Autoimmune and Chronic Inflammatory Disorders and Risk of Non-Hodgkin Lymphoma by Subtype

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Background: **Some autoimmune and chronic inflammatory disorders are associated with increased risks of non-Hodgkin lymphoma (NHL). Because different NHL subtypes develop at different stages of lymphocyte differentiation, associations of autoimmune and inflammatory disorders with specific NHL subtypes could lead to a better understanding of lymphomagenic mechanisms.** ***Methods:*** **In a population-based case–control study in Denmark and Sweden, 3055 NHL patients and 3187 matched control subjects were asked about their history of autoimmune and chronic inflammatory disorders, markers of severity, and treatment. Logistic regression with adjustment for study matching factors was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for NHL overall and for NHL subtypes.** ***Results:*** **Risks of all NHL were increased in association with rheumatoid arthritis (OR = 1.5, 95% CI = 1.1 to 1.9), primary Sjögren syndrome (OR = 6.1, 95% CI = 1.4 to 27), systemic lupus erythematosus (OR = 4.6, 95% CI = 1.0 to 22), and celiac disease (OR = 2.1, 95% CI = 1.0 to 4.8). All of these conditions were also associated with diffuse large B-cell lymphoma, and some were associated with marginal zone, lymphoplasmacytic, or T-cell lymphoma. Ever use of nonsteroidal anti-inflammatory drugs, systemic corticosteroids, and selected immunosuppressants was associated with risk of NHL in rheumatoid arthritis patients but not in subjects without rheumatoid arthritis. Also, multivariable adjustment for treatment had little impact on risk estimates. Psoriasis, sarcoidosis, and inflammatory bowel disorders were not associated with increased risk of NHL overall or of any NHL subtype.** ***Conclusions:*** **Our results confirm the associations between certain autoimmune disorders and risk of NHL and suggest that the associations may not be general but rather mediated through specific NHL subtypes. These NHL subtypes develop during postantigen exposure stages of lymphocyte differentiation, consistent with a role of antigenic drive in autoimmunity-related lymphomagenesis. [J Natl Cancer Inst 2006;98:51–60]**

Despite extensive research efforts in recent years, the causes of non-Hodgkin lymphoma (NHL) are still poorly understood *(1)*. The few known risk factors include some autoimmune disorders and chronic inflammatory conditions *(1,2)*. Rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, celiac disease, dermatitis herpetiformis, and chronic thyroiditis *(2–7)* have all been consistently linked with increased risks of NHL overall. Other autoimmune and/or inflammatory conditions that are occasionally but not invariably associated with increased risks of NHL include diabetes mellitus *(8,9)*, psoriasis *(10)*, sarcoidosis *(11)*, inflammatory bowel disorders (including Crohn disease and ulcerative colitis) *(12,13)*, systemic sclerosis *(14)*, and Wegener granulomatosis *(15)*.

One reason for the inconsistent associations of many autoimmune and chronic inflammation conditions with overall NHL risk may be variations in the composition of the NHL subtypes studied. Indeed, there is increasing awareness that the lymphoproliferative malignancies that are jointly referred to as NHL are heterogeneous, differing not only in clinical and morphologic appearance but also in their etiology *(1)*. Nevertheless, few systematic assessments of risk for NHL subtypes in association with autoimmune and chronic inflammatory disorders have been reported. Case reports and case series have described a possibly increased proportion of diffuse large B-cell lymphoma in patients with rheumatoid arthritis *(16,17)*, of parotid gland mucosa-associated lymphoid tissue (MALT) lymphoma in patients with Sjögren syndrome (primary and secondary) *(18–20)*, and of intestinal T-cell lymphoma in patients with celiac disease *(21,22)*. These reports, however, offer little information on risks for these NHL subtypes, let alone risks for other subtypes.

In addition, the biologic mechanisms that may underlie the association between autoimmune conditions and NHL are largely unknown. For rheumatoid arthritis, recent data suggest an association between disease severity and NHL risk, but whether this association is related to high inflammatory activity, treatment, and/or Epstein-Barr virus activation *(23–26)* is unclear because few studies have tried to separate these interrelated factors.

A uniform assessment of risk by NHL subtype in autoimmune and chronic inflammatory disorders may provide a better understanding of the specificity of the association between each condition and NHL risk. As NHL subtypes develop from different stages of lymphocyte differentiation, specific associations with

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subtypes may give clues to mechanisms of lymphomagenesis in these disorders. Assessments of risk stratified by autoimmune disease phenotype and treatment may also provide insight into the biologic mechanisms that underlie the associations between autoimmunity, inflammation, and immunosuppressive therapy and NHL. To develop estimates of these risks, we assessed several autoimmune and chronic inflammatory disorders in relation to risks of NHL overall, risks of major NHL subtypes, and anatomic locations of tumors in a large population-based case–control study in Denmark and Sweden.

Subjects and Methods

Study Subjects

The Scandinavian Lymphoma Etiology (SCALE) study is a population-based case–control study of residents of Denmark and Sweden who were aged 18 to 74 years old at enrollment (June 2000 through August 2002 in Denmark and October 1999 through April 2002 in Sweden) *(27)*. The study population was restricted to individuals with sufficient knowledge of the Danish or Swedish language to participate in a telephone interview and without a history of organ transplantation, human immunodeficiency virus infection, or previous hematopoietic malignancies. Patients with a first, newly diagnosed NHL, including chronic lymphocytic leukemia (CLL), were identified through a rapid case ascertainment network that included 157 hospital clinics in both countries with backup from nationwide tumor registries. Control subjects were randomly sampled from updated population registries every 6 months during the study period and were frequency matched on sex and age (in 10-year intervals) to the expected distribution of NHL case patients in each country. The participation rates were 81% among eligible case patients and 71% among control subjects. The median time from diagnosis to interview among NHL patients was 2.9 months (range = 0 to 40 months). The main reasons for nonparticipation were, among case patients, early death (n = 279 or 6%) and, among control subjects, unwillingness to participate (n = 718 or 16%). The study was approved by regional ethics committees in both countries. Informed consent (oral or written) was obtained from each participant before interview.

Uniform review of tumor material according to the World Health Organization (WHO) classification *(28)* was performed within the national lymphoma registry organization (LYFO) in Denmark and by six specially appointed expert hematopathologists or cytologists in Sweden *(27)*. Information on anatomic location of the lymphoma was obtained through LYFO (Denmark) and regional lymphoma registries (Sweden).

Exposure Measurements

Participants were interviewed by telephone regarding their medical history, history of medication use, and other possible risk factors for malignant lymphomas. Specific questions assessed medically confirmed diagnoses of rheumatoid arthritis, Sjögren syndrome (primary or secondary), systemic lupus erythematosus, celiac disease, Crohn disease, ulcerative colitis, diabetes mellitus, psoriasis, and sarcoidosis. When a participant reported such a disorder, specific subsets of questions followed. Patients with all conditions except for diabetes mellitus were asked about age at start of symptoms. (Age at start of symptoms was chosen for calculation of disease duration because most of the conditions we studied may go undiagnosed for many years.) Patients with rheumatoid arthritis were asked about daily treatment with medical drugs lasting more than 4 weeks (ever/never and age at initiation), surgery (ever/never), and degree of restraint of daily activities due to their condition (from 1 to 5, with 5 representing “a lot”). Patients with celiac disease were asked about age at initiation of a gluten-free diet and degree of dietary compliance (complete or partial). Patients with diabetes mellitus were asked about type (I/II), age at diagnosis, and treatment (tablets/insulin/both); type I diabetes was defined as report of type I, age 30 years or younger at diagnosis, and treatment with insulin only. Patients with psoriasis were asked about psoriatic arthritis (ever/never). Patients with inflammatory bowel disorders were asked about surgical treatment (ever/never). If a participant reported having two normally incompatible disorders affecting similar organs (e.g., rheumatoid arthritis and systemic lupus erythematosus), the patient was classified as having the disease reported last in the questionnaire. Data on hospital discharges listing rheumatoid arthritis, systemic lupus erythematosus, celiac disease, and psoriasis were obtained from nationwide population-based hospital discharge registries in each country *(29,30)*.

Control subjects and patients with all disorders except diabetes, celiac disease, and inflammatory bowel disorders were also asked about treatment with systemic corticosteroids and/or immunosuppressive drugs (ever/never, age at treatment initiation, and total duration of treatment). Immunosuppressive therapy was defined in each question as exposure to any of the following drugs: azathioprine, cyclosporine, methotrexate, cyclophosphamide, and chlorambucil, with mention of all trademark names currently or historically used in Denmark or Sweden. These drugs were selected because of their immunosuppressive properties and their previously reported associations with cancer *(2)*. In addition, participants were asked about treatments with systemic corticosteroids or cytostatic/immunosuppressive drugs (oral or intravenous) for any disorder other than those already reported. The questions about systemic corticosteroids and immunosuppressive treatment for any disorder were added a few months after study start, and answers were provided by approximately 80% of case patients and control subjects. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) was assessed among all study participants (ever/never use of >5 tablets/month during 1 year and total duration). The overall associations between NSAID and corticosteroid therapy and NHL risk in this study population have been reported elsewhere *(31)*.

Statistical Analyses

We used unconditional logistic regression to estimate odds ratios (ORs) as measures of relative risk. The regression model included adjustment for the matching variables age (in 5-year intervals), sex, and country. Odds ratios were not calculated if there were fewer than five exposed subjects. A reported diagnosis of any disorder was excluded if symptoms began less than 2 years before lymphoma diagnosis (or interview, for control subjects) to avoid inclusion of autoimmune phenomena due to incipient lymphoma *(2)*. Similarly, in the stratified analysis of treatment (Table 4), therapy initiated less than 2 years before lymphoma diagnosis or interview was disregarded. Additional adjustment for tobacco smoking, educational level, body mass index, blood transfusions, sun exposure habits, occupational exposure to pesticides or solvents, and family history of cancer resulted in only marginal changes in odds ratios, and such adjustments were therefore not included in the final model. Likewise, adjustment for treatment resulted in odds ratio changes of 6% or less, and such adjustment was therefore also excluded. Heterogeneity of associations by sex or age (<60 years or ≥60 years) was evaluated using a likelihood ratio test for the significance of an interaction term between each autoimmune disorder and either sex or age. The age cutoff was chosen to create two equally large age groups among the control subjects (i.e., the median age in the control subjects was 59 years). Differences in disease duration between case patients and control subjects were tested with the Wilcoxon rank sum test. Tests for linear trend in duration of medication use were conducted with medication use coded as an ordinal variable, with values at the median of each category. The population-attributable fraction for four disorders (rheumatoid arthritis, primary Sjögren syndrome, systemic lupus erythematosus, and celiac disease) was calculated with the formula $1 - \Sigma_i \Sigma_j P_{ij}/RR_{ij}$, where P is the proportion of case patients in each stratum of adjustment factors (j) and exposure levels (i) and RR is the relative risk (odds ratio) obtained from the regression model *(32)*. All statistical tests were two-sided. Analyses were performed using SAS System software, release 8.2 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of participants are shown in Table 1. Only NHL subtypes with more than 100 cases are presented (Table 1). The association between specific autoimmune disorders and

Table 1. General characteristics and self-reported autoimmune or chronic inflammatory disorders of participants in the Scandinavian Lymphoma Etiology (SCALE) study according to non-Hodgkin lymphoma (NHL) status*

Characteristic/ disorder	NHL-free control subjects (n = 3187)	All NHL patients (n = 3055)	Diffuse large B-cell (n = 796)	CLL† (n = 752)	Follicular (n = 586)	T-cell (n = 204)	Mantle cell (n = 148)	Marginal zones (n = 117)	Lymphoplasmacytic (n = 116)
Age, y									
18–24	123 (4)	35 (1)	12 (1)	0	5 (1)	11 (5)	0	0	0
25–34	189 (6)	89 (3)	38 (5)	4 (0.5)	14 (2)	18 (9)	1	3 (3)	1 (1)
35–44	264 (8)	210 (7)	81 (10)	17 (2)	54 (9)	28 (13)	3 (3)	5 (3)	3 (2)
45–54	597 (19)	588 (18)	143 (17)	138 (16)	141 (24)	38 (19)	26 (17)	22 (20)	16 (14)
55–64	906 (28)	1011 (33)	247 (31)	257 (34)	206 (36)	54 (27)	52 (34)	41 (34)	48 (38)
65–74	1108 (35)	1122 (38)	275 (36)	336 (47)	166 (29)	55 (27)	66 (47)	46 (40)	48 (46)
Median (range)	59 (18–76)	60 (18–74)	60 (19–74)	63 (30–74)	58 (22–74)	55 (18–74)	63 (34–74)	62 (26–74)	62 (28–74)
Sex									
Male	1767 (55)	1819 (60)	474 (60)	480 (64)	279 (48)	128 (63)	112 (76)	57 (49)	75 (65)
Female	1420 (45)	1236 (40)	322 (40)	272 (36)	307 (52)	76 (37)	36 (24)	60 (51)	41 (35)
Country of residence									
Denmark	1186 (37)	1075 (35)	283 (36)	296 (39)	222 (38)	77 (38)	54 (36)	49 (42)	50 (43)
Sweden	2001 (63)	1980 (65)	513 (64)	456 (61)	364 (62)	127 (62)	94 (64)	68 (58)	66 (57)
Rheumatoid arthritis									
No	3073 (97)	2905 (96)	753 (95)	714 (96)	563 (97)	194 (96)	142 (97)	110 (96)	106 (93)
Yes	89 (3)	126 (4)	39 (5)	32 (4)	17 (3)	9 (4)	5 (3)	5 (4)	8 (7)
Primary Sjögren syndrome									
No	3174 (99.94)	3023 (99.6)	782 (99.4)	748 (99.9)	581 (99.7)	204 (100)	148 (100)	111 (97.4)	114 (99.1)
Yes	2 (0.06)	12 (0.4)	5 (0.6)	1 (0.1)	2 (0.3)	0	0	3 (2.6)	1 (0.9)
Systemic lupus erythematosus									
No	3174 (99.94)	3040 (99.74)	790 (99.62)	750 (99.87)	584 (99.83)	203 (100)	148 (100)	114 (98.3)	115 (99.14)
Yes	2 (0.06)	8 (0.26)	3 (0.38)	1 (0.13)	1 (0.17)	0	0	2 (1.7)	1 (0.86)
Celiac disease									
No	3166 (99.7)	3024 (99.3)	788 (99.2)	750 (99.9)	584 (99.8)	193 (96)	146 (99.3)	117 (100)	114 (99.1)
Yes	9 (0.3)	19 (0.7)	6 (0.8)	1 (0.1)	1 (0.2)	8 (4)	1 (0.7)	0	1 (0.9)
Crohn disease									
No	3168 (99.8)	3036 (99.7)	791 (99.5)	748 (99.7)	582 (99.8)	203 (99.5)	148 (100)	115 (100)	115 (100)
Yes	6 (0.2)	9 (0.3)	4 (0.5)	2 (0.3)	1 (0.2)	1 (0.5)	0	0	0
Ulcerative colitis									
No	3156 (99.4)	3024 (99.3)	789 (99.2)	745 (99.3)	581 (99.7)	202 (99)	146 (98.6)	115 (100)	116 (100)
Yes	19 (0.6)	22 (0.7)	6 (0.8)	5 (0.7)	2 (0.3)	2 (1)	2 (1.4)	0	0
Type I diabetes									
No	3131 (99.7)	2993 (99.5)	784 (99.6)	730 (99)	574 (100)	200 (100)	145 (98.6)	115 (99.1)	114 (99.1)
Yes	9 (0.3)	14 (0.5)	3 (0.4)	7 (1)	0 (0)	0 (0)	2 (1.4)	1 (0.9)	1 (0.9)
Sarcoidosis									
No	3170 (99.6)	3040 (99.8)	794 (100)	750 (99.7)	582 (99.7)	202 (100)	148 (100)	116 (100)	115 (99.1)
Yes	12 (0.4)	6 (0.2)	0 (0)	2 (0.3)	2 (0.3)	0 (0)	0	0 (0)	1 (0.9)
Psoriasis									
No	3002 (95)	2851 (94)	743 (94)	700 (94)	554 (96)	188 (93)	136 (94)	108 (96)	110 (96)
Yes	153 (5)	172 (6)	50 (6)	45 (6)	25 (4)	13 (7)	8 (6)	5 (4)	5 (4)

*All data are given as n (%) except where indicated.

†CLL = chronic lymphocytic leukemia. This group also includes small lymphocytic lymphoma.

NHL risk did not vary statistically significantly by sex or age (defined as less than 60 years of age or 60 years and above) for all disorders for which differences by sex and age could be examined (data not shown); thus, the results are presented for all participants together. Heterogeneity of risk associations by sex was not possible to evaluate for primary Sjögren syndrome or systemic lupus erythematosus because there were few or no exposed males.

Rheumatoid Arthritis

One hundred and twenty-six case patients and 89 control subjects (60% of whom were women) reported a previous diagnosis of rheumatoid arthritis. Median disease duration was 17 years among case patients (range = 2 to 59 years) and 18 years among control subjects (range = 2 to 67 years) (P = .10). A previous diagnosis of rheumatoid arthritis was associated with a statistically significant 50% increased relative risk of NHL overall (OR = 1.5; 95% confidence interval [CI] = 1.1 to 1.9; Table 2); when NHL subtypes were examined, statistically significantly increased risks for diffuse large B-cell and lymphoplasmacytic lymphoma were observed (Table 2). Rheumatoid arthritis patients had increased risks of both extranodal NHL (OR = 1.7, 95% CI = 1.1 to 2.5; n = 36) and nodal NHL (OR = 1.4, 95% CI = 1.0 to 1.9; n = 84; information on anatomic location was missing for six patients). The anatomic locations of the extranodal lymphomas varied, and no more than four rheumatoid arthritis patients had NHL tumors at the same anatomic site (data not shown). Risks of both NHL overall and diffuse large B-cell lymphoma were most increased in individuals whose rheumatoid arthritis had characteristics implying severe disease (Table 3).

When we analyzed NHL risk according to the treatment received (Table 4), we found that risk of NHL was modestly but not statistically significantly increased in rheumatoid arthritis patients who had used NSAIDs and corticosteroids but that NHL risk was statistically significantly increased by more than threefold in ever users of any of the specified immunosuppressants. In participants without rheumatoid arthritis, by contrast, there were no associations with ever use of any of these medication types and NHL risk. In stratified analyses of NSAID frequency and cumulative dose (data not shown), the results were similar to those of NSAID duration, with indications of increased risks of NHL in the highest exposure categories among patients with rheumatoid arthritis, but no associations in individuals without rheumatoid arthritis. When participants without rheumatoid arthritis were stratified by treatment indication for analysis of associations of NHL risk with ever use of immunosuppressants, neither treatment for other autoimmune/inflammatory disorders (OR = 1.4,

Table 2. Relative risks of non-Hodgkin lymphoma (NHL) overall and of NHL subtypes in relation to history of selected autoimmune and chronic inflammatory disorders*

		NHL subtype						
Disorder	All NHL (n = 3055)	Diffuse large B-cell (n = 796)	CLL (n =752)†	Follicular (n = 586)	T-cell (n = 204)	Mantle cell (n = 148)	Marginal zone (n = 117)	Lymphoplasmacytic (n = 116)
Rheumatoid arthritis								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	**1.5 (1.1 to 1.9)**	**1.8 (1.2 to 2.6)**	1.4 (0.9 to 2.2)	1.0 (0.6 to 1.7)	1.9 (0.9 to 3.9)	1.2 (0.5 to 3.1)	1.4 (0.5 to 3.5)	**2.5 (1.2 to 5.4)**
Primary Sjögren syndrome								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	**6.1 (1.4 to 27)**	**11 (2.1 to 58)**	—‡	—	Undefined§	Undefined	**28 (4.4 to 176)**	—
Systemic lupus erythematosus								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	**4.6 (1.0 to 22)**	**6.2 (1.0 to 37)**	—	—	Undefined	Undefined	—	—
Celiac disease								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	**2.1 (1.0 to 4.8)**	**2.8 (1.0 to 8.0)**	0.5 (0.1 to 4.0)	0.4 (0.1 to 3.6)	**17 (6.3 to 46)**	3.3 (0.4 to 28)	Undefined	3.4 (0.4 to 28)
Crohn disease								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	1.4 (0.5 to 4.1)	2.7 (0.7 to 9.5)	1.3 (0.3 to 6.5)	0.6 (0.1 to 5.2)	3.0 (0.3 to 25)	Undefined	Undefined	Undefined
Ulcerative colitis								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	1.1 (0.6 to 2.0)	1.2 (0.5 to 2.9)	0.9 (0.3 to 2.3)	0.5 (0.1 to 2.3)	1.8 (0.4 to 7.9)	1.6 (0.4 to 7.1)	Undefined	Undefined
Type I diabetes								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	1.5 (0.7 to 3.5)	1.3 (0.3 to 4.8)	**3.6 (1.3 to 10)**	Undefined	Undefined	**5.0 (1.0 to 25)**	2.8 (0.3 to 23)	3.9 (0.5 to 33)
Sarcoidosis								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	0.5 (0.2 to 1.3)	Undefined	0.7 (0.2 to 3.2)	0.7 (0.2 to 3.3)	Undefined	Undefined	2.2 (0.3 to 18)	2.5 (0.3 to 20)
Psoriasis								
No	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Yes	1.2 (0.9 to 1.5)	1.3 (0.9 to 1.8)	1.2 (0.8 to 1.7)	0.9 (0.6 to 1.3)	1.4 (0.8 to 2.5)	1.1 (0.5 to 2.4)	0.9 (0.4 to 2.2)	0.8 (0.3 to 2.1)

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals and were adjusted for age (in 5-year intervals), sex, and country. A reported diagnosis of any disorder was excluded if symptoms began less than 2 years before lymphoma diagnosis (or interview, for control subjects). Statistically significant ORs are shown in bold type.

†The group of chronic lymphocytic leukemia (CLL) also includes cases of small lymphocytic lymphoma.

‡— = ORs were not calculated because fewer than five case patients and control subjects were exposed.

§Undefined = no case patients were exposed.

Table 3. Relative risks of non-Hodgkin lymphoma (NHL) overall and subtypes in relation to characteristics of rheumatoid arthritis (RA)*

Characteristic	No. of control subjects	All NHL		NHL subtype: Diffuse large B-cell		NHL subtype: Other B-cell		NHL subtype: T-cell	
		No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)
RA history*									
No	3073	2905	1.0 (referent)	753	1.0 (referent)	1922	1.0 (referent)	194	1.0 (referent)
Yes	89	126	**1.5 (1.1 to 1.9)**	39	**1.8 (1.2 to 2.6)**	78	1.3 (0.9 to 1.8)	9	1.9 (0.9 to 3.9)
Treatment >4 weeks†									
No RA	3073	2905	1.0 (referent)	753	1.0 (referent)	1922	1.0 (referent)	194	1.0 (referent)
RA, never treated‡	36	34	1.0 (0.6 to 1.6)	13	1.4 (0.7 to 2.7)	20	0.8 (0.5 to 1.5)	2	1.0 (0.2 to 4.4)
RA, ever treated	52	90	**1.8 (1.3 to 2.5)**	26	**2.2 (1.4 to 3.5)**	53	**1.5 (1.0 to 2.3)**	7	**2.6 (1.2 to 6.0)**
Disease duration, y									
No RA	3073	2905	1.0 (referent)	753	1.0 (referent)	1922	1.0 (referent)	194	1.0 (referent)
2–5	13	15	1.1 (0.5 to 2.4)	2	0.6 (0.1 to 2.7)	10	1.1 (0.5 to 2.6)	2	2.8 (0.6 to 13)
6–20	34	50	**1.6 (1.0 to 2.5)**	18	**2.2 (1.3 to 4.0)**	29	1.3 (0.8 to 2.2)	2	1.1 (0.3 to 4.8)
>20	38	50	1.3 (0.9 to 2.0)	14	1.5 (0.8 to 2.9)	30	1.2 (0.7 to 1.9)	5	**2.7 (1.0 to 6.9)**
Surgery for RA									
No RA	3073	2905	1.0 (referent)	753	1.0 (referent)	1922	1.0 (referent)	194	1.0 (referent)
Never	76	101	**1.4 (1.0 to 1.9)**	29	**1.6 (1.0 to 2.5)**	63	1.2 (0.9 to 1.7)	7	1.7 (0.8 to 3.8)
Ever	13	24	**1.9 (1.0 to 3.8)**	9	**2.9 (1.2 to 6.9)**	12	1.4 (0.7 to 3.2)	2	3.4 (0.7 to 15)
Restraints of daily life									
No RA	3073	2905	1.0 (referent)	753	1.0 (referent)	1922	1.0 (referent)	194	1.0 (referent)
No restraints	46	46	1.0 (0.7 to 1.6)	18	1.6 (0.9 to 2.8)	24	0.8 (0.5 to 1.3)	4	1.6 (0.6 to 4.6)
Little/some	31	58	**1.9 (1.2 to 3.0)**	15	**2.0 (1.1 to 3.8)**	38	**1.8 (1.1 to 2.9)**	3	1.9 (0.6 to 6.3)
A lot	9	20	**2.2 (1.0 to 4.9)**	6	**2.8 (1.0 to 7.8)**	11	1.8 (0.7 to 4.3)	2	4.1 (0.9 to 19)
Hospital discharge with RA									
No	3035	3003	1.0 (referent)	779	1.0 (referent)	1988	1.0 (referent)	201	1.0 (referent)
Yes	14	40	**2.8 (1.5 to 5.1)**	13	**3.7 (1.7 to 7.9)**	23	**2.3 (1.2 to 4.6)**	3	**4.1 (1.2 to 14)**

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals (CIs) and were adjusted for age (in 5-year intervals), sex, and country. A reported diagnosis of RA was excluded if symptoms began less than 2 years before lymphoma diagnosis (or interview, for control subjects). Statistically significant ORs are shown in bold type.

†Includes any daily tablet treatment during more than 4 weeks.

‡"Never treated" can include use of local corticosteroid injections and/or irregular use of nonsteroidal anti-inflammatory drugs.

95% CI = 0.6 to 3.0) nor prior nonhematopoietic malignancy (OR = 0.6, 95% CI = 0.2 to 2.1) was associated with NHL risk.

Primary Sjögren Syndrome

Twelve case patients and two control subjects (80% of all were women) reported a previous diagnosis of primary Sjögren syndrome (i.e., without concomitant rheumatoid arthritis, systemic lupus erythematosus, or myositis). Median disease duration was 11 years among case patients (range = 2 to 30 years) and 8 years among control subjects (range = 4 to 11 years) (P = .53). Primary Sjögren syndrome was associated with a sixfold increased risk of NHL overall (OR = 6.1, 95% CI = 1.4 to 27; Table 2) and with statistically significant increases in risk of diffuse large B-cell and marginal zone lymphoma. However, the precision of the subtype-specific estimates was limited by small numbers (Table 2). Six patients had extranodal disease (two in the parotid gland) (extranodal NHL: OR = 13, 95% CI = 2.5 to 63; nodal NHL: OR = 4.8, 95% CI = 1.0 to 24). None of the primary Sjögren syndrome patients reported previous treatment with the specified immunosuppressants.

Systemic Lupus Erythematosus

Eight case patients and two control subjects (all women) reported a previous diagnosis of systemic lupus erythematosus. Median disease duration was 22 years among case patients (range = 8 to 36 years) and 10 years among control subjects (range = 6 to 14 years) (P = .20). Systemic lupus erythematosus was associated with a more than fourfold increased risk of NHL overall (OR = 4.6, 95% CI = 1.0 to 22; Table 2), and a sixfold increased risk of diffuse large B-cell lymphoma. Again, however, the small numbers rendered the estimates imprecise. In five of the patients, the lymphomas were located in extranodal sites (extranodal NHL: OR = 12, 95% CI = 2.3 to 63; nodal NHL: OR = 2.8, 95% CI = 0.5 to 17). Five case patients and one control subject had been hospitalized with systemic lupus erythematosus, and only one systemic lupus erythematosus case patient reported previous treatment with the specified immunosuppressants.

Celiac Disease

Nineteen case patients and nine control subjects (68% of whom were women) reported a previous diagnosis of celiac disease (Table 1). Median disease duration was 13 years among case patients (range = 2 to 64 years) and 16 years among control subjects (range = 4 to 56 years) (P = .96). Celiac disease was associated with a doubled risk of NHL overall (OR = 2.1, 95% CI = 1.0 to 4.8; Table 2) that was due mainly to a nearly 20-fold increased risk for T-cell lymphoma and to a nearly threefold increased risk for diffuse large B-cell lymphoma (Table 2). Ten lymphomas involved extranodal sites, of which five were located in the gastrointestinal tract. Thus, there was a substantially, and statistically significantly, increased risk of gastrointestinal NHL (OR = 12, 95% CI = 3.8 to 37) whereas there was only weak evidence for an increase in nongastrointestinal lymphoma (OR = 1.7, 95%

Table 4. Relative risks of non-Hodgkin lymphoma (NHL) overall in relation to regular treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and treatment with systemic corticosteroids and selected immunosuppressive drugs stratified on history of rheumatoid arthritis (RA)*

	History of RA (n = 126 case patients, 89 control subjects)		No history of RA (n = 2905 case patients, 3070 control subjects)		
Treatment	No. of cases/controls	OR (95% CI)	No. of cases/controls	OR (95% CI)	$P_{heterogeneity}$†
Regular‡ use of NSAIDs					
No	61/50	1.0 (referent)	2346/2536	1.0 (referent)	
Yes	58/33	1.5 (0.8 to 2.6)	398/414	1.0 (0.9 to 1.2)	.22
NSAID treatment duration					
No use	61/50	1.0 (referent)	2346/2536	1.0 (referent)	
1–10 y	23/16	1.2 (0.5 to 2.5)	138/142	1.0 (0.8 to 1.3)	
>10 y	24/11	1.9 (0.8 to 4.4)	150/139	1.1 (0.9 to 1.4)	.50
P_{trend}		0.14		0.42	
Use of corticosteroids					
No	43/35	1.0 (referent)	1908/1985	1.0 (referent)	
Yes	45/25	1.5 (0.8 to 3.1)	210/225	1.0 (0.8 to 1.2)	.43
Corticosteroid treatment duration					
No use	43/35	1.0 (referent)	1908/1985	1.0 (referent)	
≤2 y	24/12	1.8 (0.8 to 4.4)	108/120	0.9 (0.7 to 1.2)	
>2 y	20/12	1.1 (0.5 to 2.7)	85/86	1.0 (0.7 to 1.3)	.46
P_{trend}		0.85		0.21	
Use of immunosuppressants§					
No	60/49	1.0 (referent)	2098/2174	1.0 (referent)	
Yes	25/6	3.5 (1.3 to 9.5)	19/18	1.0 (0.5 to 1.9)	.13
Immunosuppressant duration§					
No use	60/49	1.0 (referent)	2098/2174	1.0 (referent)	
≤4 y	17/5	2.7 (0.9 to 8.1)	17/16	0.9 (0.4 to 1.7)	
>4 y	8/1	5.8 (0.7 to 49)	3/1	—‖	.07
P_{trend}		0.08		—	

*Relative risks are provided as odds ratios (OR) with 95% confidence intervals (CI) and were adjusted for age (in 5-year intervals), sex, and country. Treatment during less than 2 years before NHL diagnosis (or interview, for control subjects) was disregarded.

†Likelihood ratio test for statistical significance of interaction term between the exposure (medication type) and RA.

‡Regular use was defined as ever use of >5 tablets/month during 1 year.

§Immunosuppressants included methotrexate, azathioprine, cyclosporine, cyclophosphamide, and chlorambucil.

‖OR was not calculated because fewer than five case patients and control subjects were exposed.

CI = 0.7 to 4.0). When NHL risks were examined with respect to celiac disease characteristics, only those in whom gluten-free diet therapy was initiated in adulthood and those who reported complete diet compliance had increased risks for NHL overall and for diffuse large B-cell, T-cell, and gastrointestinal lymphomas (Table 5). Five NHL patients and no control subjects had a

Table 5. Relative risks of non-Hodgkin lymphoma (NHL) overall and by subtype and anatomic location in relation to characteristics of celiac disease*

				NHL subtype				NHL location			
		All NHL		Diffuse large B-cell		T-cell		Gastrointestinal		Nongastrointestinal	
Celiac disease characteristic	No. of control subjects	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)	No. of subjects	OR (95% CI)
Age at initiation of GFD therapy†											
No celiac disease	3165	3024	1.0 (referent)	788	1.0 (referent)	193	1.0 (referent)	157	1.0 (referent)	2586	1.0 (referent)
≤18 y	1	1	—‡	0	Undefined§	1	—	0	Undefined	1	—
>18 y	6	17	**2.7 (1.1 to 7.0)**	6	**4.1 (1.3 to 13)**	7	**23 (7.6 to 72)**	5	**16 (4.8 to 56)**	11	2.0 (0.8 to 5.6)
Disease duration											
No celiac disease	3165	3024	1.0 (referent)	788	1.0 (referent)	193	1.0 (referent)	157	1.0 (referent)	2586	1.0 (referent)
2–10 y	4	6	1.5 (0.4 to 5.4)	2	2.1 (0.4 to 11)	3	**16 (3.3 to 74)**	2	**11 (1.9 to 61)**	3	0.9 (0.2 to 4.0)
>10 y	5	11	2.3 (0.8 to 6.6)	3	2.6 (0.6 to 11)	4	**14 (3.8 to 55)**	3	**14 (3.1 to 60)**	9	2.1 (0.7 to 6.4)
Compliance with GFD therapy†											
No celiac disease	3165	3024	1.0 (referent)	788	1.0 (referent)		1.0 (referent)	157	1.0 (referent)	2586	1.0 (referent)
Complete	5	13	2.6 (0.9 to 7.3)	5	**4.2 (1.2 to 15)**	7	**29 (8.8 to 94)**	5	**21 (5.8 to 76)**	7	1.7 (0.5 to 5.2)
Partial	2	6	3.0 (0.6 to 15)	1	—	1	—	0	Undefined	6	3.5 (0.7 to 17)

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals (CIs) and were adjusted for age (in 5-year intervals), sex, and country. Individuals with celiac disease diagnosed within 2 years of lymphoma diagnosis (for case patients) or interview (for control subjects) were excluded. Statistically significant ORs are shown in bold type.

†GFD = gluten-free diet. Two control subjects had not been treated with a gluten-free diet.

‡— = OR was not calculated because fewer than five case patients and control subjects were exposed.

§Undefined = no case patients were exposed.

Table 6. Relative risks of non-Hodgkin lymphoma (NHL) and estimated proportion in the population attributed to autoimmune and chronic inflammatory disorders*

Disorder	NHL OR (95% CI)	Proportion of exposed NHL case patients	Population-attributable fraction†
Rheumatoid arthritis	1.5 (1.1 to 1.9)	4.2%	1.3%
Primary Sjögren syndrome	6.1 (1.4 to 27)	0.4%	0.4%
Systemic lupus erythematosus	4.5 (1.0 to 21)	0.3%	0.2%
Celiac disease	2.1 (1.0 to 4.8)	0.6%	0.4%

*Relative risks are provided as odds ratios (ORs) with 95% confidence intervals (CIs) and were adjusted for age (in 5-year intervals), sex, and country.

†Population-attributable fraction = $1 - \Sigma_i\Sigma_j P_{ij}/RR_{ij}$ *(32)*.

hospital discharge diagnosis of celiac disease, indicating that celiac disease was associated with increased NHL risk even if exposure was defined as hospitalization for celiac disease.

Inflammatory Bowel Diseases, Diabetes Mellitus, Sarcoidosis, and Psoriasis

Neither Crohn disease nor ulcerative colitis, whether surgically treated or not, was statistically significantly associated with risk of NHL overall (Table 2), with risk of any NHL subtype studied (Table 2), or with risk of gastrointestinal lymphoma (Crohn disease: OR = 3.7, 95% CI = 0.4 to 32, n = 1; ulcerative colitis: OR = 0.9, 95% CI = 0.1 to 6.5, n = 1). Type I diabetes was associated with a statistically significantly increased risk of CLL but not of NHL overall (Table 2). We did not observe any overall or NHL subtype–specific associations with type II diabetes (data not shown), with ever use of antidiabetic tablet treatment, or with ever use of insulin in type II diabetes (data not shown). There were no associations between a self-reported diagnosis of psoriasis and risk of NHL overall, of any NHL subtype (Table 2), or of cutaneous lymphoma (OR = 0.8, 95% CI = 0.3 to 2.2, n = 4). Likewise, there were no associations between psoriatic arthritis, a history of immunosuppressive therapy, or a hospital discharge diagnosis of psoriasis and risk of NHL overall or of any NHL subtype (data not shown). Sarcoidosis was not associated with risk of NHL overall or of any NHL subtype (Table 2).

Population-Attributable Fraction

The fraction of all NHL cases in the population that could be attributed to rheumatoid arthritis, primary Sjögren syndrome, systemic lupus erythematosus, or celiac disease was estimated to be 2.3% in total (Table 6). For diffuse large B-cell lymphoma, the total population-attributable fraction rose to 3.7%. Celiac disease was estimated as being responsible for 25% of all intestinal T-cell lymphomas in the population.

Discussion

The results of this large, population-based binational case–control study of NHL confirm previous reports of increased risks of NHL in association with certain autoimmune/inflammatory diseases (rheumatoid arthritis, primary Sjögren syndrome, systemic lupus erythematosus, and celiac disease) and contradict reported increased risks in association with other such conditions (type I diabetes mellitus, inflammatory bowel disorders, psoriasis, and sarcoidosis). Positive associations were most evident for several specific NHL subtypes, primarily diffuse large B-cell lymphoma (increased in association with rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, and celiac disease) but also marginal zone (associated with Sjögren syndrome), lymphoplasmacytic (associated with rheumatoid arthritis), and T-cell lymphoma (associated with celiac disease). Increased risks were generally observed for both nodal and extranodal NHL. With regard to anatomic location of extranodal NHL, we observed a highly increased risk of gastrointestinal lymphoma in association with celiac disease and an overrepresentation of parotid NHL in primary Sjögren syndrome, as expected based on previous reports *(19–22)*, although unlike in most previous reports *(19–21)* case patients with these typical locations were not in the majority. Moreover, we found some evidence that risks were higher in individuals with severe (i.e., rheumatoid arthritis) and long-standing (i.e., celiac disease) inflammation, but there was little evidence to support previous notions that increased NHL risks are associated with the medical treatments in these conditions.

The risk increases we observed for NHL overall were consistent with or slightly lower than those seen in previous reports. For example, recent large cohort studies have reported approximately doubled NHL risks in rheumatoid arthritis patients *(3,25,33)*. Estimates of NHL risk in patients with Sjögren syndrome, systemic lupus erythematosus, and celiac disease have varied greatly—from 8.7 to 44 in Sjögren syndrome *(2,34)*, from 3.7 to 44 in systemic lupus erythematosus *(4)*, and from 3.1 to 42.7 in celiac disease *(5,6,35)*. Most *(3–5,33)* although not all *(25,35)* previous studies of NHL risk in these disorders (i.e., rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, and celiac disease) have been confined to patients with a hospital discharge diagnosis of the disorder in question, and such patients are likely to have more severe disease than patients in general. Indeed, we found that a hospital discharge diagnosis of rheumatoid arthritis and other indicators of rheumatoid arthritis severity were associated with higher risks of NHL and of diffuse large B-cell lymphoma in particular than were indicators of less severe rheumatoid arthritis.

Our observation of an increased risk of diffuse large B-cell lymphoma in patients with rheumatoid arthritis is consistent with most *(16,17,36)* although not all *(24)* studies. However, only two of the previous studies were population based *(16,24)*, and none was able to estimate subtype-specific relative risks. In one study *(36)*, increased proportions of diffuse large B-cell lymphoma were further noted among patients with systemic lupus erythematosus, dermatomyositis, or systemic sclerosis, but the study population was poorly defined, thus leaving room for selection bias. Numerous case reports and case series from specialty clinics have identified an increased occurrence of parotid gland MALT lymphoma in patients with Sjögren syndrome *(18,19,37)*, but a recent systematic assessment suggests that the proportion of MALT lymphoma may be lower than previously believed *(38)*. A strong association between enteropathy-type T-cell lymphoma and celiac disease is well documented *(22)*. Our finding that the risk of diffuse large B-cell lymphoma may also be increased in patients with celiac disease has not been previously described, but it is consistent with a reported risk increase of B-cell lymphoma in general in patients with celiac disease *(6,39)*, given that diffuse large B-cell lymphoma is the most common B-cell type.

When risks of NHL were evaluated with respect to treatment, we observed that treatment with NSAIDs, systemic corticosteroids, or selected immunosuppressants was associated with increased risks of NHL in subjects with rheumatoid arthritis but not in subjects without rheumatoid arthritis. Moreover, multivariable adjustment for treatment affected NHL risk estimates only marginally. These observations suggest that the studied treatment groups do not, in themselves, play a major role in lymphomagenesis. Instead, the association of treatment with NHL risks in rheumatoid arthritis patients might be explained by covariation of treatment with rheumatoid arthritis disease severity.

Our analysis of patients with celiac disease confirmed a previous finding that increased NHL risks are confined to patients diagnosed as adults *(5)*, but our results did not support the hypothesis that complete compliance with gluten-free diet therapy would protect against lymphoma *(35)*. However, in patients diagnosed as adults, noncompliance during a long prediagnostic period may be a stronger risk determinant than the much shorter postdiagnostic period of compliance or noncompliance. Although self-reported level of compliance should be interpreted with caution, these results point to a need for further studies of the association of diet therapy with lymphoma risk. In patients with type I diabetes, risk of NHL overall was not increased, but risk of CLL was increased. The few previous studies that have evaluated risks of hematopoietic cancer in individuals with type I diabetes have found no association with NHL overall *(40,41)*. Although these previous studies did not preclude the possibility of NHL subtype–specific associations, the associations we identified could be due to chance.

We did not observe increased risks of NHL overall or of any NHL subtype in association with psoriasis. Previous studies have shown both positive *(10)* and no *(42)* associations with NHL overall, whereas one previous report *(10)* suggested increased risks of T-cell lymphoma specifically in patients with psoriasis. However, cutaneous T-cell lymphoma may mimic psoriasis *(43)* and go undiagnosed for many years, which could lead to false-positive associations. Our finding that inflammatory bowel disorders are not associated with NHL risk overall is consistent with the results of several recent large studies *(44,45)*, although no previous investigations distinguished among NHL subtypes or gastrointestinal location.

Rheumatoid arthritis, primary Sjögren syndrome, systemic lupus erythematosus, and celiac disease—the disorders that were associated with increased risks of NHL overall and of diffuse B-cell lymphoma in our study—are all characterized by B-cell proliferation and autoantibody production *(4,46–48)*. The development of mature B-cell neoplasms tends to mimic stages of normal B-cell differentiation *(28)*. Diffuse large B-cell, marginal zone, and lymphoplasmacytic lymphomas all arise from B cells that have somatic hypermutations in the variable region immunoglobulin genes; these mutations occur during the germinal center stage due to T-cell–dependent antigen exposure *(28)*. Half of all CLLs and most mantle cell lymphomas arise from CD5-positive B cells that lack such somatic hypermutations and thus have not passed through the germinal center stage *(28,49)*. Although the cells of NHL types without evidence of somatic hypermutation may be antigen stimulated, such antigen stimulation is thought to occur through a T-cell–independent mechanism outside of the germinal centers *(49)*. Thus, the observed NHL subtype pattern in these four conditions is consistent with the hypothesis that chronic B-cell stimulation and antigenic drive, either during or after the germinal center stage, play roles in autoimmunity-related lymphomagenesis *(50)*. The relevance of similar mechanisms is well established in some settings: both the development of parotid marginal zone (i.e., MALT) lymphoma in patients with Sjögren syndrome and small intestinal T-cell lymphoma in patients with celiac disease are thought to represent endpoints of a multistep process of local antigen-driven chronic inflammation that is characterized by organ-specific B- or T-cell proliferation, polyclonality, and, eventually, monoclonality *(22,47)*. Systemic autoimmune features such as increased resistance to apoptosis may further enhance the carcinogenic effects of sustained B-cell proliferation *(51)*.

Our study has a number of strengths. These include a large size, a population-based design, rapid case ascertainment, and a thorough and uniform classification of NHL cases. Although the case–control study design is not optimal for investigations of associations with rare exposures, such as autoimmune and chronic inflammatory disorders, cohort studies seldom permit detailed analyses of the outcome. Outcomes are of special concern in malignant lymphomas, given their inherent heterogeneity and changing subtype classifications over the years *(1)*. However, inferences from observed NHL subtype–specific relative risk estimates in our study were sometimes hampered by small numbers.

Our study also had some additional limitations. The most important limitation was the use of self-reported diagnoses and the lack of validation other than matching with hospital discharge diagnoses. The prevalences of the studied disorders in our control population were in line with reported population prevalences for most of the disorders we investigated *(52–57)*. The prevalence of rheumatoid arthritis among the control subjects (2.8%) corresponded to a population prevalence of approximately 1.5% after adjustment for age and sex. This figure is in the upper range of what has been reported *(45,58)*, but previously reported rheumatoid arthritis prevalences must be viewed in light of the methodologic difficulties of ascertaining criteria-based diagnoses (such as rheumatoid arthritis) in population surveys *(58,59)*. Thus, although we cannot exclude diagnostic misclassification and both nondifferential and differential misclassification could have biased the results in either direction, misclassification bias is unlikely to be the sole explanation for the positive associations observed. Furthermore, although separate risk estimates for lymphoma subtypes may have been influenced by misclassification bias, their relationships to one another, i.e., the pattern of subtype-specific risks, were less likely to have been affected by this bias. Because most patients with rheumatoid arthritis are under regular treatment, the observed relative risk level for regularly treated rheumatoid arthritis patients may be most representative. Reassuringly, the NHL subtype pattern for regularly treated rheumatoid arthritis was similar to that for all rheumatoid arthritis. Also, the observed differences between strata (rheumatoid arthritis versus other) in the analyses of treatment cannot be explained by misclassification bias.

Another limitation was the lack of detail in the analyses of use of immunosuppressants, for which we did not assess exposure to individual drugs but to at least one in a group of specified drugs. Hence, although our results did not support the hypothesis that a moderate degree of therapy-related immunosuppression is associated with increased risk of NHL, we cannot exclude the possibility that any of these drugs separately influence NHL risk to some extent. Other possible limitations include selection bias due to differing participation rates among case patients and control subjects, but this bias is also unlikely to explain the observed differences in associations with NHL subtypes. Finally, considering the multiple comparisons performed, we cannot exclude chance as an explanation for some of our findings.

In summary, our results confirm the associations between certain autoimmune disorders and risk of NHL and extend these by suggesting that the associations may not be general but rather mediated though specific NHL subtypes. Moreover, increased NHL risks in these conditions were associated not with treatment but with factors that relate to disease severity and antigenic drive. However, further studies with detailed assessment of both inflammatory activity and drug use are needed to confirm this finding. Although the estimated fractions of all NHL cases that were attributable to diagnosed autoimmune disorders in the population were low (about 2% overall, although the attributable fractions were higher for specific NHL subtypes), lymphomagenesis in autoimmunity may serve as a model for a larger number of NHL patients.

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