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Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies

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Some autoimmune conditions are associated with increased risk of lymphoid malignancies, but information on specific malignancy subtypes is limited. From the U.S. Surveillance Epidemiology and End Results-Medicare database, we selected 44,350 lymphoid malignancy cases (≥67 years) and 122,531 population-based controls. Logistic regression was used to derive odds ratios (ORs) comparing the prevalence of autoimmune conditions in cases and controls, by lymphoid malignancy subtype, adjusted for gender, age at malignancy/selection, year of malignancy/selection, race and number of physician claims. The strongest associations observed by non-Hodgkin lymphoma (NHL) subtypes were diffuse large B-cell lymphoma with rheumatoid arthritis (OR 1.4, 95%CI 1.2–1.5) and Sjögren syndrome (2.0, 1.5–2.8); T-cell lymphoma with hemolytic anemia (9.7, 4.3–22), psoriasis (3.1, 2.5–4.0), discoid lupus erythematosus (4.4, 2.3–8.4) and celiac disease (5.0, 2.4–14.); and marginal zone lymphoma with Sjögren syndrome (6.6, 4.6–9.5), systemic lupus erythematosus (2.8, 1.7–4.7) and hemolytic anemia (7.4, 3.1–18). Hodgkin lymphoma was associated with systemic lupus erythematosus (3.5, 1.9–6.7). Multiple myeloma was associated only with pernicious anemia (1.5, 1.3–1.7). Several autoimmune conditions were associated with increased risk of lymphoid neoplasms, especially NHLs of diffuse large B-cell, marginal zone and T-cell subtypes. These results support a mechanism whereby chronic antigenic stimulation leads to lymphoid malignancy.

Key words: epidemiology; lymphoma; chronic lymphocytic leukemia; autoimmune; risk

Lymphoid malignancies are a heterogeneous group of neoplasms originating from B- and T-lymphocytes.[1] Although the etiology of lymphoid malignancies remains largely unexplained, immune deficiency is the strongest known risk factor, with human immunodeficiency virus (HIV) infection conferring a more than 20-fold increased risk of non-Hodgkin lymphoma (NHL).[2] Other factors affecting the immune system have also been postulated to increase the risk of developing lymphoid malignancies, particularly NHL.[3]

Several autoimmune conditions, including rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus have consistently been associated with NHL.[4] Although based on fewer studies celiac disease, Crohn disease, psoriasis, Hashimoto thyroiditis and autoimmune hemolytic anemia have also been associated with increased risk of NHL.[5–9] Recent etiologic investigations have focused on specific histologic subtypes of NHL, given their differing incidence patterns, clinical features, gene profiles and associations with HIV infection.[1,2,10] However, studies investigating associations between autoimmune conditions and NHL subtypes have been limited by the low prevalence of autoimmune conditions and the rarity of some NHL subtypes.[6,7,9] Hodgkin lymphoma (HL) has also been associated with several autoimmune conditions including rheumatoid arthritis,[11–14] systemic lupus erythematosus[12,15] and sarcoidosis.[12] In contrast, multiple myeloma does not appear to be strongly associated with autoimmune conditions,[16,17] except pernicious anemia.[16–19]

Identification of specific associations between autoimmune conditions and lymphoid malignancy subtypes may help identify mechanisms by which these neoplasms develop. We used data from the Surveillance Epidemiology and End Results (SEER)-Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) Study, to investigate the associations between 28 autoimmune conditions and lymphoid malignancy subtypes in 44,350 cases with lymphoid malignancies and 122,531 controls.

Material and methods

Study design

The SMAHRT Study is a population-based case-control study of hematopoietic malignancies using SEER-Medicare data.[20] The SEER cancer registry program has collected data on cancer diagnoses from multiple sites throughout the U.S. since 1973 and now covers ~25% of the U.S. population.[20] Medicare provides federally funded health insurance for ~97% of persons aged 65 years or older in the U.S. All beneficiaries are entitled to Part A coverage, which includes hospital inpatient care. Approximately 96% of participants subscribe to Part B coverage, which covers physician and outpatient services. The SEER-Medicare database contains demographic and clinical information from SEER on all newly diagnosed cancer patients through December 2002. Medicare enrollment and claims data (part A claims: 1986–2002; part B claims: 1991–2002) for all cancer patients were available through linkage with SEER, and were likewise available for a 5% random sample of Medicare beneficiaries residing in SEER areas.[20]

Subject selection and exposure ascertainment

The SMAHRT study includes cases diagnosed in SEER with a first primary hematopoietic malignancy. For the present analyses, we restricted the cases to those with a lymphoid malignancy, which we grouped into diagnostic entities according to a recently proposed hierarchical system,[21] based on the World Health Organization classification.[22] To ensure adequate sample sizes we limited our investigations for NHL to the most common subtypes including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, T-cell lymphoma, marginal zone lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma. The present study included cases diagnosed between 1993 and 2002,

Abbreviations: NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; SEER, Surveillance Epidemiology and End Results; DLBCL, diffuse large B-cell lymphoma; OR, odds ratio; CI, confidence interval.

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aged 67–99 years at diagnosis of malignancy and who had at least 12 months of Medicare coverage (Parts A and Part B and not enrolled in a health maintenance organization) prior to diagnosis. These restrictions were implemented to allow adequate ascertainment of medical conditions more than 12 months prior to malignancy diagnosis using the linked Medicare data. Cases with a Medicare diagnosis of HIV infection and those diagnosed with malignancy at autopsy or by death certificate only, were excluded.

For each included case, two controls were randomly selected from the 5% random sample of Medicare beneficiaries who were alive, free of any malignancy and had at least 12 months of prior Medicare coverage (Parts A and Part B and not enrolled in a health maintenance organization) as of July 1 in the calendar year of selection. Controls were frequency matched to all hematopoietic malignancy cases by calendar year of diagnosis, age at diagnosis in five categories (67–69, 70–74, 75–79, 80–84, 85–99 years) and gender. As for cases, controls with a Medicare diagnosis of HIV infection were excluded. A person could be selected multiple times as a control for cases in different calendar years. All SMAHRT Study controls (frequency matched to the entire group of hematopoietic malignancy cases) were included in the present investigation.

We used hospital, physician and outpatient Medicare claims to determine whether subjects had a range of specified autoimmune conditions. Primary Sjögren syndrome was defined as Sjögren syndrome in individuals with no other autoimmune conditions. Secondary Sjögren syndrome was defined as Sjögren syndrome in individuals with any of the other autoimmune conditions investigated. In assessing exposures, we required that the autoimmune condition was specified on at least one hospital claim or on at least two physician or outpatient claims at least 30 days apart, as done in prior work using SEER-Medicare data.[23] We excluded claims occurring during the 12 month period prior to case diagnosis/control selection to minimize the possibility of reverse causality (the malignancy causing the autoimmune condition) or ascertainment bias (heightened evaluation for autoimmune conditions in cases due to the work-up for the malignancy). In additional analyses, we further extended this exclusion period to 2 and 5 years before diagnosis.

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) comparing the prevalence of 28 autoimmune conditions between cases with each type of lymphoid malignancy and controls. We accommodated the fact that each case subtype was compared with the same control population, the fact that some controls later served as cases, and the repeat selection of individuals as controls, in the variance computation for the ORs (additional details available on request). All analyses were adjusted for age group at the time of diagnosis/selection (67–69, 70–74, 75–79, 80–84, 85–99 years), gender, year of diagnosis/selection (1993–1996, 1997–1999, 2000–2001, 2002), race (white, other/unknown) and as a measure of overall healthcare utilization, the number of physician claims more than 12 months prior to diagnosis/selection (according to quartiles based on controls: 0–20, 21–57, 58–127, $\geq$128). We investigated the associations with each autoimmune condition separately, without taking into consideration that subjects may have had other autoimmune conditions. Multiple autoimmune conditions were reported in 1930 (1.6%) controls and 658 (2.0%), 27 (2.3%) and 177 (1.9%) NHL, HL and multiple myeloma cases, respectively.

Since we conducted 224 separate analyses to investigate the associations between 28 autoimmune conditions and NHL, HL, multiple myeloma and 5 NHL subtypes, some associations could have appeared significant as a result of chance. Thus, although we indicate associations with a p-value <0.05 as nominally significant in the tables, we emphasize in our Results and Discussion those associations that were significant at a p-value determined by Bonferroni correction, *i.e.,* $0.05/224 = 0.0002$.

Results

The study included 44,350 cases with a lymphoid neoplasm and 122,531 control observations corresponding to 100,527 unique individuals. Although cases and controls differed with respect to gender, age at diagnosis and selection year, these differences were small in magnitude (Table I). Cases were more likely than controls to be white and to have more physician, outpatient and hospital claims (Table I).

Associations with non-Hodgkin lymphoma

Several autoimmune conditions were associated with an increased risk of NHL overall (Table II). Following adjustment for multiple comparisons, significant associations were observed for several systemic autoimmune conditions, including rheumatoid arthritis (OR 1.2), Sjögren syndrome (OR 1.9) and systemic lupus erythematosus (OR 1.5), and for autoimmune hemolytic anemia (OR 6.5), Table II.

Among NHL subtypes, most associations with autoimmune conditions were seen for DLBCL, marginal zone and T-cell NHL subtypes (Table II). Specifically, an increased risk of DLBCL was observed with rheumatoid arthritis (OR 1.4), Sjögren syndrome (OR 2.0) and autoimmune hemolytic anemia (OR 3.3). Primary and secondary Sjögren syndrome were both associated with DLBCL (ORs, 95% CIs: 2.11, 1.38–3.23 and 1.89, 1.19–3.00, respectively). The associations with rheumatoid arthritis and autoimmune hemolytic anemia remained significant when autoimmune conditions in the 5-year period prior to NHL diagnosis/selection were excluded (ORs 1.5 and 3.6, respectively) (Table III).

After Bonferroni correction cases with T-cell NHL were more likely than controls to have had autoimmune hemolytic anemia (OR 9.7), psoriasis (OR 3.1), discoid lupus erythematosus (OR 4.4) and celiac disease (OR 5.9) (Table II). These associations remained significant when the 5-year period prior to diagnosis/selection was excluded (Table III). The associations with autoimmune conditions of the skin were limited to cutaneous T-cell lymphomas. Specifically, an increased risk of cutaneous T-cell lymphomas (n = 997 cases) was observed with psoriasis (OR 5.3, 95%CI 4.1–7.0), pemphigus (OR 13, 95%CI 2.9–56) and discoid lupus erythematosus (OR 5.7, 95%CI 2.5–13). Of the cutaneous T-cell lymphomas, mycosis fungoides/Sezary syndrome (n = 373 cases) manifested strong associations with psoriasis (OR 5.7, 95%CI 4.0–8.1), pemphigus (OR 12, 95%CI 1.6–89) and discoid lupus erythematosus (OR 7.0, 95%CI 2.5–19). Noncutaneous T-cell lymphomas were not associated with psoriasis, pemphigus, or discoid lupus erythematosus (ORs 1.0–1.1). In addition, cutaneous T-cell lymphomas were not significantly associated with other autoimmune conditions of the skin, including alopecia areata, scleroderma and systemic sclerosis (data not shown). T-cell lymphomas of the small intestine (n = 576) were strongly associated with celiac disease (OR 520, 95%CI 160–1700), Crohn disease (OR 17, 95%CI 2.3–120) and ulcerative colitis (OR 22, 95%CI 5.3–94).

Marginal zone lymphoma was strongly associated with Sjögren syndrome (OR 6.6) and autoimmune hemolytic anemia (OR 7.4) (Table II). These associations remained significant when the 5-year period prior to diagnosis was excluded (Table III). Marginal zone lymphoma was also strongly associated with systemic lupus erythematosus (OR 2.8). Primary and secondary Sjögren syndrome were both strongly associated with marginal zone lymphoma (ORs, 95% CIs: 7.1, 4.4–12 and 5.9, 3.5–10, respectively). In addition, Sjögren syndrome was strongly associated with salivary gland lymphoma (OR 22, 95% CI 14–36) and specifically, salivary gland marginal zone lymphoma (OR 71, 95% CI 40–120). Finally, follicular lymphoma was not significantly associated with any autoimmune conditions after Bonferroni correction and chronic lymphocytic leukemia (including small lymphocyte lymphoma) was associated only with autoimmune hemolytic anemia (OR 8.7) (Table II).

TABLE I – CHARACTERISTICS OF CASES WITH LYMPHOID NEOPLASMS AND CONTROLS IN THE SMAHRT STUDY (1993–2002)

	Lymphoid neoplasm[1] (n = 44,350)	Controls (n = 122,531)	p-value[2]
Gender			<0.001
Male	21,547 (48.6%)	60,295 (49.2%)	
Female	22,803 (51.4%)	62,236 (50.8%)	
Age, years			<0.001
67–69	5,382 (12.1%)	13,635 (11.1%)	
70–74	11,315 (25.5%)	30,217 (24.7%)	
75–79	11,863 (26.8%)	32,550 (26.6%)	
80–84	8,880 (19.8%)	25,227 (20.6%)	
85–99	6,990 (15.8%)	20,902 (17.1%)	
Selection year			<0.001
1993–1996	12,861 (29.0%)	33,841 (27.6%)	
1997–1999	10,197 (23.0%)	26,946 (22.0%)	
2000–2001	14,297 (32.2%)	40,750 (33.3%)	
2002	6,995 (15.8%)	20,994 (17.1%)	
Race/ethnicity			<0.001
White	38,731 (87.3%)	102,520 (83.7%)	
Black	2,869 (6.5%)	8,439 (6.9%)	
Asian	997 (2.3%)	4,973 (4.1%)	
Hispanic	762 (1.7%)	3,122 (2.6%)	
Native American Indian	86 (0.2%)	343 (0.3%)	
Other/unknown	905 (2.0%)	3,134 (2.6%)	
Duration of Medicare coverage, months[3]			<0.001
12–57	10,807 (24.4%)	30,747 (25.1%)	
58–93	11,016 (24.8%)	30,804 (25.1%)	
94–136	12,134 (27.4%)	30,696 (25.1%)	
≥137	10,393 (23.4%)	30,284 (24.7%)	
Number of physician claims[4]			<0.001
0–20	10,026 (22.6%)	31,568 (25.8%)	
21–57	10,707 (24.1%)	29,802 (24.3%)	
58–127	11,531 (26.0%)	30,699 (25.1%)	
≥128	12,086 (27.3%)	30,462 (24.9%)	
Number of outpatient claims[4]			<0.001
0	8,658 (19.5%)	27,545 (22.5%)	
1–3	10,688 (24.1%)	29,975 (24.5%)	
4–7	7,805 (17.6%)	20,930 (17.1%)	
8–15	7,760 (17.5%)	20,637 (16.8%)	
≥16	9,439 (21.3%)	23,444 (19.1%)	
Number of hospital claims[4]			<0.001
0	21,025 (47.4%)	60,548 (49.4%)	
1	8,574 (19.3%)	22,545 (18.4%)	
2–3	8,412 (19.0%)	21,574 (17.6%)	
≥4	6,339 (14.3%)	17,864 (14.6%)	

[1]Lymphid neoplasm cases include patients with non-Hodgkin lymphoma (n = 33,721), Hodgkin lymphoma (n = 1,155), and multiple myeloma (n = 9,474).–[2]p-values were derived using the chi-square test.–[3]Duration of coverage refers to simultaneous coverage by Part A and Part B while the subject was not enrolled in a health maintenance organization.–[4]The number of claims excludes the 12 months prior to hematopoietic malignancy diagnosis (cases) or selection (controls).

Associations with Hodgkin lymphoma and multiple myeloma

Fewer autoimmune conditions were associated with HL and multiple myeloma after Bonferroni correction than with NHL. Specifically, HL was associated with systemic lupus erythematosus (ORs 3.5) and pernicious anemia was associated with an increased risk of multiple myeloma (OR 1.5) (Table IV). The ORs for multiple myeloma and pernicious anemia remained elevated when the 2 and 5 years before diagnosis/selection were excluded (ORs, 95% CIs: 1.4, 1.2–1.6 and 1.3, 1.0–1.6, respectively).

Discussion

In this large nested case-control study of over 44,000 lymphoid malignancy cases, we observed that several autoimmune conditions were associated with increased risk of NHL, especially the diffuse large B-cell, marginal zone and T-cell subtypes. Other NHL subtypes, HL and multiple myeloma were also associated with some autoimmune conditions. Of note, among the autoimmune conditions, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus and autoimmune hemolytic anemia were associated with multiple NHL subtypes.

Our study adds substantially to the existing body of evidence linking autoimmune conditions with the development of lymphoid malignancies.[24] By expanding previous work to systematically investigate associations between specific lymphoid malignancy subtypes and numerous autoimmune conditions, we clarified and added further evidence about associations that may help in the identification of the underlying mechanisms of lymphomagenesis. Consistent with our findings, other studies have demonstrated an increased risk of NHL overall in patients with autoimmune conditions that have major systemic manifestations, particularly rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus.[4,6–9] A recent meta-analysis reported pooled standardized incidence ratios for NHL of 3.9 in rheumatoid arthritis, 18.8 in Sjögren syndrome and 7.4 in systemic lupus erythematosus.[4] Sarcoidosis, a multi-system disorder characterized by granulomatous inflammation, has been linked with NHL in several case reports, suggesting a "sarcoidosis-lymphoma" syndrome.[25,26] In keeping with our results, Mellemkjaer *et al.*[8] reported that NHL patients were more likely than controls to have had a hospital discharge for sarcoidosis. Extending upon this prior work, our results suggest that this association is limited to the DLBCL subtype. The InterLymph consortium of NHL case-control studies also investigated

TABLE II – AUTOIMMUNE CONDITIONS AMONG PATIENTS WITH NON-HODGKIN LYMPHOMA AND MAIN NON-HODGKIN LYMPHOMA SUBTYPES

Autoimmune condition, by system	Controls (n = 122,531)	Non-Hodgkin lymphoma[1] (n = 33,721)		Diffuse large B-cell lymphoma (n = 10,144)	T-cell non-Hodgkin lymphoma (n = 1,870)	Marginal zone lymphoma (n = 1,908)	Follicular lymphoma (n = 4,491)	Chronic lymphocytic leukemia[2] (n = 9,171)
	No.	No.	OR (95% CI)[3]	OR (95% CI)[3]	OR (95% CI)[3]	OR (95% CI)[3]	OR (95% CI)[3]	OR (95% CI)[3]
Systemic/Connective Tissue								
Rheumatoid arthritis	3,289	1,157	1.2 (1.1–1.3)[4]	1.4 (1.2–1.5)[4]	1.5 (1.1–1.8)	1.2 (1.0–1.6)	1.3 (1.1–1.5)	1.1 (1.0–1.2)
Sjögren syndrome	255	142	1.9 (1.5–2.3)[4]	2.0 (1.5–2.8)[4]	0.8 (0.2–2.4)	6.6 (4.6–9.5)[4]	1.3 (0.7–2.2)	1.1 (0.7—1.7)
Systemic lupus erythematosus	285	129	1.5 (1.2–1.9)[4]	1.4 (1.0–2.0)	2.4 (1.3–4.4)	2.8 (1.7–4.7)[4]	1.0 (0.6–1.8)	1.4 (0.9–2.0)
Sarcoidosis	96	42	1.5 (1.0–2.2)	2.0 (1.2–3.3)	0.6 (0.1–4.6)	1.6 (0.5–5.0)	1.3 (0.5–3.1)	0.7 (0.3–1.8)
Systemic sclerosis	79	33	1.4 (0.9–2.2)	2.0 (1.1–3.6)	0.8 (0.1–5.8)	1.8 (0.5–5.8)	0.8 (0.3–2.7)	0.7 (0.3–1.9)
Polymyalgia rheumatica	1,244	344	0.9 (0.8–1.0)	0.9 (0.8–1.1)	1.2 (0.8–1.8)	0.7 (0.4–1.1)	0.8 (0.6–1.1)	0.8 (0.7–1.0)
Ankylosing spondylitis	128	40	1.1 (0.7–1.5)	0.9 (0.5–1.7)	0.9 (0.2–3.4)	2.2 (0.9–5.4)	0.8 (0.3–2.3)	1.1 (0.6–2.0)
Dermatomyositis/polymyositis	128	38	1.0 (0.7–1.4)	0.8 (0.4–1.5)	1.0 (0.2–3.9)	0.4 (0.1–2.7)	1.1 (0.5–2.5)	1.2 (0.7–2.2)
Blood								
Autoimmune hemolytic anemia	44	87	6.5 (4.4–9.4)[4]	3.3 (1.7–6.3)[4]	9.7 (4.3–22)[4]	7.4 (3.1–18)[4]	3.4 (1.4–8.2)	8.7 (5.5–14)[4]
Aplastic anemia	84	45	1.8 (1.3–2.7)	1.9 (1.1–3.3)	2.8 (1.0–7.8)	1.3 (0.3–5.4)	2.4 (1.1–5.2)	1.2 (0.6–2.5)
Cardiovascular								
Systemic vasculitis	25	9	1.1 (0.5–2.7)	1.3 (0.4–4.4)	4.2 (0.9–18)	–	0.9 (0.1–6.6)	1.4 (0.4–4.8)
Chronic rheumatic heart disease	3,948	1,221	1.1 (1.0–1.1)	1.1 (1.0–1.2)	1.0 (0.8–1.3)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.0 (0.9–1.1)
Giant cell arteritis	397	91	0.8 (0.6–1.0)	0.7 (0.5–1.0)	1.0 (0.4–2.2)	0.3 (0.1–1.0)	0.8 (0.4–1.3)	0.9 (0.6–1.3)
Polyarteritis nodosa	34	11	1.1 (0.5–2.2)	2.3 (1.0–5.2)	1.8 (0.2–13)	–	1.5 (0.3–6.5)	0.4 (0.1–2.7)
Endocrine								
Addison disease	185	54	1.0 (0.7–1.3)	1.3 (0.8–2.0)	0.6 (0.2–2.6)	0.5 (0.1–2.2)	0.8 (0.4–1.8)	0.7 (0.4–1.4)
Graves disease	354	91	0.9 (0.7–1.1)	1.1 (0.7–1.5)	0.5 (0.2–1.6)	1.0 (0.5–2.2)	0.6 (0.3–1.1)	0.7 (0.4–1.1)
Hashimoto thyroiditis	286	94	1.1 (0.8–1.4)	1.2 (0.8–1.7)	0.7 (0.2–2.1)	1.0 (0.4–2.2)	1.0 (0.6–1.8)	0.9 (0.6–1.4)
Skin								
Psoriasis	1,513	520	1.2 (1.0–1.3)	1.2 (1.0–1.4)	3.1 (2.5–4.0)[4]	1.3 (1.0–1.9)	1.0 (0.8–1.3)	0.8 (0.7–1.0)
Alopecia areata	97	19	0.7 (0.4–1.1)	0.7 (0.3–1.6)	1.3 (0.3–5.2)	–	0.5 (0.1–2.1)	0.6 (0.2–1.7)
Pemphigus	22	12	1.8 (0.9–3.8)	2.5 (0.9–6.6)	5.9 (1.4–25)	2.3 (0.3–17)	1.3 (0.2–10)	1.1 (0.3–5.0)
Localised scleroderma	178	48	0.9 (0.6–1.2)	0.9 (0.5–1.5)	1.9 (0.8–4.6)	0.8 (0.3–2.5)	0.6 (0.3–1.6)	0.7 (0.4–1.4)
Discoid lupus erythematosus	143	53	1.2 (0.9–1.7)	1.5 (0.9–2.4)	4.4 (2.3–8.4)[4]	1.0 (0.3–3.3)	0.7 (0.2–1.8)	0.8 (0.4–1.7)
Gastrointestinal								
Celiac disease	53	25	1.5 (0.9–2.5)	1.8 (0.9–3.7)	5.9 (2.4–14)[4]	3.5 (1.3–9.8)	–	0.9 (0.3–2.6)
Crohn disease	295	114	1.2 (1.0–1.7)	1.4 (1.0–1.9)	1.0 (0.4–2.4)	1.1 (0.5–2.4)	1.2 (0.7–2.0)	1.3 (0.9–1.9)
Ulcerative colitis	487	162	1.1 (0.9–1.3)	1.3 (1.0–1.7)	2.0 (1.2–3.3)	1.2 (0.6–2.1)	0.8 (0.5–1.3)	0.8 (0.5–1.1)
Pernicious anemia	1,935	565	1.0 (0.9–1.1)	1.0 (0.8–1.2)	1.0 (0.7–1.4)	1.4 (1.0–1.8)	0.7 (0.5—0.9)	1.1 (0.9–1.3)
Nervous system								
Multiple sclerosis	173	31	0.6 (0.4–0.9)	0.4 (0.2–0.9)	0.4 (0.1–2.5)	0.3 (0.1–2.3)	0.3 (0.1–1.0)	1.1 (0.6–1.8)
Myasthenia gravis	109	21	0.7 (0.4–1.1)	0.6 (0.3–1.5)	0.6 (0.1–4.0)	1.6 (0.5–5.1)	0.3 (0.0–1.9)	0.8 (0.4–1.7)

Associations significant at the $p < 0.05$ level are underlined.

[1]Non-Hodgkin lymphoma cases include cases with diffuse large B-cell lymphoma (n = 10,144), T-cell lymphoma (n = 1,870), follicular lymphoma (n = 4,491), marginal zone lymphoma (n = 1,908), chronic lymphocytic leukemia/ small lymphocytic lymphoma (n = 9,171), B-cell NHL not otherwise specified (n = 1,667), Burkitt lymphoma (n = 197), hairy cell leukemia (n = 317), lymphoplasmacytic lymphoma (n = 1,148), NHL not otherwise specified (n = 1,809), and mantel cell lymphoma (n = 999).–[2]Includes small lymphocytic lymphoma.–[3]Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (67–69, 70–74, 75–79, 80–84 and 85–99 years), gender, selection year (1993–1996, 1997–1999, 2000–2001, 2002), race (white, non-white), and number of physician claims (0–20, 21–57, 58–127, ≥128).–[4]Associations significant at $p < 0.0002$ (Bonferroni correction for 224 comparisons).

TABLE III – ASSOCIATIONS BETWEEN SELECTED AUTOIMMUNE CONDITIONS AND HISTOLOGIC SUBTYPES OF NON-HODGKIN LYMPHOMA (NHL), WITH EXCLUSIONS OF TIME INTERVALS PRIOR TO DIAGNOSIS/SELECTION

NHL subtype and autoimmune condition	Excluded time interval prior to NHL diagnosis/control selection		
	1 year excluded	2 years excluded	5 years excluded
	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Diffuse large B-cell lymphoma			
Rheumatoid arthritis	1.4 (1.2–1.5)	1.4 (1.2–1.6)	1.5 (1.3–1.8)
Sjögren syndrome	2.0 (1.5–2.8)	2.1 (1.5–3.0)	1.6 (0.9–2.7)
Systemic lupus erythematosus	1.4 (1.0–2.0)	1.5 (1.0–2.2)	1.6 (1.0–2.7)
Sarcoidosis	2.0 (1.2–3.3)	1.7 (0.9–3.1)	1.7 (0.7–3.9)
Systemic sclerosis	2.0 (1.1–3.6)	1.7 (0.9–3.3)	1.7 (0.8–3.9)
Autoimmune hemolytic anemia	3.3 (1.7–6.3)	2.6 (1.2–6.0)	3.6 (1.2–10)
Aplastic anemia	1.9 (1.1–3.3)	2.0 (1.0–3.7)	1.1 (0.3–3.5)
Multiple sclerosis	0.4 (0.2–0.9)	0.5 (0.2–1.0)	0.3 (0.1–1.1)
T-cell non-Hodgkin lymphoma			
Rheumatoid arthritis	1.5 (1.1–1.8)	1.3 (1.0–1.7)	1.6 (1.1–2.2)
Systemic lupus erythematosus	2.4 (1.3–4.4)	2.0 (1.0–4.1)	2.5 (1.0–6.2)
Autoimmune hemolytic anemia	9.7 (4.3–22)	13 (5.6–30)	21 (7.4–61)
Aplastic anemia	2.8 (1.0–7.8)	1.9 (0.5–7.6)	3.9 (0.9–16)
Psoriasis	3.1 (2.5–4.0)	2.8 (2.2–3.7)	2.8 (1.9–4.0)
Pemphigus	5.9 (1.4–25)	4.0 (0.5–30)	9.1 (1.2–68)
Discoid lupus erythematosus	4.4 (2.3–8.4)	3.4 (1.6–7.3)	4.6 (1.9–12)
Celiac disease	5.9 (2.4–14)	8.0 (3.2–20)	7.0 (1.8–26)
Ulcerative colitis	2.0 (1.2–3.3)	1.9 (1.1–3.4)	1.5 (0.6–3.6)
Follicular lymphoma			
Rheumatoid arthritis	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.4 (1.1–1.8)
Autoimmune hemolytic anemia	3.4 (1.4–8.2)	3.7 (1.4–9.7)	4.9 (1.3–19)
Aplastic anemia	2.4 (1.1–5.2)	1.8 (0.7–5.1)	1.0 (0.1–7.2)
Marginal zone lymphoma			
Sjögren syndrome	6.6 (4.6–9.5)	5.3 (3.5–8.2)	6.7 (3.9–11)
Systemic lupus erythematosus	2.8 (1.7–4.7)	2.9 (1.7–4.9)	1.5 (0.6–4.1)
Autoimmune hemolytic anemia	7.4 (3.1–17)	4.8 (1.4–16)	6.3 (1.4–29)
Celiac disease	3.5 (1.3–9.8)	3.7 (1.1–12)	2.3 (0.3–18)
Pernicious anemia	1.4 (1.0–1.8)	1.3 (1.0–1.8)	0.9 (0.5–1.5)
Chronic lymphocytic leukemia[2]			
Autoimmune hemolytic anemia	8.7 (5.5–13)	9.5 (5.7–16)	9.6 (4.4–21)

Associations significant at the $p < 0.05$ level are underlined.

[1]Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (67–69, 70–74, 75–79, 80–84 and 85–99 years), gender, selection year (1993–1996, 1997–1999, 2000–2001, 2002), race (white, non-white), and number of physician claims (0–20, 21–57, 58–127, ≥128).–[2]Includes small lymphocytic lymphoma.

autoimmune conditions and risk of several NHL subtypes.[7] They also observed an increased prevalence of Sjögren syndrome and systemic lupus erythematosus in patients with DLBCL and marginal zone lymphoma.[7] In contrast to the InterLymph study, we did not confirm an association between follicular lymphoma and Sjögren syndrome, but found T-cell NHL to be associated with rheumatoid arthritis and systemic lupus erythematosus.

Evidence is accumulating that the chronic inflammatory response caused by autoimmune conditions is responsible for an increased risk for defined lymphoma subtypes.[27–29] In patients with autoimmune conditions, dysregulation and hyperreactivity of B-cells, as well as impairment of T-cell control, may lead to the development of B-cell NHLs.[30] We observed that aggressive B-cell neoplasms, particularly DLBCL, were more frequently associated with autoimmune conditions than were more indolent lymphomas, such as chronic lymphocytic leukemia and follicular lymphoma. The aggressive NHL subtypes are thought to derive from normal lymphocytes at a stage of development at, or after, the germinal center stage, when lymphocytes typically encounter antigen. Systemic autoimmune conditions, which cause widespread antigen-driven chronic inflammation, may induce NHL and increase risk of several NHL subtypes as seen for rheumatoid arthritis and systemic lupus erythematosus. Additionally, immunosuppressive medications (*e.g.,* methotrexate for rheumatoid arthritis) may cause reactivation of Epstein Barr virus (EBV) which can lead to the development of lymphoma. These EBV-positive DLBCLs resemble post-transplant lymphomas,[31] although some recent studies cast doubt about this hypothesis.[24,32] More localized antigen-driven chronic inflammation, as seen in the salivary gland of patients with Sjögren syndrome, could explain the strong association observed between Sjögren syndrome and marginal zone lymphoma of the salivary gland in this and other studies.[6,7,9] Likewise, celiac disease which causes inflammation of the small intestine,[33] was associated with a 520-fold increased risk of T-cell lymphomas of the small intestine in our study, similar to previous reports.[6,34] In addition, we found that autoimmune conditions of the skin, including psoriasis, pemphigus and discoid lupus erythematosus, were related to increased risk of cutaneous T-cell lymphomas. Although our results on pemphigus and discoid lupus erythematosus are novel, the association between psoriasis and T-cell NHL has been documented previously.[7,35–37]

We also found that autoimmune hemolytic anemia was strongly associated with increased risk of NHL, including all major subtypes. This observation agrees with results from previous epidemiological studies[5,7,8,38] and a recent review of case-reports.[39] Autoimmune hemolytic anemia may occur as a complication of NHL and has been reported to occur "spontaneously" or as a result of treatment in patients with chronic lymphocytic leukemia.[40] Since autoimmune hemolytic anemia can arise after the lymphoma,[39] epidemiologic associations have been attributed to reverse causality, *i.e.,* that the neoplasm causes autoimmune hemolytic anemia. However, we observed strong associations between autoimmune hemolytic anemia and lymphoid neoplasms, even when a 5-year period before lymphoma diagnosis was excluded, suggesting that other mechanisms could be involved. For example, autoimmune hemolytic anemia and NHL could share a similar genetic predisposition. In support of this possibility, patients with autoimmune lymphoproliferative syndrome, an

TABLE IV – AUTOIMMUNE CONDITIONS REPORTED MORE THAN ONE YEAR PRIOR TO DIAGNOSIS AND RISK OF HODGKIN LYMPHOMA AND MULTIPLE MYELOMA

Autoimmune condition, by system	Controls (n = 122,531)	Hodgkin lymphoma (n = 1,155)		Multiple myeloma (n = 9,474)	
	No.	No.	OR (95% CI)[1]	No.	OR (95% CI)[1]
Systemic/Connective Tissue					
Rheumatoid arthritis	3,289	45	1.5 (1.1–2.0)	263	1.0 (0.9–1.1)
Sjögren syndrome	255	<5	1.6 (0.6–4.4)	22	1.1 (0.7–1.7)
Systemic lupus erythematosus	285	10	3.5 (1.9–6.7)[2]	18	0.8 (0.5–1.2)
Sarcoidosis	96	<5	3.1 (1.0–10)	11	1.4 (0.7–2.6)
Systemic sclerosis	79	<5	2.5 (0.6–10)	8	1.2 (0.6–2.6)
Polymyalgia rheumatica	1,244	15	1.3 (0.8–2.2)	99	1.0 (0.8–1.3)
Ankylosing spondylitis	128	0	–	10	1.0 (0.5–1.9)
Dermatomyositis/polymyositis	128	<5	1.6 (0.4–6.6)	7	0.7 (0.3–1.5)
Blood					
Autoimmune hemolytic anemia	44	0	–	7	1.9 (0.9–4.4)
Aplastic anemia	84	<5	1.4 (0.2–9.5)	9	1.3 (0.6–2.5)
Cardiovascular					
Systemic vasculitis	25	0	–	<5	1.4 (0.4–4.8)
Chronic rheumatic heart disease	3,948	35	1.0 (0.7–1.4)	342	1.1 (1.0–1.2)
Giant cell arteritis	397	<5	0.3 (0.0–1.9)	37	1.2 (0.8–1.7)
Polyarteritis nodosa	34	0	–	<5	0.7 (0.2–3.1)
Endocrine					
Addison disease	185	<5	1.7 (0.5–5.3)	14	0.9 (0.5–1.6)
Graves disease	354	<5	0.6 (0.2–2.4)	31	1.1 (0.8–1.6)
Hashimoto thyroiditis	286	6	2.1 (1.0–4.8)	25	1.1 (0.8–1.7)
Skin					
Psoriasis	1,513	15	1.0 (0.6–1.7)	113	0.9 (0.8–1.2)
Alopecia areata	97	<5	1.1 (0.2–7.9)	10	1.2 (0.6–2.3)
Pemphigus	22	0	–	0	–
Localised scleroderma	178	5	2.9 (1.2–7.2)	9	0.7 (0.3–1.3)
Discoid lupus erythematosus	143	<5	2.9 (1.1–8.0)	9	0.8 (0.4–1.5)
Gastrointestinal					
Celiac disease	53	0	–	<5	1.0 (0.4–2.8)
Crohn disease	295	<5	1.0 (0.3–3.1)	26	1.1 (0.7–1.7)
Ulcerative colitis	487	<5	0.6 (0.2–2.0)	46	1.2 (0.9–1.6)
Pernicious anemia	1,935	11	0.6 (0.3–1.1)	222	1.5 (1.3–1.7)[2]
Nervous system					
Multiple sclerosis	173	<5	1.1 (0.3–4.4)	8	0.6 (0.3–1.2)
Myasthenia gravis	109	<5	1.0 (0.1–7.3)	9	1.1 (0.5–2.1)

Observations where the number of exposed cases or controls is between 1 and 4 are listed as "<5" to preserve subjects' anonymity, in accordance with the SEER-Medicare data use agreement.

Associations significant at the $p < 0.05$ level are underlined.

[1]Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (67–69, 70–74, 75–79, 80–84 and 85–99 years), gender, selection year (1993–1996, 1997–1999, 2000–2001, 2002), race (white, non-white), and number of physician claims (0–20, 21–57, 58–127, ≥128).–[2]Associations significant at $p < 0.0002$ (Bonferroni correction for 224 comparisons).

inherited disorder due to mutations in the *Fas* gene, frequently develop both autoimmune hemolytic anemia and NHL.[41]

Associations with autoimmune conditions were also apparent for HL. The strongest association was with systemic lupus erythematosus. These results are supported by a large study which utilized linked registry data in Scandinavia.[12] In addition, a pooled analysis of cohort studies of systemic lupus erythematosus also reported a 3-fold increased risk of HL.[42] HL has previously been reported in patients with scleroderma.[43,44] These associations may be explained by similar mechanisms to those described above for NHL, *e.g.,* EBV reactivation related to use of methotrexate or other immunomodulatory medications.[45]

For multiple myeloma, increased risk was seen only with pernicious anemia, an inflammatory condition in the stomach leading to vitamin B12 deficiency. This association was also demonstrated in two other large studies, which found few other autoimmune conditions associated with multiple myeloma.[16,17] Because of the lack of association with other autoimmune conditions, our finding may point towards the involvement of vitamin B12 deficiency. Indeed, vitamin B12 deficiency has been reported in patients with multiple myeloma and in patients with the precursor condition, monoclonal gammopathy of undetermined significance.[16–19,46] Although multiple myeloma may cause vitamin B12 deficiency by consuming stored vitamin B12,[47] we speculate that vitamin B12 deficiency could promote the development of multiple myeloma by causing derangement of one-carbon metabolism, as proposed in other cancers.[48]

Major strengths of our study include its large sample size, population-based sampling of cases and detailed data from SEER, which allowed us to evaluate defined subtypes of lymphoid malignancy. The Medicare claims files enabled the identification of numerous autoimmune conditions. By including inpatient, physician and outpatient clinic diagnoses of autoimmune conditions, we sought to capture a broad spectrum of autoimmune disease severity. This approach may explain why some associations (for example, associations between NHL and rheumatoid arthritis, Sjögren syndrome and systemic lupus erythematosus) were weaker than in previous studies, which included only hospitalized patients.[4,8] Along these lines, severity of autoimmune conditions could influence lymphoma risk through the degree of chronic immune stimulation or the likelihood of the use of immune-modulating therapies.[28] By including cases with a range of disease severity our results may reflect the overall associations of these autoimmune conditions with the subsequent development of malignancy.

Nonetheless, several limitations should be highlighted. The SMAHRT Study includes only individuals aged over 67 years which limits the generalizability of our findings, although our findings should be generalizable to the elderly population. Since claims files, and not clinical data, were utilized to determine diagnoses, it is possible that individuals were incorrectly categorized as having an autoimmune condition potentially biasing our findings. To reduce misclassification, we categorized individuals as having an autoimmune condition only if they had a hospital diag-

nosis, shown to be highly accurate,[20] or at least two physician or outpatient claims at least 30 days apart. In addition, certain autoimmune conditions, particularly those requiring limited medical attention, may have been underascertained, reducing our ability to detect associations. As noted above, our results could have been partly influenced by reverse causality, *i.e*. that autoimmune conditions were caused by the malignancy. For this reason, we conducted additional analyses excluding data for up to 5 years before the diagnosis of malignancy. Notably, several associations persisted, suggesting that reverse causality was not a likely explanation for all the findings. The large number of comparisons could have led to some chance associations. However, many of the associations of particular interest remained significant following Bonferroni correction (Tables II and IV), while others were consistent with prior reports. Finally, associations with malignancy may differ according to clinical features or treatment of the autoimmune condition, but we did not have this information available.

In conclusion, several autoimmune conditions, especially those associated with systemic manifestations, were associated with NHL, and there were differences in the associations with specific NHL subtypes. Aggressive B-cell neoplasms, particularly DLBCL, were more frequently associated with autoimmune conditions than more indolent lymphomas. While HL was associated with several autoimmune conditions, multiple myeloma was only associated with pernicious anemia. Notable site-specific associations (*i.e*., Sjögren syndrome with salivary gland NHL, autoimmune conditions of the skin with cutaneous T-cell lymphomas and celiac disease with small intestine NHL) suggest that a localized inflammatory response is involved in the development of these lymphomas. Other biological differences among autoimmune conditions could explain some of the associations with specific lymphoma subtypes. Gaining further insight into the mechanisms underlying the associations between specific autoimmune conditions and lymphoid malignancy subtypes will advance our understanding of the etiology of these malignancies and may lead to preventative strategies.

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