be HIV-associated, exclusion of HIV infected cases enabled us to focus our interpretation on adult sporadic BL. The limitations include possible selection and recall biases common to case–control studies, and possible diagnostic errors related to the use of older lymphoma classification systems such as the Working Formulation (16,17) and the 2001 WHO classification for hematologic malignancies (42). Lack of access to archival tissues and slides precluded a central pathology review to confirm and update the diagnoses (1). Lack of tumor Epstein–Barr virus status or molecular characterization also precluded us from evaluating whether Epstein–Barr

virus or molecular abnormalities are correlated with the epidemiological clues for distinct BL biology and/or etiology (43). Other limitations include multiple significance tests, which increases the number of expected false-positive findings, and missing data, for example, for HCV infection status, which could have reduced the power to detect weak associations.

To summarize, we found both similar and contrasting age-specific patterns of associations for BL with medical history, anthropometric, lifestyle, and occupational risk factors in younger and older participants. These results support the hypothesis that BL in younger and older patients may be etiologically distinct.

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