

ARTICLE

Immune-Related and Inflammatory Conditions and Risk of Lymphoplasmacytic Lymphoma or Waldenström Macroglobulinemia

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- Background** Chronic immune stimulation appears to be associated with lymphoplasmacytic lymphoma (LPL)-Waldenström macroglobulinemia (WM); however, available information is sparse. We conducted, to our knowledge, the most comprehensive study to date to evaluate associations between a personal or family history of many immune-related and/or inflammatory disorders and the subsequent risk of LPL-WM.
- Methods** We used Swedish population-based registries to identify 2470 case patients with LPL-WM, 9698 matched control subjects, and almost 30000 first-degree relatives of either case patients or control subjects. We evaluated a wide range of autoimmune, infectious, allergic, and inflammatory conditions. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for each condition by use of logistic regression.
- Results** An increased risk of LPL-WM was associated with a personal history of the following autoimmune diseases: systemic sclerosis (OR = 4.7, 95% CI = 1.4 to 15.3), Sjögren syndrome (OR = 12.1, 95% CI = 3.3 to 45.0), autoimmune hemolytic anemia (OR = 24.2, 95% CI = 5.4 to 108.2), polymyalgia rheumatica (OR = 2.9, 95% CI = 1.6 to 5.2), and giant cell arteritis (OR = 8.3, 95% CI = 2.1 to 33.1). An increased risk of LPL-WM was associated with a personal history of the following infectious diseases: pneumonia (OR = 1.4, 95% CI = 1.1 to 1.7), septicemia (OR = 2.4, 95% CI = 1.2 to 4.3), pyelonephritis (OR = 1.7, 95% CI = 1.1 to 2.5), sinusitis (OR = 2.7, 95% CI = 1.4 to 4.9), herpes zoster (OR = 3.4, 95% CI = 2.0 to 5.6), and influenza (OR = 2.9, 95% CI = 1.7 to 5.0). An increased risk of LPL-WM was associated with a family history of the following autoimmune or infectious diseases: Sjögren syndrome (OR = 5.0, 95% CI = 2.1 to 12.0), autoimmune hemolytic anemia (OR = 3.8, 95% CI = 1.1 to 13.2), Guillain-Barré syndrome (OR = 4.1, 95% CI = 1.8 to 9.4), cytomegalovirus (OR = 2.7, 95% CI = 1.4 to 5.3), gingivitis and periodontitis (OR = 1.9, 95% CI = 1.3 to 2.7), and chronic prostatitis (OR = 4.3, 95% CI = 1.7 to 11.1).
- Conclusions** Personal history of certain immune-related and/or infectious conditions was strongly associated with increased risk of LPL-WM. The association of both personal and family history of Sjögren syndrome and autoimmune hemolytic anemia with risk of LPL-WM indicates the potential for shared susceptibility for these conditions.

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Lymphoplasmacytic lymphoma (LPL)-Waldenström macroglobulinemia (WM) is a chronic lymphoproliferative tumor characterized by small B lymphocytes, plasmacytoid lymphocytes, and plasma cells and involves the bone marrow, lymph nodes, and spleen. The World Health Organization criteria for classification of hematological diseases list WM as a subset of LPL that is defined as LPL with bone marrow involvement and a detectable monoclonal IgM spike in serum (1,2). LPL-WM is a rare disease, with an annual incidence rate of three to four cases per million people (3,4). It is more common among the elderly, men, and white persons (3–5).

Although the etiology of LPL-WM is unknown, there are a few clues in the literature. For example, familial aggregation of WM was demonstrated in 1962 (6). Since then, several studies of multi-

ply affected families (7–9), case-control studies (10), and cohort studies (11) have been published showing familial clustering of LPL and WM. Recently, we conducted a large population-based case-control study (12) in Sweden and found that, compared with first-degree relatives of control subjects, first-degree relatives of LPL-WM patients have an increased risk for LPL-WM (odds ratio [OR] = 20, 95% confidence interval [CI] = 4.1 to 98.4), non-Hodgkin lymphoma (OR = 3.0, 95% CI = 2.0 to 4.4), chronic lymphocytic leukemia (OR = 3.4, 95% CI = 1.7 to 6.6), and monoclonal gammopathy of undetermined significance (OR = 5.0, 95% CI = 1.3 to 18.9). These findings support the hypothesis that there are shared common susceptibility genes that predispose individuals to LPL-WM and related lymphoproliferative disorders (7,8,10,11). Simultaneously, a few preclinical studies have reported evidence of

CONTEXT AND CAVEATS

Prior knowledge

Lymphoplasmacytic lymphoma (LPL)-Waldenström macroglobulinemia (WM) is a chronic lymphoproliferative tumor. Chronic immune stimulation appears to be associated with LPL-WM.

Study design

Swedish population-based registries were used to identify case patients with LPL-WM, matched control subjects, and the first-degree relatives of either case patients or control subjects, as well as the occurrence and date of immune-related and/or inflammatory condition for all study participants. Associations between previous personal or family history of immune-related and/or inflammatory conditions and LPL-WM were assessed.

Contribution

Personal history of certain immune-related and/or infectious conditions (including systemic sclerosis, Sjögren syndrome, or autoimmune hemolytic anemia) was strongly associated with increased risk of LPL-WM. Both personal and family history of Sjögren syndrome or autoimmune hemolytic anemia were associated with risk of LPL-WM.

Implications

There may be a potential for shared susceptibility between LPL-WM and Sjögren syndrome or autoimmune hemolytic anemia.

Limitations

Many immune-related conditions were assessed. Clinical data and information on potential confounders were not available. A systematic blinded validation of all LPL-WM diagnoses was not conducted.

From the Editors

somatic immunoglobulin gene mutations in WM, indicating a role for antigenic stimulation in the development of WM (13–15).

Because of the rarity of LPL-WM, only a few epidemiological studies (10,16–18) have assessed the role of various types of chronic antigenic stimulatory conditions in relation to risk of developing LPL-WM, and their results have been conflicting. For example, a hospital-based study (10) of 65 WM patients reported no association between a personal history of autoimmune disease and subsequent risk of developing WM. In contrast, two nationwide US veterans studies (17,18) that included 361 and 165 WM patients, respectively, found increased risk of WM among individuals with a personal history of autoimmune disease, infection with hepatitis B and C virus or HIV, or rickettsiosis.

To increase understanding of the association between immune-related and/or inflammatory conditions and subsequent risk of LPL-WM, we conducted a large population-based case-control study by use of linked registry data from Sweden to examine the association between a personal history of various immune-related and/or inflammatory conditions and risk of LPL-WM. This study contained 2470 LPL-WM patients and 9698 matched control subjects. On the basis of previous observations that first-degree relatives of WM patients (compared with first-degree relatives of control subjects) might be more prone to developing various immunologic abnormalities (10) and that immune and inflammatory

genes might play a role in lymphomagenesis (19,20), we hypothesized that the association between immune-related and/or inflammatory conditions and risk of LPL-WM was modulated, to some degree, by polymorphisms in common genes that predisposed individuals to both types of conditions. If true, immune-related and/or inflammatory conditions and LPL-WM should aggregate in the same families. To test this hypothesis, we investigated 5710 first-degree relatives of case patients with LPL-WM and 22 799 first-degree relatives of control subjects to evaluate risk of LPL-WM among individuals with a family history of immune-related and/or inflammatory conditions.

Patients and Methods

Registries, Patients, Control Subjects, and First-Degree Relatives

Details of the study population have been described previously (12). In brief, Sweden provides universal medical health care for the entire population, which is currently approximately 9 million people. In contrast to many other countries, patients with lymphoproliferative malignancies in Sweden are typically diagnosed, treated, and followed clinically by physicians at hospital-based hematology or oncology centers.

Since 1958, all physicians, pathologists, and cytologists in Sweden have been obliged by law to report each case of cancer they diagnose or treat to the centralized nationwide Swedish Cancer Registry (21). In a recent validation study (22) that focused on lymphoproliferative malignancies diagnosed from January 1, 1964, through December 31, 2003, we found the overall completeness and diagnostic accuracy of the registry to be greater than 90%. For WM, the diagnostic accuracy was 93%, but the completeness was 68% (22). From these findings, we used parallel approaches to establish a nationwide LPL-WM cohort. First, we identified all LPL-WM patients who were diagnosed from January 1, 1958, through December 31, 2005, in the nationwide Swedish Cancer Registry. Second, we retrieved information on patients with incident LPL-WM through our national network including all major hematology or oncology centers in Sweden. Third, we identified all patients reported in the Swedish Inpatient Registry (23), which captures information on individual patient-based discharge diagnosis and discharge listings from all inpatient care, with a very high coverage. By using these three sources, we created a nationwide LPL-WM cohort. In this study, we excluded patients with another cancer that was diagnosed before their LPL-WM diagnosis.

For each LPL-WM patient, four population-based control subjects (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All control subjects had to be alive at the time of LPL-WM diagnosis for the corresponding case patient and without a hematological malignancy at the date of LPL-WM diagnosis for their corresponding case patient.

From the Swedish Multigenerational Registry (23), which includes information on parents, siblings, and offspring of all Swedish citizens who were born in 1932 or later, we obtained information on all first-degree relatives (parents, siblings, and offspring) of case patients and control subjects. LPL-WM case

patients and control subjects with no relatives identified from the linkage were not included in the familial part of this study. We used Swedish population-based registries to identify 2470 case patients with LPL-WM, 9698 matched control subjects, and their almost 30 000 first-degree relatives of either case patients or control subjects.

Information on occurrence and date of immune-related and/or inflammatory condition was obtained from the Inpatient Registry. The seventh, eighth, ninth, and 10th revisions of the *International Classification of Diseases* were used to code diagnoses for specific autoimmune, infectious, allergic, and other inflammatory conditions because the study period covered such a long period. Conditions included in the analyses were in accord with previously published studies (Appendix Table 1) (10,16,17). In accord with a previous study (24), autoimmune conditions were categorized according to those that generally have detectable autoantibodies and those that do not. We presented results for individual immune stimulatory conditions only if three or more people with the condition developed LPL-WM.

Statistical Analysis

We used polytomous regression to calculate separate odds ratios and 95% confidence intervals for the association of LPL and WM with immune-related and/or inflammatory conditions by adjusting for year of birth (<1913, 1913–1920, 1921–1928, or ≥1929), year of diagnosis (<1990, 1990–1994, 1995–1999, or ≥2000), sex, and county. Because results for LPL and WM were similar according to the Wald test for homogeneity, we also used unconditional logistic regression to calculate odds ratios and 95% confidence intervals for all LPL and WM patients combined. Results from conditional logistic regression were similar to those from unconditional logistic regression. When no LPL-WM patients or control subjects had an immune-related or inflammatory condition, we presented unadjusted *P* values that were derived from the Fisher exact test. All *P* values and 95% confidence intervals were from two-sided statistical tests. To avoid detection bias, we excluded the first year before LPL-WM diagnosis from the analyses.

To evaluate the possibility that undetected LPL-WM could cause immune-related and/or inflammatory conditions (ie, reverse causality), models that were adjusted for year of birth, sex, and county were stratified by latency (time from first hospital discharge date to subsequent date of LPL-WM diagnosis = 1–5 years or >5 years for immune-related and/or inflammatory conditions that were statistically significantly associated with LPL-WM). We evaluated models that were stratified by median calendar time (<1995 or ≥1995) and adjusted for sex and county to assess whether the estimates were stable over time. We also examined the results by age at LPL-WM diagnosis (<70 or ≥70 years) that were adjusted for sex and county and by sex that were adjusted for year of birth, year of diagnosis, and county. Modification of the association by latency, calendar time, age at LPL-WM diagnosis, and sex was then evaluated by use of the likelihood ratio test for multiplicative interaction.

We also examined the association between a family history of many immune-related and/or inflammatory conditions and risk of LPL-WM. Data from first-degree relatives were used to determine family history of immune-related and inflammatory condi-

tions for LPL-WM patients and matched control subjects. Associations of a family history of immune-related and inflammatory conditions with risk of LPL-WM were estimated by use of unconditional logistic regression that was adjusted for personal history of the condition, year of birth, year of diagnosis, sex, and county.

Results

A total of 2470 case patients with incident LPL-WM (647 with LPL and 1823 with WM) that was diagnosed in Sweden from January 1, 1958, through December 31, 2005; 9698 population-based control subjects; and first-degree relatives of case patients (*n* = 5710) and control subjects (*n* = 22 799) were included in the study. As shown in Table 1, most LPL-WM case patients and control subjects were men (59%). The median age at diagnosis was 74 years (range = 19–98 years). Although the patients were diagnosed over a long period, most were diagnosed from January 1, 1990, through December 31, 2005 (Table 1).

Personal and Family History of Autoimmune Diseases

Associations between an autoimmune disease and LPL-WM are shown in Table 2. A total of 122 patients had a history of any autoimmune disease before their LPL-WM diagnosis. Overall, autoimmune disease was associated with an increased risk of subsequent LPL-WM (OR = 1.7, 95% CI = 1.4 to 2.1). The strongest association between an autoimmune disease and risk of developing LPL-WM was found among individuals with a personal history of Sjögren syndrome (OR = 12.1, 95% CI = 3.3 to 45.0). Strong associations were also found among individuals with a personal history of systemic sclerosis (OR = 4.7, 95% CI = 1.4 to 15.3), autoimmune hemolytic anemia (OR = 24.2, 95% CI = 5.4 to

Table 1. Characteristics of lymphoplasmacytic lymphoma-Waldenström macroglobulinemia (LPL-WM) patients and matched control subjects

Variable	Case patients with LPL-WM			Control subjects
	WM	LPL	Combined	
No. total	1823	647	2470	9698
Median age at diagnosis, y	75	71	74	74
Median year of birth	1920	1925	1921	1921
% Men	58.2	59.0	58.4	58.6
Age group, No. (%)				
<40 y	8 (0.4)	11 (1.7)	19 (0.8)	76 (0.8)
40–49 y	51 (2.8)	33 (5.1)	84 (3.4)	316 (3.3)
50–59 y	181 (9.9)	89 (13.8)	270 (10.9)	987 (10.2)
60–69 y	354 (19.4)	153 (23.7)	507 (20.5)	1992 (20.5)
70–79 y	679 (37.3)	207 (32.0)	886 (35.9)	3421 (35.3)
≥80 y	550 (30.2)	154 (23.8)	704 (28.5)	2906 (30.0)
Year of diagnosis, % of total				
<1990	33.3	12.4	27.2	25.7
1990–1995	25.2	26.9	25.2	24.7
1995–2000	21.4	36.0	25.0	25.4
>2000	20.1	24.9	22.6	24.3

Table 2. Personal history of autoimmune disease and risk of lymphoplasmacytic lymphoma-Waldenström macroglobulinemia (LPL-WM)*

Category or condition	WM			LPL			LPL-WM		
	No. of WM case patients (n = 1823)	No. of control subjects (n = 7158)	OR (95% CI) [P]	No. of LPL case patients (n = 647)	No. of control subjects (n = 2540)	OR (95% CI) [P]	No. of LPL-WM case patients (n = 2470)	No. of control subjects (n = 9698)	OR (95% CI)
Total autoimmune disease†	81	224	1.5 (1.2 to 2.0)	41	69	2.2 (1.6 to 3.1)	122	293	1.7 (1.4 to 2.1)
Autoantibodies detectable	48	147	1.4 (0.98 to 1.9)	34	40	3.0 (2.0 to 4.4)	82	187	1.8 (1.4 to 2.3)
Systemic involvement	26	76	1.4 (0.9 to 2.1)	21	25	3.4 (2.1 to 5.5)	47	101	1.9 (1.3 to 2.7)
Rheumatoid arthritis	16	62	1.1 (0.7 to 1.9)	11	15	2.2 (1.2 to 4.3)	27	77	1.4 (0.9 to 2.2)
Systemic sclerosis	2	4	1.8 (0.4 to 9.5)	4	1	19.4 (5.0 to 75.0)	6	5	4.7 (1.4 to 15.3)
Sjögren syndrome	6	2	11.0 (2.7 to 44.4)	3	1	15.3 (3.0 to 78.6)	9	3	12.1 (3.3 to 45.0)
Systemic lupus erythematosus	2	2	1.8 (0.4 to 9.1)	3	4	6.2 (1.5 to 25.7)	5	6	3.1 (0.95 to 10.2)
Organ involvement	22	75	1.3 (0.8 to 2.0)	13	16	2.3 (1.3 to 4.4)	35	91	1.5 (1.0 to 2.2)
Graves disease	1	11	0.4 (0.1 to 3.0)	0	2	0.0 [1.00]	1	13	0.3 (0.0 to 2.3)
Pernicious anemia	2	27	0.3 (0.1 to 1.4)	2	3	1.3 (0.3 to 5.4)	4	30	0.5 (0.2 to 1.4)
Autoimmune hemolytic anemia	7	1	19.5 (4.0 to 95.0)	5	1	35.4 (6.7 to 187.6)	12	2	24.2 (5.4 to 108.2)
Guillain-Barré syndrome	0	3	0.0 [1.00]	1	0	∞ [2.0]	1	3	1.3 (0.1 to 12.6)
Chronic rheumatic heart disease	7	16	1.8 (0.8 to 4.4)	0	3	0.0 [1.00]	7	19	1.4 (0.6 to 3.4)
Multiple sclerosis	0	6	0.0 [61]	1	4	1.2 (0.2 to 9.4)	1	10	0.4 (0.1 to 3.1)
Autoantibodies not detectable	36	94	1.6 (1.1 to 2.4)	10	33	1.1 (0.6 to 2.1)	46	127	1.5 (1.1 to 2.1)
Rheumatic fever	1	9	0.4 (0.1 to 3.4)	0	4	0.0 [59]	1	13	0.3 (0.0 to 2.4)
Sarcoidosis	0	9	0.0 [22]	1	4	0.9 (0.1 to 7.2)	1	13	0.3 (0.0 to 2.4)
Crohn disease	3	6	1.5 (0.4 to 5.5)	1	5	1.1 (0.1 to 8.6)	4	11	1.4 (0.5 to 4.4)
Ulcerative colitis	7	15	2.0 (0.8 to 4.8)	3	5	2.1 (0.6 to 7.1)	10	20	2.0 (0.9 to 4.3)
Ankylosing spondylitis	2	9	1.0 (0.2 to 4.6)	0	3	0.0 [1.00]	2	12	0.7 (0.2 to 3.0)
Polymyalgia rheumatica	15	23	3.2 (1.7 to 6.1)	3	3	1.9 (0.6 to 6.5)	18	26	2.9 (1.6 to 5.2)
Psoriasis	5	22	1.0 (0.4 to 2.7)	1	5	0.5 (0.1 to 9.9)	6	27	0.9 (0.4 to 2.2)
Giant cell arteritis	4	2	8.0 (1.8 to 35.9)	2	1	9.1 (1.5 to 55.2)	6	3	8.3 (2.1 to 33.1)
Aplastic anemia	2	2	2.9 (0.5 to 16.1)	1	2	4.0 (0.4 to 37.0)	3	4	3.2 (0.7 to 14.4)

* When presented in square brackets, *P* values (two-sided) that were based on Fisher exact test are given when no case patient or control subject has the specified condition. Odds ratios (ORs) were adjusted for categorical year of birth, date of diagnosis, sex, and county. CI = confidence interval.

† Overall categories total to less than the sum of the individual categories because some individuals have more than one autoimmune disease.

108.2), polymyalgia rheumatica (OR = 2.9, 95% CI = 1.6 to 5.2), or giant cell arteritis (OR = 8.3, 95% CI = 2.1 to 33.1). When LPL and WM were analyzed separately, although the number of patients was small, associations for each disease were similar to those in the combined analyses (Table 2). When we evaluated risk for LPL-WM by age at diagnosis, sex, calendar time at diagnosis, and source of case patient data (Swedish Cancer Registry, Swedish Inpatient Registry, or our national network including all major hematology or oncology centers in Sweden), associations were again similar (data not shown). When we assessed the observed statistically significant associations by latency (time between immune-related or inflammatory conditions and LPL-WM), the increased risk of LPL-WM that was associated with most autoimmune diseases remained statistically significant at more than 5 years of latency (Table 3).

When we assessed the association between a family history of autoimmune diseases and risk of LPL-WM, after adjusting for a personal history of autoimmune disease, we found that a family history of Sjögren syndrome (OR = 5.0, 95% CI = 2.1 to 12.0), autoimmune hemolytic anemia (OR = 3.8, 95% CI = 1.1 to 13.2), or Guillain-Barré syndrome (OR = 4.1, 95% CI = 1.8 to 9.4) was associated with a statistically significantly increased risk for LPL-WM (Table 4). Also, a family history of systemic lupus erythematosus was associated with a borderline increased risk for LPL-WM (OR = 3.9, 95% CI = 1.0 to 15.6).

Personal and Family History of Infectious Disease

Overall, a history of any infectious disease was associated with an increased risk of LPL-WM (OR = 1.3, 95% CI = 1.1 to 1.5)

(Table 5). We found that a history of pneumonia (OR = 1.4, 95% CI = 1.1 to 1.7), septicemia (OR = 2.4, 95% CI = 1.2 to 4.3), pyelonephritis (OR = 1.7, 95% CI = 1.1 to 2.5), sinusitis (OR = 2.7, 95% CI = 1.4 to 4.9), herpes zoster (OR = 3.4, 95% CI = 2.0 to 5.6), or influenza (OR = 2.9, 95% CI = 1.7 to 5.0) was associated with an increased risk of LPL-WM. When LPL and WM were analyzed separately, these associations were similar (Table 5). The risk estimates tended to be non-statistically significantly higher for infections diagnosed 1–5 years before the LPL-WM diagnosis than for those diagnosed more than 5 years earlier; however, most risks were still statistically significantly increased after more than 5 years (Table 3). Similar to the association between a personal history of autoimmune diseases and risk of LPL-WM, we found that the risk for LPL-WM did not vary by age at diagnosis, sex, calendar time at diagnosis, and data source (data not shown). In a subanalysis that investigated whether the number of infections was associated with risk of LPL-WM, we found that an increasing number of pneumonias was associated with increasing risk for LPL-WM (for patients with one pneumonia, OR = 1.1, 95% CI = 0.86 to 1.4; for patients with two pneumonias, OR = 3.5, 95% CI = 2.2 to 5.4; and for patients with three or more pneumonias, OR = 2.5, 95% CI = 1.3 to 4.9) ($P_{\text{trend}} < .001$). When we assessed the risk of LPL-WM in relation to the number of other types of infections, we did not find a statistically significant dose–effect association (data not shown). However, when we assessed the association between family history of infectious disease and risk of LPL-WM, we found that a family history of cytomegalovirus infection (OR = 2.7, 95% CI = 1.4 to 5.3) or gingivitis and periodontitis (OR = 1.9, 95% CI = 1.3 to 2.7) was statistically significantly associated with the risk (Table 4).

Table 3. Personal history of autoimmune disease and risk of lymphoplasmacytic lymphoma-Waldenström macroglobulinemia (LPL-WM) by latency*

Category or condition	Time since LPL-WM diagnosis					
	1–5 y			>5 y		
	No. of LPL-WM case patients	No. of control subjects	OR* (95% CI)	No. of LPL-WM case patients	No. of control subjects	OR* (95% CI)
Autoimmune disease						
Autoantibodies detectable						
Systemic involvement						
Rheumatoid arthritis	7	14	2.0 (0.8 to 4.9)	20	63	1.3 (0.8 to 2.1)
Systemic sclerosis	1	2	2.0 (0.2 to 22.0)	5	3	6.5 (1.6 to 27.4)
Sjögren syndrome	3	2	5.9 (0.99 to 35.7)	6	1	24.0 (2.9 to 199.8)
Systemic lupus erythematosus	2	1	7.9 (0.7 to 86.6)	3	5	2.4 (0.6 to 10.0)
Organ involvement						
Autoimmune hemolytic anemia	5	1	20.1 (2.3 to 172.6)	7	1	27.6 (3.3 to 224.7)
Autoantibodies not detectable						
Polymyalgia rheumatica	8	12	2.6 (1.1 to 6.5)	10	14	2.8 (1.3 to 6.4)
Giant cell arteritis	2	1	7.9 (0.7 to 86.8)	2	4	7.8 (1.4 to 42.5)
Infections						
Pneumonia	54	148	1.5 (1.1 to 2.0)	65	208	1.3 (0.9 to 1.7)
Septicemia	4	6	2.6 (0.7 to 9.3)	14	24	2.3 (1.2 to 4.5)
Herpes zoster	15	14	4.2 (2.0 to 8.8)	12	19	2.5 (1.2 to 5.2)
Pyelonephritis	16	34	1.9 (1.0 to 3.4)	21	57	1.5 (0.9 to 2.4)
Sinusitis	3	5	2.4 (0.6 to 10.1)	14	21	2.7 (1.3 to 5.2)
Influenza	13	10	5.1 (2.2 to 11.7)	9	21	1.7 (0.8 to 3.7)

* Odds ratio (OR) was adjusted for categorical year of birth, sex, and county. CI = confidence interval.

Table 4. Family history of autoimmune and infectious diseases and risk of lymphoplasmacytic lymphoma-Waldenström macroglobulinemia (LPL-WM)*

Category or condition	No. of LPL-WM case patients (n = 1980)	No. of control subjects (n = 7643)	OR† (95% CI)
Autoimmune disease	301	1108	1.1 (0.9 to 1.2)
Autoantibodies detectable	193	671	1.1 (1.0 to 1.3)
Systemic involvement	79	279	1.1 (0.9 to 1.4)
Rheumatoid arthritis	55	218	1.0 (0.7 to 1.3)
Systemic sclerosis	5	8	2.4 (0.8 to 7.4)
Sjögren syndrome	11	9	5.0 (2.1 to 12.0)
Systemic lupus erythematosus	9	16	2.2 (1.0 to 5.0)
Organ involvement	124	429	1.1 (0.9 to 1.4)
Graves disease	15	43	1.3 (0.7 to 2.4)
Addison disease	6	18	1.3 (0.5 to 3.2)
Pernicious anemia	11	48	0.9 (0.5 to 1.7)
Autoimmune hemolytic anemia	5	5	3.8 (1.1 to 13.2)
Primary biliary cirrhosis	4	12	1.3 (0.4 to 4.0)
Discoid lupus erythematosus	4	6	2.5 (0.7 to 9.1)
Myasthenia gravis	3	17	0.7 (0.2 to 2.4)
Guillain-Barré syndrome	12	11	4.1 (1.8 to 9.4)
Diabetes mellitus type I	28	106	1.0 (0.7 to 1.6)
Chronic rheumatic heart disease	20	60	1.3 (0.8 to 2.2)
Multiple sclerosis	18	45	1.6 (0.9 to 2.7)
Amyotrophic lateral sclerosis	4	25	0.6 (0.2 to 1.8)
Autoantibodies not detectable	130	538	0.9 (0.8 to 1.1)
Rheumatic fever	8	19	1.6 (0.7 to 3.7)
Sarcoidosis	10	55	0.7 (0.4 to 1.4)
Crohn disease	29	123	0.9 (0.6 to 1.4)
Ulcerative colitis	45	163	1.1 (0.8 to 1.5)
Ankylosing spondylitis	13	54	1.0 (0.5 to 1.8)
Polymyalgia rheumatica	17	87	0.8 (0.5 to 1.3)
Psoriasis	17	54	1.2 (0.7 to 2.1)
Giant cell arteritis	5	15	1.3 (0.5 to 3.5)
Aplastic anemia	5	25	0.8 (0.3 to 2.0)
Infection	805	2943	1.1 (1.0 to 1.2)
Pneumonia	1120	299	1.1 (0.9 to 1.2)
Tuberculosis	24	72	1.3 (0.8 to 2.1)
Intestinal infection	182	749	0.9 (0.8 to 1.1)
Gonorrhea	16	46	1.3 (0.8 to 2.4)
Septicemia	31	90	1.4 (0.9 to 2.1)
Herpes simplex	15	66	0.9 (0.5 to 1.5)
Herpes zoster	24	64	1.5 (0.9 to 2.3)
Viral hepatitis (A, B, or C)	3	19	0.6 (0.2 to 2.1)
Infectious mononucleosis	38	79	1.4 (0.9 to 2.2)
Pyelonephritis	75	317	0.9 (0.7 to 1.2)
Cystitis	89	355	1.0 (0.8 to 1.2)
Sinusitis	40	183	0.9 (0.6 to 1.2)
Otitis media	58	214	1.1 (0.8 to 1.4)
Nasopharyngitis/laryngitis	50	231	0.8 (0.6 to 1.1)
Influenza	30	99	1.2 (0.8 to 1.8)
Encephalitis	6	35	0.6 (0.3 to 1.5)
Meningitis	32	127	0.4 (0.1 to 1.7)
Pericarditis	20	79	0.8 (0.1 to 6.8)
Myocarditis	10	34	1.2 (0.6 to 2.4)
Endocarditis	23	68	1.3 (0.8 to 2.1)
Osteomyelitis	18	54	1.3 (0.8 to 2.2)
Cytomegalovirus	15	21	2.7 (1.4 to 5.3)
Epstein-Barr virus	26	8	1.2 (0.6 to 2.7)
HIV	3	9	1.2 (0.3 to 4.6)
Gingivitis and periodontitis	45	96	1.9 (1.3 to 2.7)
Tonsillitis	58	273	0.8 (0.6 to 1.1)
Fasciitis	5	18	1.1 (0.4 to 2.9)
Empyema	7	22	1.3 (0.5 to 3.0)
Erysipelas (cellulitis)	72	356	0.8 (0.6 to 1.0)

* Overall categories total to less than the sum of the individual categories because some individuals have more than one autoimmune or infectious disease.
CI = confidence interval; OR = odds ratio.

† ORs were adjusted for categorical year of birth, sex, county, and personal history of the chronic immune condition.

Table 5. Personal history of infectious disease and risk of lymphoplasmacytic lymphoma-Waldenström macroglobulinemia (LPL-WM)*

Category or condition	WM patients			LPL patients			LPL-WM patients		
	No. of WM case patients (n = 1823)	No. of control subjects (n = 7158)	OR (95% CI)	No. of LPL case patients (n = 647)	No. of control subjects (n = 2540)	OR (95% CI) [P]	No. of LPL-WM case patients (n = 2470)	No. of control subjects (n = 9698)	OR (95% CI)
Total infection†	278	856	1.4 (1.2 to 1.6)	80	288	1.1 (0.9 to 1.45)	358	1144	1.3 (1.1 to 1.45)
Pneumonia	95	268	1.5 (1.1 to 1.8)	24	88	1.1 (0.7 to 1.7)	119	356	1.4 (1.1 to 1.7)
Tuberculosis	13	38	1.4 (0.8 to 2.7)	1	9	0.4 (0.1 to 2.6)	14	47	1.2 (0.6 to 2.1)
Intestinal infection	33	116	1.2 (0.8 to 1.8)	13	32	1.4 (0.8 to 2.5)	46	148	1.3 (0.9 to 1.8)
Septicemia	16	27	2.6 (1.4 to 4.8)	2	3	1.4 (0.3 to 5.8)	18	30	2.4 (1.2 to 4.3)
Herpes simplex	3	5	2.2 (0.6 to 8.5)	0	2	0 [1.00]	3	7	1.7 (0.4 to 6.5)
Herpes zoster	26	25	4.2 (2.5 to 7.0)	1	8	0.5 (0.1 to 4.0)	27	33	3.4 (2.0 to 5.6)
Infectious mononucleosis	1	2	2.4 (0.2 to 23.2)	0	1	0 [1.00]	1	3	1.4 (0.2 to 13.5)
Pyelonephritis	25	71	1.5 (0.9 to 2.3)	12	20	2.4 (1.3 to 4.4)	37	91	1.7 (1.1 to 2.5)
Cystitis	18	96	0.8 (0.5 to 1.3)	5	29	0.6 (0.3 to 1.6)	23	125	0.8 (0.5 to 1.2)
Sinusitis	13	16	2.9 (1.5 to 5.7)	4	10	2.2 (0.7 to 6.3)	17	26	2.7 (1.4 to 4.9)
Otitis media	10	39	1.0 (0.5 to 2.0)	7	14	1.9 (0.8 to 4.1)	17	53	1.3 (0.7 to 2.2)
Nasopharyngitis or laryngitis	6	21	1.1 (0.5 to 2.7)	1	7	0.6 (0.1 to 4.4)	7	28	1.0 (0.4 to 2.3)
Influenza	19	21	3.2 (1.8 to 5.8)	3	10	1.8 (0.54 to 5.91)	22	31	2.9 (1.7 to 5.0)
Meningitis	3	8	1.2 (0.4 to 4.3)	1	6	0.8 (0.1 to 6.6)	4	14	1.1 (0.4 to 3.4)
Pericarditis	2	20	0.4 (0.1 to 1.8)	2	7	1.0 (0.3 to 4.2)	4	27	0.6 (0.2 to 1.7)
Myocarditis	2	5	1.3 (0.3 to 6.3)	0	4	0 [1.00]	2	9	0.9 (0.2 to 4.1)
Endocarditis	3	22	0.5 (0.2 to 1.6)	0	8	0 [1.00]	3	30	0.4 (0.1 to 1.3)
Osteomyelitis	1	17	0.3 (0.0 to 1.9)	0	5	0 [1.00]	1	22	0.2 (0.0 to 1.4)
Gingivitis and periodontitis	17	58	1.1 (0.7 to 1.8)	3	23	0.6 (0.2 to 2.0)	20	81	1.0 (0.6 to 1.6)
Tonsillitis	5	18	1.2 (0.5 to 3.2)	3	4	2.2 (0.6 to 7.5)	8	22	1.4 (0.6 to 3.3)
Fasciitis	3	4	3.6 (0.8 to 16.3)	0	0	—	3	4	2.9 (0.6 to 12.8)
Empyema	2	5	2.5 (0.5 to 12.7)	0	0	—	2	5	1.7 (0.3 to 8.6)
Erysipelas (cellulitis)	22	108	0.8 (0.5 to 1.3)	12	31	1.4 (0.8 to 2.5)	34	139	1.0 (0.7 to 1.4)

* When presented in square brackets, *P* values (two-sided) that were based on Fisher exact test are given when no case patient or control subjects have the specified condition. Odds ratios (ORs) were adjusted for categorical year of birth, date of diagnosis, gender, and county. CI = confidence interval.

† Overall categories that total to less than the sum of the individual categories because some individuals have more than one infectious disease.

Personal and Family History of Allergic or Chronic Inflammatory Disease

Patients with a history of any previous allergic or chronic inflammatory conditions had an increased risk for LPL-WM (OR = 1.2, 95% CI = 1.0 to 1.4). However, no individual allergic or chronic inflammatory condition was statistically significantly associated with risk (data not shown). We also found that a family history of chronic prostatitis (OR = 4.3, 95% CI = 1.7 to 11.1) was statistically significantly associated with an increased risk of LPL-WM (data not shown).

Discussion

In this large population-based case-control study that included approximately 2500 LPL-WM case patients, more than 9000 matched control subjects, and approximately 30,000 first-degree relatives of either case patients or control subjects, we found that personal history of certain immune-related and inflammatory conditions was associated with increased risk of LPL-WM, supporting the theory that chronic immune stimulation plays a role in the pathogenesis of LPL-WM (17). Our findings that both personal and family history of Sjögren syndrome or autoimmune hemolytic anemia were statistically significantly associated with increased risk of LPL-WM are, to our knowledge, novel and indicate that there might be some shared (genetic, environmental, or both) susceptibility for these conditions.

The rarity of LPL-WM makes identification of risk factors difficult, which is reflected by limited number of published studies, which are primarily smaller studies. Recently, we assessed the risk of WM in relation to various chronic immune stimulatory conditions among 4 million US veterans and were able to identify a total of 361 patients with WM (17). We found that an increased risk of WM was associated with a personal history of autoimmune diseases with detectable levels of autoantibodies (rate ratio [RR] = 2.5, 95% CI = 1.6 to 4.0) and with hepatitis (RR = 3.4, 95% CI = 1.4 to 8.3) or HIV infections (RR = 12.1, 95% CI = 2.8 to 51.5) and rickettsiosis (RR = 3.4, 95% CI = 1.4 to 8.1) (17). Although the number of subjects was small, we found that a history of Sjögren syndrome was strongly associated with an increased risk of WM. To validate and to expand on these findings, we conducted this substantially larger study, which also includes information on first-degree relatives. In accord with our US veterans study (17), we observed that a personal history of Sjögren syndrome was strongly associated with an increased risk of LPL-WM and that a personal history of an autoimmune disease with detectable autoantibodies was also associated with an increased risk of developing LPL-WM. In contrast to our US veterans study (17), we found that a history of autoimmune disease without detectable autoantibodies was associated with an increased risk of LPL-WM (OR = 1.5, 95% CI = 1.1 to 2.1). Several specific autoimmune diseases were also associated with increased risk of LPL-WM, including polymyalgia rheumatica (OR = 2.9, 95% CI = 1.6 to 5.2) and autoimmune hemolytic anemia (OR = 24.2, 95% CI = 5.4 to 108.2). These patterns are also consistent with previous studies (16,24,25) focusing on other subtypes of non-Hodgkin lymphoma.

Interestingly, to our knowledge, for the first time, and based on small numbers, we found that a family history of Sjögren

syndrome was associated with an increased risk of developing LPL-WM (OR = 5.0, 95% CI = 2.1 to 12.0), although this result was based on small numbers of patients. Our findings are intriguing in that both personal and family history of Sjögren syndrome were independently associated with an increased risk of LPL-WM. Similarly, both personal and family history of autoimmune hemolytic anemia were independently associated with an increased risk of LPL-WM, and both personal and family history of systemic lupus erythematosus were associated with a borderline statistically significantly increased risk for LPL-WM. These findings raise the question whether there might be some shared susceptibility (genetic, environmental, or both) for the two conditions. A number of explanations have been proposed for the underlying mechanisms of the observed association between personal history of autoimmune disease and risk of lymphoma, such as the impact of systemic immune stimulation and secondary inflammation, use of immunosuppressive therapy for the autoimmune disease, and the possible influence of modifier genes (26). Finally, we found a statistically significant association with a family history of Guillain-Barré syndrome, cytomegalovirus infection, gingivitis and periodontitis, or chronic prostatitis and risk of LPL-WM. Although it is possible that some of these results are a chance finding because of multiple testing, additional studies are needed to better define the potential biological mechanisms of these associations.

We also found that a personal history of several types of bacterial and viral infections (eg, pneumonia, septicemia, herpes zoster, and influenza) was associated with an increased risk of LPL-WM, suggesting that a broad range of infectious conditions might be capable of triggering LPL-WM development. Interestingly, we found that an increasing number of pneumonias was associated with a higher risk of LPL-WM ($P_{\text{trend}} < .001$), indicative of a dose-effect association. We did not find such an association for any of the other infections under study. Because of the small numbers of subjects, we were not able to evaluate and verify the findings of a statistically significantly increased risk of WM in individuals with a history of infection with hepatitis or HIV or of rickettsiosis, which we observed in our study of US veterans (17). In that study (17), several other types of infections (such as respiratory tract, skin and soft tissue, and herpes zoster) were associated with excess risk of WM, although not statistically significantly. Furthermore, associations between personal history of various types of bacterial infections and increased risk of other plasma cell disorders have been found, including monoclonal gammopathy of undetermined significance (27,28), multiple myeloma (27,28), and various types of lymphomas (29).

An alternative explanation for the observed association between autoimmune and infectious conditions and risk of LPL-WM is that these diseases are premalignant manifestations that are caused by the immune disruption that precedes the development of LPL-WM (30). In fact, late-stage precursor disease (eg, monoclonal gammopathy of undetermined significance) might lead to decreased IgG, IgA, and IgM levels, thereby enhancing vulnerability to infectious diseases. Similarly, we recently reported (28,31) an increased risk of chronic lymphocytic leukemia and multiple myeloma among individuals with a personal history of pneumonia.

It is also possible that an association between autoimmune and infectious diseases and subsequent risk of LPL-WM might arise from the influence of undetected early-stage LPL-WM. However, given the increased risk of LPL-WM among individuals with autoimmune and infectious diseases in the 5-year period before diagnosis of LPL-WM, we do not feel that this explanation is likely. Unfortunately, the information available in our database does not allow retrieval of detailed individual clinical data that would allow us to evaluate the role of IgM monoclonal gammopathy of undetermined significance or undetected early-stage LPL-WM directly. Thus, our findings need to be verified in future studies that integrate clinical, molecular, and treatment data.

Our study had several strengths, including its large size and high-quality data from Sweden in a stable population with access to standardized universal medical health care during the entire study period. Furthermore, the use of the nationwide register-

based case-control design ruled out recall bias and ensured a population-based setting and generalizability of our findings.

Our study has several limitations including lack of clinical data, lack of information on potential confounders (although the study design ensured adjustment for sex, age, and geography), and absence of a systematic blinded validation of all LPL-WM diagnoses. Also, because of the nature of this hypothesis-generating study, one has to interpret our findings with caution because of the many immune-related conditions assessed. The use of inpatient data led to underascertainment of less severe forms of chronic immune-related conditions, reducing the power of our study. Thus, our findings may apply mainly to severe forms of immune-related conditions. However, because personal history of immune stimulatory conditions was assessed similarly among the patients with LPL-WM and control subjects, any underdiagnosis should be nondifferential and any bias should be toward the null. Because of

Appendix Table 1. Conditions analyzed in the study

Autoimmune disease	Infections	Chronic inflammation	Allergies
Autoantibodies detectable	Pneumonia	Chronic bronchitis	Allergic alveolitis
Systemic involvement	Tuberculosis	Nephrotic syndrome	Rhinitis (hay fever)
Rheumatoid arthritis	Intestinal infection	Chronic glomerulonephritis	Erythema
Systemic sclerosis	Rickettsioses	Chronic prostatitis	Urticaria
Sjögren syndrome	Syphilis	Dermatitis herpetiformis	Atopic eczema
Systemic lupus erythematosus	Gonorrhea	Pemphigus	
Polymyositis or dermatomyositis	Chlamydia	Chronic atrophic gastritis	
Collagenoses	Septicemia	Pancreatitis	
Organ involvement	Herpes simplex	Acute nephritis	
Hashimoto thyroiditis	Herpes zoster	Chronic osteoarthritis	
Graves disease	Viral hepatitis	Acute appendicitis	
Addison disease	Hepatitis A	Diverticulitis	
Pernicious anemia	Hepatitis B		
Autoimmune hemolytic anemia	Hepatitis C		
Immune thrombocytopenic purpura	Infectious mononucleosis		
Primary biliary cirrhosis	Pyelonephritis		
Discoid lupus erythematosus	Cystitis		
Localized scleroderma	Sinusitis		
Myasthenia gravis	Otitis media		
Autoimmune hepatitis	Nasopharyngitis/laryngitis		
Polyarteritis nodosa	Influenza		
Guillain-Barré syndrome	Encephalitis		
Diabetes I	Malaria		
Lupoid hepatitis	Meningitis		
Celiac disease	Lyme disease		
Wegener granulomatosis	Pericarditis		
Dressler syndrome	Myocarditis		
Chronic rheumatic heart disease	Endocarditis		
Multiple sclerosis	Osteomyelitis		
Amyotrophic lateral sclerosis	Cytomegalovirus		
Autoantibodies not detectable	Epstein-Barr virus		
Rheumatic fever	<i>Helicobacter pylori</i>		
Sarcoidosis	HIV		
Reiter disease	Gingivitis and periodontitis		
Crohn disease	Tonsillitis		
Ulcerative colitis	Fasciitis		
Ankylosing spondylitis	Empyema		
Polymyalgia rheumatica	Erysipelas (cellulitis)		
Psoriasis			
Behcet disease			
Giant cell arteritis			
Vitiligo			
Aplastic anemia			

the large study size, we were not able to validate individual medical records. An inherent limitation of our study, which includes patients who were diagnosed with LPL-WM during a 40-year study period, is that diagnostic criteria have evolved over time. However, in our large nationwide study (22) on the ascertainment and diagnostic accuracy of lymphoproliferative malignancies that were diagnosed in Sweden, we found that the diagnostic accuracy for LPL-WM was 93%.

In summary, we found that a personal history of certain autoimmune and infectious diseases was associated with an increased risk of LPL-WM. This result raises the possibility that immune-related conditions might act as triggers for LPL-WM or could represent premalignant immune disruptions that precede the development of LPL-WM. The statistically significantly increased risk of LPL-WM that was associated with both personal and family history of Sjögren syndrome and both personal and family history of autoimmune hemolytic anemia indicates these conditions share susceptibility with LPL-WM. Future studies are needed to clarify the underlying biological mechanisms of these associations.

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