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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

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Background Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM), a rare non-Hodgkin lymphoma subtype, shows strong familial aggregation and a positive association with chronic immune stimulation, but evidence regarding other risk factors is very limited.

Methods The International Lymphoma Epidemiology Consortium (InterLymph) pooled data from 11 predominantly population-based case–control studies from North America, Europe, and Australia to examine medical history, lifestyle, family history, and occupational risk factors for LPL/WM. Age-, sex-, race/ethnicity-, and study-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression for a total of 374 LPL/WM cases and 23 096 controls.

Results In multivariate analysis including all putative risk factors, LPL/WM risk was associated with history of Sjögren's syndrome (OR = 14.0, 95% CI = 3.60 to 54.6), systemic lupus erythematosus (OR = 8.23, 95% CI = 2.69 to 25.2), hay fever (OR = 0.73, 95% CI = 0.54 to 0.99), positive hepatitis C serology (OR = 2.51, 95% CI = 1.03 to 6.17), hematologic malignancy in a first-degree relative (OR = 1.64, 95% CI = 1.02 to 2.64), adult weight (OR = 0.61, 95% CI = 0.44 to 0.85 for highest vs. lowest quartile), duration of cigarette smoking (OR = 1.46, 95% CI = 1.04 to 2.05 for ≥ 40 years vs. nonsmokers), and occupation as a medical doctor (OR = 5.54, 95% CI = 2.19 to 14.0). There was no association with other medical conditions, lifestyle factors, or occupations.

Conclusions This pooled analysis confirmed associations with immune conditions and family history of hematologic malignancy, and identified new associations with hay fever, weight, smoking, and occupation, and no association with other lifestyle factors. These findings offer clues to LPL/WM biology and prevention.

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Lymphoplasmacytic lymphoma (LPL) is a non-Hodgkin lymphoma (NHL) subtype characterized by the proliferation of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells. Most patients with LPL have IgM paraproteins and a minority have both IgM and IgG or other paraproteins, although this is not diagnostic (1). Waldenström's macroglobulinemia (WM) is a clinicopathological subset of LPL defined as LPL with bone marrow involvement and monoclonal IgM gammopathy (2). LPL/WM is rare, with incidence estimates ranging from 0.031 to 0.043/100 000 person-years in Japan and Taiwan (3) to 0.63/100 000 person-years in the United States (4).

Established risk factors for LPL/WM are older age, male gender, white race/ethnicity (4), family history of LPL/WM or another B-cell malignancy (5–7), and history of the precursor condition monoclonal gammopathy of undetermined significance of IgM class (8,9). Other putative risk factors are a history of infectious disease (10–14), autoimmune disease (11,13–15), allergies (13,14), and certain genetic characteristics (16–19). In one study, increased risk of familial LPL/WM (n = 103) was associated with farming and exposure to pesticides, wood dust, and organic solvents (14), whereas another identified no lifestyle or occupational risk factors based on 65 WM cases (20). Together these findings support a role for germline susceptibility genes, antigenic drive, chronic immune stimulation, and possibly occupational factors in LPL/WM carcinogenesis. The largest prior studies have used health record linkage (7,13); thus, there has been no comprehensive evaluation of risk factors for LPL/WM, particularly lifestyle and occupational exposures, and assessment in a multivariate setting.

We investigated LPL/WM associations with medical and family history, lifestyle, and occupational risk factors in a pooled analysis of 374 cases and 23 096 controls from 11 case–control studies from Europe, North America, and Australia as part of the International Lymphoma Epidemiology Consortium (InterLymph) NHL Subtypes Project.

Methods

Study Design and Population

Detailed methodology is provided elsewhere in this issue. Studies eligible for inclusion in this pooled analysis of 11 studies met the following criteria: 1) case–control design, with incident, histologically confirmed cases of LPL/WM, and 2) availability of individual-level data for at least several risk factors of interest by December 31, 2011. Seven studies were population based (21–27), one was a combination of population based and hospital based (28), and three were hospital based (29–31). Most studies excluded individuals with a history of solid organ transplantation or HIV/AIDS.

Contributing studies were approved by local ethics review committees, and all participants provided informed consent before interview.

NHL Subtype Ascertainment and Harmonization

All LPL/WM cases met the criteria for LPL/WM described by the World Health Organization classification (1,32) and satisfied the classification suggested subsequently by the InterLymph Pathology Working Group (33,34). Most studies confirmed diagnoses by centralized pathology review by at least one expert hematopathologist.

Risk Factor Ascertainment and Harmonization

Each study collected data on putative NHL risk factors in a standardized, structured format using self-administered questionnaires. Risk factor categories included medical, lifestyle, family, and occupations. A requirement for inclusion was that a factor was ascertained in a minimum of two studies that enrolled at least one case of LPL/WM. Centralized harmonization of individual-level, de-identified data from each study was performed. Each variable was harmonized across studies and then data were reviewed for consistency among related exposure variables.

Statistical Analysis

Risk of LPL/WM associated with each exposure variable was examined using unconditional logistic regression models adjusted for age, race/ethnicity, sex, and study ("basic adjusted model"). Individuals with missing data for the exposure variable were excluded. Statistical significance was evaluated by a likelihood ratio test, comparing models with and without the exposure variable, with *P* values less than .05 used to identify putatively influential factors to be considered for the multivariate model. When two highly correlated factors or exposures were significant, only one exposure was taken forward. In such instances, the most clinically meaningful or specific exposure was selected, for example, a specific autoimmune disease rather than the composite autoimmune disease variable. Further, if the *P* value for only one exposure from several related exposures was less than.05, it was not automatically examined in the multivariate model. In these cases, the balance of evidence was taken into account, including whether there was evidence of a dose–response.

To evaluate potential effect of heterogeneity among the 11 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 by Higgins and Thompson (35) to categorical variables.

We then examined the relationship between case/control status and each putative risk factor considering possible effect modification and accounting for other potential confounders. To consider possible effect modification, we repeated the basic adjusted models and stratified individuals by age (<30, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years), sex, race/ethnicity, region (North America, Northern Europe, Southern Europe, and Australia), study, study design, and other putative risk factors identified in the analysis. To account for other potential confounders, we conducted two analyses. First, we evaluated the risk estimate for each putative risk factor in a series of models that adjusted for one other putative risk factor as well as age, sex, race/ethnicity, and study. Second, we assessed all putative risk factors in a multivariate logistic regression model, this time including a separate missing category for each variable to ensure that the whole study population was included in the analysis. Lastly, we conducted a forward stepwise logistic regression adding a single putative risk factor at a time, adjusting for age, sex, race/ethnicity, and study ("final model").

As controls for most original studies were chosen to frequency match the age and sex of all eligible lymphoma cases, rather than just LPL/WM, we conducted sensitivity analyses using a subset of controls that were frequency matched by age and sex to cases of

Table 1. Characteristics of the pooled lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia case and control participants

Characteristic	Cases, No. (%) (n = 374)	Controls, No. (%) (n = 23 096)
Age, y		
<30	2 (0.5)	1306 (5.9)
30–39	7 (1.9)	2180 (9.4)
40–49	33 (8.8)	3159 (13.7)
50–59	90 (24.1)	4992 (21.6)
60–69	128 (34.2)	6380 (27.6)
70–79	96 (25.7)	4136 (17.9)
≥80	17 (4.5)	873 (3.8)
Unknown	1 (0.3)	16 (0.1)
Sex		
Male	227 (60.7)	13 495 (58.4)
Female	147 (39.3)	9601 (41.6)
Race/ethnicity		
White non-Hispanic	352 (94.1)	21 576 (93.4)
Black	4 (1.1)	351 (1.5)
Asian	3 (0.8)	321 (1.4)
Hispanic	1 (0.3)	360 (1.6)
Other/unknown	14 (3.7)	488 (2.1)
Socioeconomic status*		
Low	142 (38.0)	9335 (40.4)
Medium	108 (28.9)	6709 (29.0)
High	118 (31.6)	6642 (28.8)
Other/unknown	6 (1.6)	410 (1.8)
Region		
North America	156 (41.7)	11 462 (49.6)
Northern Europe	156 (41.7)	6542 (28.3)
Southern Europe	35 (9.4)	4398 (19.0)
Australia	27 (7.2)	694 (3.0)
Study design		
Population based	291 (77.8)	17 846 (77.3)
Hospital based	83 (22.2)	5250 (22.7)

*Socioeconomic status was measured by years of education for studies in North America or by dividing measures of education or socioeconomic status into tertiles for studies in Europe or Australia.

Table 2. Basic adjusted association between personal history of autoimmune or allergic disease and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM) risk*

Disease†	Cases, No.‡	Controls, No.‡	OR (95% CI)§	*P*
Autoimmune diseases				
Sjögren syndrome				
No	174	6079	Referent	.003
Yes	3	9	13.2 (3.42 to 50.9)	
Systemic lupus erythematosus				
No	270	10 470	Referent	.002
Yes	4	24	8.73 (2.91 to 26.2)	
Myasthenia gravis				
No	228	7506	Referent	.171
Yes	1	4	6.60 (0.70 to 62.3)	
Sarcoidosis				
No	318	9379	Referent	.362
Yes	2	27	2.11 (0.49 to 9.01)	
Rheumatoid arthritis‖				
No	208	6368	Referent	.474
Yes	4	82	1.48 (0.53 to 4.13)	
Celiac disease				
No	268	7593	Referent	.790
Yes	1	25	1.33 (0.18 to 10.1)	
Crohn's disease				
No	315	9787	Referent	.994
Yes	1	29	0.99 (0.13 to 7.48)	
Type 1 diabetes				
No	207	7402	Referent	.967
Yes	1	43	0.96 (0.13 to 7.09)	
Psoriasis				
No	199	7333	Referent	.819
Yes	7	228	0.92 (0.42 to 1.98)	
Inflammatory bowel disorder				
No	343	10 932	Referent	.825
Yes	4	111	0.89 (0.32 to 2.47)	
Ulcerative colitis				
No	279	7777	Referent	.849
Yes	3	81	0.89 (0.28 to 2.89)	
Polymyositis or dermatomyositis				
No	61	3580	Referent	.419
Yes	0	18	—	
Multiple sclerosis				
No	314	9365	Referent	.332
Yes	0	13	—	
Pernicious anemia				
No	71	3146	Referent	.401
Yes	0	8	—	
Hemolytic anemia				
No	94	3793	Referent	.562
Yes	0	7	—	
Systemic sclerosis or scleroderma				
No	142	3848	Referent	.576
Yes	0	4	—	
Any autoimmune disease¶				
None	349	11 911	Referent	.054
B-cell activation	10	121	2.78 (1.43 to 5.43)	
T-cell activation	15	444	1.02 (0.60 to 1.74)	
Both B- and T-cell activation	0	12	—	
Atopic disorders				
Hay fever				
No	218	7235	Referent	.022
Yes	64	2511	0.70 (0.51 to 0.96)	
Asthma				
No	295	9923	Referent	.932
Yes	33	1075	0.98 (0.68 to 1.42)	

(*Table Continues*)

Table 2. Continued

Disease†	Cases, No.‡	Controls, No.‡	OR (95% CI)§	*P*
Eczema				
No	309	9941	Referent	.891
Yes	36	1291	0.98 (0.68 to 1.39)	
Any specific allergy#				
No	226	7233	Referent	.409
Yes	92	3168	0.90 (0.69 to 1.16)	
Food allergy				
No	274	8939	Referent	.157
Yes	20	908	0.72 (0.45 to 1.16)	
Any atopic disorder**				
No	225	7392	Referent	.229
Yes	140	4868	0.87 (0.70 to 1.09)	

* CI = confidence interval; OR = odds ratio.
† Self-reported condition diagnosed at least 2 years before LPL/WM diagnosis/interview.
‡ 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.
‖ Only those who also reported receiving corticosteroid or immunosuppressive treatment for rheumatoid arthritis.
¶ Includes self-reported history of specific autoimmune diseases occurring ≥2 years before diagnosis/interview (except the New South Wales study, which did not ascertain date of onset). Autoimmune diseases were classified according to whether they are primarily mediated by B-cell or T-cell responses. B-cell-activating diseases included Hashimoto thyroiditis, hemolytic anemia, myasthenia gravis, pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. T-cell-activating diseases included celiac disease, immune thrombocytopenic purpura, inflammatory bowel disorder (Crohn's disease, ulcerative colitis), multiple sclerosis, polymyositis or dermatomyositis, psoriasis, sarcoidosis, systemic sclerosis or scleroderma, and type 1 diabetes.
# Any specific allergy included plant, food, animal, dust, insect, or mold and excluded drug allergies, asthma, eczema, and hay fever.
**Atopic disorders include asthma, eczema, hay fever, or other allergies, excluding drug allergies.

LPL/WM. The results from these sensitivity analyses were very similar to the results obtained using the full set of controls. We thus retained the full set of controls for our main analyses to maximize statistical power.

Analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

A total of 374 LPL/WM cases (371 LPL and 3 WM; diagnosed 1995–2008) and 23 096 controls were included in this study. Most cases were identified in case–control studies in North America or Northern Europe (Table 1). Sixty-one percent of cases were men and the median age at diagnosis was 64 years (range 27–89). Compared with controls, cases were older and more likely to be men, but there was no difference by race/ethnicity or socioeconomic status (Table 1).

There was no statistically significant between-study heterogeneity for any of the risk factors examined (data not shown), and there was no evidence of effect modification by study, study design factors, or the other putative risk factors examined (data not shown).

Basic Adjusted Model

Medical History. Twenty-five LPL/WM cases (7.2%) and 577 controls (4.6%) had a history of autoimmune disease (Table 2); two cases and 26 controls reported more than one. These two cases reported rheumatoid arthritis and Sjögren's syndrome, as did two of the controls. Individually, Sjögren's syndrome and systemic lupus erythematosus were very strongly associated with LPL/WM risk, but the case numbers were too small to examine the relationship with disease latency (n = 3 and n = 4, respectively; Table 2). There was no association between LPL/WM risk and history of other selected autoimmune conditions (Table 2). Risk was strongly increased in association with autoimmune disease characterized by B-cell activation but not T-cell activation (Table 2). LPL/WM risk was inversely associated with a history of hay fever (odds ratio [OR] = 0.70, 95% confidence interval

Table 3. Basic adjusted association between first-degree family history of hematological malignancy and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia risk*

Family member malignancy type and relationship to case/control†	Cases, No.‡	Controls, No.‡	OR (95% CI)§	*P*
Any hematological malignancy				
No	177	7303	Referent	.050
Yes	21	452	1.65 (1.03 to 2.65)	
Hodgkin lymphoma				
No	166	6496	Referent	.369
Yes	2	34	2.10 (0.48 to 9.10)	
Non-Hodgkin lymphoma				
No	172	6837	Referent	.683
Yes	6	197	1.20 (0.52 to 2.76)	
Leukemia‖				
No	165	6819	Referent	.018
Yes	13	215	2.19 (1.21 to 3.96)	
Multiple myeloma				
No	168	6496	Referent	.143
Yes	0	34	-	

* CI = confidence interval; OR = odds ratio.
† Self-reported family history; some participants had more than one affected relative.
‡ 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.
‖ Leukemia includes chronic lymphocytic leukemia/small lymphocytic lymphoma.

Table 4. Basic adjusted association between lifestyle factors and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia risk*

Lifestyle factor	Cases, No.†	Controls, No.†	OR (95% CI)‡	*P*
Adult height				.731
Quartile 1 (low)	82	2787	Referent	
Quartile 2	85	2816	0.97 (0.70 to 1.33)	
Quartile 3	75	2747	0.82 (0.59 to 1.14)	
Quartile 4 (high)	82	2873	0.93 (0.67 to 1.29)	
Usual adult weight§				
Quartile 1 (low)	88	2432	Referent	.015
Quartile 2	66	2377	0.68 (0.49 to 0.95)	
Quartile 3	91	3115	0.70 (0.52 to 0.95)	
Quartile 4 (high)	79	3299	0.60 (0.44 to 0.83)	
Usual adult BMI‖ (kg/m^2)				
15–<18.5	4	178	0.74 (0.26 to 2.10)	
18.5–<22.5	67	2058	Referent	.034
22.5–<25	90	2659	0.86 (0.62 to 1.20)	
25–<30	124	4335	0.69 (0.50 to 0.94)	
30–<35	31	1454	0.56 (0.36 to 0.87)	
35–50	8	539	0.43 (0.20 to 0.91)	
BMI as a young adult (kg/m^2)				
15–<18.5	9	226	1.71 (0.79 to 3.70)	
18.5–<22.5	36	1432	Referent	.624
22.5–<25	21	667	1.32 (0.74 to 2.35)	
25–<30	8	362	0.93 (0.41 to 2.08)	
30–50	1	82	0.86 (0.11 to 6.61)	
Physical activity				
None	18	686	Referent	.617
Mild	15	426	1.08 (0.49 to 2.37)	
Moderate	30	883	0.95 (0.47 to 1.90)	
Vigorous	55	3027	0.68 (0.38 to 1.22)	
History of cigarette smoking‖				
No	118	4935	Referent	.076
Yes	188	5782	1.25 (0.98 to 1.59)	
Cigarette smoking status				
Nonsmoker	118	4935	Referent	.354
Former smoker	126	3616	1.22 (0.94 to 1.59)	
Current smoker	59	2090	1.31 (0.95 to 1.82)	
Smoker, status unknown	3	76	1.18 (0.28 to 4.93)	
Age started smoking cigarettes				
Nonsmoker	118	4935	Referent	.386
<14 years	15	514	1.16 (0.67 to 2.03)	
14–<18 years	76	2401	1.21 (0.89 to 1.63)	
18–<20 years	36	1224	1.11 (0.76 to 1.63)	
≥20 years	60	1583	1.45 (1.05 to 2.00)	
Smoker, age started unknown	1	60	0.79 (0.11 to 5.82)	
Years since quitting smoking				
Nonsmoker	118	4935	Referent	.304
>25 years ago	38	1160	1.01 (0.69 to 1.48)	
16–25 years ago	38	947	1.35 (0.92 to 1.97)	
5–15 years ago	30	963	1.22 (0.81 to 1.84)	
<5 years ago	16	496	1.38 (0.81 to 2.37)	
Former smoker, unknown when quit	4	50	3.01 (1.05 to 8.67)	
Current smoker	59	2090	1.32 (0.95 to 1.83)	
Smoking frequency				
Nonsmoker	118	4935	Referent	.086
≤10 cigarettes/day	76	2125	1.37 (1.02 to 1.85)	
11–20 cigarettes/day	71	2387	1.12 (0.83 to 1.53)	
21–30 cigarettes/day	23	548	1.72 (1.07 to 2.77)	
>30 cigarettes/day	11	529	0.76 (0.40 to 1.44)	
Smoker, frequency unknown	7	193	1.45 (0.65 to 3.22)	
Continuous (per-year)			1.00 (1.00 to 1.00)	.390
Duration of cigarette smoking				
Nonsmoker	118	4935	Referent	.324
1–20 years	44	2007	1.01 (0.71 to 1.44)	

(*Table Continues*)

Table 4. Continued

Lifestyle factor	Cases, No.†	Controls, No.†	OR (95% CI)‡	*P*
21–30 years	39	1258	1.23 (0.84 to 1.79)	
30–39 years	46	1235	1.32 (0.93 to 1.89)	
≥40 years	57	1194	1.49 (1.06 to 2.09)	
Smoker, duration unknown	2	88	1.14 (0.27 to 4.75)	
Continuous (per-year)			1.01 (1.00 to 1.02)	.022
Lifetime cigarette exposure				
Nonsmoker	118	4935	Referent	.612
1–10 pack-years	52	1827	1.27 (0.91 to 1.78)	
11–20 pack-years	35	1206	1.13 (0.76 to 1.66)	
21–35 pack-years	44	1274	1.25 (0.87 to 1.78)	
≥36 pack-years	50	1247	1.33 (0.93 to 1.89)	
Smoker, pack-years unknown	7	228	1.24 (0.56 to 2.75)	
Continuous (per-year)			1.00 (1.00 to 1.01)	.376
History of alcohol consumption				
Nondrinker	42	1960	Referent	.808
Drinker¶	135	4621	1.04 (0.71 to 1.53)	
Alcohol consumption status				
Nondrinker	42	1960	Referent	.812
Former drinker	16	583	1.45 (0.76 to 2.78)	
Current drinker	78	3200	1.01 (0.62 to 1.65)	
Drinker, status unknown	41	838	0.96 (0.51 to 1.82)	

* BMI = body mass index; CI = confidence interval; 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.
§ Quartile 1 (<72.6 kg males, <58.1 kg females), quartile 2 (72.6–79.9 kg males, 58.1–64.9 kg females), quartile 3 (80.0–88.9 kg males, 65.0–74.7 kg females), and quartile 4 (≥89.0 kg males, ≥74.8 kg females).
|| Smoked longer than 6 months or more than 100 cigarettes in a lifetime.
¶ At least one drink per month.

[CI] = 0.51 to 0.96) but was unrelated to history of asthma, eczema, any specific allergy, or any atopic condition (Table 2).

LPL/WM risk was strongly increased in association with positive serology for hepatitis C virus (HCV) infection (OR = 2.70, 95% CI = 1.11 to 6.56; n = 6). No other infectious diseases were examined. Risk was not associated with the receipt of one or more blood transfusions (OR = 1.06, 95% CI = 0.74 to 1.53), transfusion age, transfusion number, or year of transfusion (data not shown). Neither history of gastric ulcer nor peptic ulcer predicted LPL/WM risk (data not shown).

LPL/WM risk was associated with the number of children (*P* = .023); relative to women with a single child, risk was decreased for women with no children (OR = 0.32, 95% CI = 0.12 to 0.87) and two children (OR = 0.34, 95% CI = 0.15 to 0.77) but was attenuated and not statistically significant for three or more children (OR = 0.63, 95% CI = 0.32 to 1.22). As LPL/WM risk was not associated with time since the last birth, oral contraceptive use, the age contraceptives were first used, hormone replacement therapy, or the age hormone replacement therapy was first used (data not shown), this variable was not taken forward to multivariable analysis.

Family History. Hematological malignancy in one or more first-degree relatives was reported by 21 cases (10.6%) and 452 controls (5.8%). Risk was moderately increased for having a family member with history of any hematological malignancy (OR = 1.65, 95% CI = 1.03 to 2.65) or with leukemia (OR = 2.19, 95% CI = 1.21 to 3.96). There was no association between LPL/WM risk and family history of Hodgkin lymphoma, NHL, or multiple myeloma (Table 3).

Lifestyle Factors. Usual adult weight was inversely associated with risk of LPL/WM (*P* = .015); relative to the first quartile, LPL/WM risk was 0.68 (95% CI = 0.49 to 0.95) for the second quartile, 0.70 (95% CI = 0.52 to 0.95) for the third quartile, and 0.60 (95% CI = 0.44 to 0.83) for the fourth quartile. The same association was observed for body mass index as an adult (*P* = .034), but not body mass index as a young adult (*P* = .63; Table 4). Neither usual adult height nor physical activity predicted LPL/WM risk (Table 4).

Ever smoking cigarettes was unrelated to LPL/WM risk (OR = 1.25, 95% CI = 0.98 to 1.59). There was also no association with smoking status, years since quitting, pack-years, or frequency of smoking (Table 4). LPL/WM risk was elevated for those who started smoking when they were at least 20 years of age (OR = 1.45, 95% CI = 1.05 to 2.00, relative to nonsmokers). LPL/WM risk was also positively associated with duration of cigarette smoking, both when examined as a continuous variable (*P* = .022), and for the highest category of smoking duration (OR = 1.49, 95% CI = 1.06 to 2.09, for ≥ 40 years relative to nonsmokers; Table 4).

LPL/WM risk was not associated with any measure of alcohol consumption, including ever drinking alcohol (OR = 1.04, 95% CI = 0.71 to 1.53), consumption 2 years before diagnosis/interview (Table 4), or age started, duration, servings per week as an adult, lifetime consumption, or beer, liquor, or wine consumption (data not shown).

Sun exposure history was unrelated to LPL/WM risk, either total (OR = 0.86, 95% CI = 0.49 to 1.52 for highest vs. lowest quartile) or recreational (OR = 0.83, 95% CI = 0.59 to 1.18 for highest

Table 5. Basic adjusted association between farm residence or farm/animal-related occupation and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia risk*

Personal farm-related history	Cases, No.†	Controls, No.†	OR (95% CI)‡	*P*
Ever lived or worked on a farm				
No	143	5424	Ref	.744
Yes	65	3170	0.95 (0.67 to 1.33)	
Ever lived on a farm				
No	66	3230	Ref	.262
Yes	45	2617	0.79 (0.53 to 1.19)	
Ever worked on a farm				
No	166	6727	Ref	.651
Yes	27	1210	0.90 (0.58 to 1.40)	
Any farming occupation§				
No	156	6189	Ref	.563
Yes	27	835	1.14 (0.73 to 1.78)	
Animal farming				
No	178	6847	Ref	.929
Yes	5	177	0.96 (0.38 to 2.41)	
Crop farming				
No	174	6757	Ref	.736
Yes	9	267	1.14 (0.55 to 2.37)	
Field crop and vegetables				
No	131	5520	Ref	.588
Yes	5	115	1.35 (0.48 to 3.78)	
Mixed animal and crop				
No	163	6036	Ref	.697
Yes	15	455	1.12 (0.64 to 1.96)	
General farmer				
No	152	5491	Ref	.519
Yes	10	272	1.26 (0.64 to 2.47)	
Forestry worker				
No	158	5740	Ref	.066‖
Yes	4	34	3.17 (1.08 to 9.34)	
Meat worker				
No	181	6958	Ref	.960
Yes	2	66	1.03 (0.25 to 4.35)	

* CI = confidence interval; 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.
§ Occupation at any time in life (eight studies) or the longest held occupation (two studies); occupations coded according to the International Standard Classification of Occupations (ISCO), Revised Edition 1968 (53).
‖ *P* value using likelihood ratio test; *P* value using Wald test .036.

vs. lowest quartile). No measure of hair dye use in women predicted risk of LPL/WM (data not shown).

Occupations. On the basis of four exposed cases (2.5%), LPL/WM risk was positively associated with occupation as a forestry worker (OR = 3.17, 95% CI = 1.08 to 9.34). There was no association between risk of LPL/WM and any other farming or animal-related occupation or farm residence (Table 5). Risk was increased for medical doctors (n = 6 exposed cases, OR = 5.23, 95% CI = 2.11 to 12.9), specifically those working in this occupation for more than 10 years (n = 5 exposed cases, OR = 12.7, 95% CI = 4.41 to 36.8). There was no association between LPL/WM risk and all medical occupations combined (OR = 1.42, 95% CI = 0.84 to 2.41).

Final Model

We observed no strong evidence of confounding; factors that were statistically significantly associated with LPL/WM risk in basic adjusted models remained statistically significant in multivariate analysis and the point estimates were largely unattenuated after inclusion of the covariates (Table 6).

Discussion

In a large-scale, international pooled case–control analysis of predominantly nonfamilial LPL/WM, risk was increased in those with a history of Sjögren's syndrome, systemic lupus erythematosus, HCV infection, and a family history of hematologic malignancy. These findings support and extend prior studies suggesting a role for conditions characterized by chronic immune stimulation and genetic factors in LPL/WM pathogenesis. Novel findings were a decreased risk for history of hay fever and high usual adult weight, an increased risk for smoking cigarettes for 40 or more years, and occupation as a medical doctor, and no evidence of an association for other lifestyle factors and occupations.

We observed a very strong association between LPL/WM risk and Sjögren's syndrome, in agreement with previous large-scale medical record–based studies in the United States and Sweden (11,13). A marked increased risk was also observed for systemic lupus erythematosus, consistent with a report from one study in our pooled analysis (15), and a medical record study (13). Unlike the medical record studies, we did not find an increased risk for

Table 6. Factors associated with lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia risk, basic adjusted, and final stepwise model risk estimates*

Factor	Cases, No.†	Controls, No.†	Basic adjusted model‡		Final model§	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Sjögren syndrome						
No	174	6079	Referent	.003	Referent§	.002
Yes	3	9	13.2 (3.42 to 50.9)		14.0 (3.60 to 54.6)	
Systemic lupus erythematosus						
No	270	10 470	Referent	.002	Referent	.003
Yes	4	24	8.73 (2.91 to 26.2)		8.23 (2.69 to 25.2)	
Serology hepatitis C virus infection						
Negative	201	5259	Referent	.050	Referent	.075‖
Positive	6	95	2.70 (1.11 to 6.56)		2.51 (1.03 to 6.17)	
Hay fever						
No	218	7235	Referent	.022	Referent	.017
Yes	64	2511	0.70 (0.51 to 0.96)		0.73 (0.54 to 0.99)	
Usual adult weight¶						
Quartile 1 (low)	88	2432	Referent	.015	Referent	.024
Quartile 2	66	2377	0.68 (0.49 to 0.95)		0.71 (0.51 to 0.99)	
Quartile 3	91	3115	0.70 (0.52 to 0.95)		0.72 (0.53 to 0.98)	
Quartile 4 (high)	79	3299	0.60 (0.44 to 0.83)		0.61 (0.44 to 0.85)	
Duration of cigarette smoking						
Nonsmoker	118	4935	Referent	.145	Referent	.148
1–20 years	44	2007	1.01 (0.71 to 1.44)		1.01 (0.71 to 1.45)	
21–30 years	39	1258	1.23 (0.84 to 1.79)		1.26 (0.86 to 1.84)	
30–39 years	46	1235	1.32 (0.93 to 1.89)		1.35 (0.95 to 1.94)	
≥40 years	57	1194	1.49 (1.06 to 2.09)		1.46 (1.04 to 2.05)	
Smoker, duration unknown	2	88	1.14 (0.27 to 4.75)		1.10 (0.26 to 4.66)	
Family history hematological malignancy						
No	177	7303	Referent	.050	Referent	.060#
Yes	21	452	1.65 (1.03 to 2.65)		1.64 (1.02 to 2.64)	
Occupation: medical doctor**						
No	177	6970	Referent	.003	Referent	.002
Yes	6	43	5.23 (2.11 to 12.9)		5.54 (2.19 to 14.0)	

* CI = confidence interval; 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.
§ Adjusted for age, sex, race/ethnicity, study, Sjögren syndrome, systemic lupus erythematosus, serology hepatitis C virus infection, hay fever, usual adult weight, smoking duration, family history of hematological malignancy, and medical occupation.
‖ *P* value using likelihood ratio test; *P* value using Wald test .021.
¶ Quartile 1 (<72.6 kg males, <58.1 kg females), quartile 2 (72.6–79.9 kg males, 58.1–64.9 kg females), quartile 3 (80.0–88.9 kg males, 65.0–74.7 kg females), quartile 4 (≥89.0 kg males, ≥74.8 kg females).
# Occupation at any time in life (eight studies) or the longest held occupation (two studies); occupations coded according to the International Standard Classification of Occupations (ISCO), Revised Edition 1968 (53); code 061 = medical doctor.

rheumatoid arthritis (11), Crohn's disease (11), or autoimmune hemolytic anemia (13). However, our composite autoimmune variable indicated an increased risk for autoimmune conditions with activated B cells, but not activated T cells. This association is consistent with the finding that familial LPL/WM patients are twice as likely as unaffected relatives to report a history of autoimmune disorders (14). The pathogenic mechanism is believed to involve chronic antigen-driven inflammation and activated proliferating lymphocytes (36,37).

We confirmed an association between LPL/WM risk and family history of hematologic malignancy (5–7). Our data favored an association with leukemia but not NHL, Hodgkin lymphoma, or multiple myeloma, in partial agreement with a case–control study (7) that reported coaggregation with chronic lymphocytic leukemia and NHL, but not Hodgkin lymphoma or multiple myeloma. This association is thought to suggest a role for common susceptibility genes, as supported by an increased risk of LPL/WM among first-degree relatives of people with monoclonal gammopathy of undetermined significance (9,38). Further, recent evidence of an association of both personal and family history of Sjögren's syndrome and autoimmune hemolytic anemia with LPL/WM risk (13) supports a role for shared susceptibility for LPL/WM and certain autoimmune conditions. At this time, information on specific genes or genomic regions in LPL/WM susceptibility is limited (15,16,23).

The five studies in our analysis with HCV serology data formed the basis of an earlier InterLymph report showing a statistically significant association between HCV and LPL (12), consistent with US (10,11), but not Swedish (13), medical record studies. The known association of HCV infection with type II mixed cryoglobulinemia and monoclonal gammopathy of undetermined significance (10), both of which increase LPL/WM risk (39,40), supports a true association between HCV and LPL/WM. In addition, antiviral treatment can be an effective first-line therapy for

HCV-positive LPL (40). HCV infection is believed to promote lymphomagenesis via chronic immune stimulation and elevated IgM levels (10,41–43).

Our finding of an inverse association between LPL/WM risk and personal history of hay fever is not consistent with prior studies that observed a positive (13,14) or no association (11,20) with individual allergic conditions or any allergy. Large-scale cohort study data are needed to clarify the relationship with this exposure (44).

Even though the relationship has not been previously examined, our observation that LPL/WM risk appears lower for individuals with higher adult weight is unexpected. Not only is there evidence of an increased risk of NHL and some other NHL subtypes for those of higher adiposity (45–47), but obesity is a chronic low-grade inflammatory state characterized by lymphocyte proliferation (48). It is possible the association we observed is due to chance or selection bias. Uniquely to LPL/WM, however, IgM-producing B1 B cells are found in milky spots on the omentum and fat-associated lymphoid clusters on the mesentery [reviewed in (49)]. It is possible their physical proximity to adipose tissue uniquely affects their physiology and progression to LPL/WM.

Although not entirely consistent across all of the smoking variables we examined, we found evidence of a weak positive association between LPL/WM risk and cigarette smoking. LPL/WM risk was increased 1.4-fold among those who had smoked for 40 or more years. Smoking history was not associated with LPL/WM risk in two previous studies, one based on 65 cases (20) and the other 103 cases (14). Although this finding requires confirmation in larger studies, a history of smoking has been weakly positively associated with other NHL subtypes (50), and an association is biologically plausible given the immunosuppressive effects of chronic cigarette smoke (51,52).

We observed an elevated risk of LPL/WM for medical doctors but not health-care workers more generally. There is no prior evidence of such a relationship. We did not confirm the previously reported increased risk of familial LPL/WM and exposure to farming, pesticides, wood dust, and organic solvents (14); however, our analyses were limited to a small number of job titles rather than exposure to specific chemical compounds.

This is the first pooled analysis of medical history, lifestyle, family history, and occupational risk factors for LPL/WM using the 2001 and 2008 WHO classification for LPL/WM and pathology report review. It is the only observational study of LPL/WM to examine the role of potential effect modification and confounding and, thus, determine the independence of these putative risk factors. The exposure data are of high quality and the findings are generalizable to predominantly white populations because most studies were population based and were conducted in Europe, North America, and Australia.

Some limitations need to be considered. The study populations were predominantly Caucasian and the number of LPL/WM cases was relatively small, although this is one of the largest case–control interview-based studies of this rare lymphoma subtype to date. Given the rarity of LPL/WM, we undertook an exploratory analytical approach, without adjustment for multiple statistical tests. Lack of data on Ig levels, therapy for autoimmune diseases, duration and therapy for HCV, and history of infections other than HCV restricted our interpretation of some findings. We are also unable to exclude recall bias or reverse causality, with underlying LPL/WM misdiagnosed as Sjögren's syndrome or systemic lupus erythematosus. Further, misdiagnosis of MALT or splenic marginal zone lymphoma as LPL/WM is an alternative explanation for the associations we observed with autoimmune disease and HCV infection. Finally, our occupational analyses are based on job titles, not exposure to specific agents.

We have confirmed an association between LPL/WM risk and history of specific immune-stimulatory medical conditions and a family history of hematologic malignancy, and we have shown for the first time that these risk factors appear to be independent. These findings have future translational potential both biologically and clinically. Other novel findings, specifically the associations with hay fever, adult weight, smoking for 40 or more years, and occupation as a medical doctor, require confirmation in large-scale case–control studies of LPL/WM and long-term cohort studies of monoclonal gammopathy of undetermined significance.

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