

Autoimmunity and Susceptibility to Hodgkin Lymphoma: A Population-Based Case–Control Study in Scandinavia

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Background: Personal history of autoimmune diseases is consistently associated with increased risk of non-Hodgkin lymphoma. In contrast, there are limited data on risk of Hodgkin lymphoma following autoimmune diseases and almost no data addressing whether there is a familial association between the conditions. **Methods:** Using population-based linked registry data from Sweden and Denmark, 32 separate autoimmune and related conditions were identified from hospital diagnoses in 7476 case subjects with Hodgkin lymphoma, 18 573 matched control subjects, and more than 86 000 first-degree relatives of case and control subjects. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of relative risks for each condition using logistic regression and also applied multivariable hierarchical regression models. All *P* values are two-sided. **Results:** We found statistically significantly increased risks of Hodgkin lymphoma associated with personal histories of several autoimmune conditions, including rheumatoid arthritis (OR = 2.7, 95% CI = 1.9 to 4.0), systemic lupus erythematosus (OR = 5.8, 95% CI = 2.2 to 15.1), sarcoidosis (OR = 14.1, 95% CI = 5.4 to 36.8), and immune thrombocytopenic purpura (OR = ∞, *P* = .002). A statistically significant increase in risk of Hodgkin lymphoma was associated with family histories of sarcoidosis (OR = 1.8, 95% CI = 1.01 to 3.1) and ulcerative colitis (OR = 1.6, 95% CI = 1.02 to 2.6). **Conclusions:** Personal or family history of certain autoimmune conditions was strongly associated with increased risk of Hodgkin lymphoma. The association between both personal and family histories of sarcoidosis and a statistically significantly increased risk of Hodgkin lymphoma suggests shared susceptibility for these conditions. [J Natl Cancer Inst 2006;98:1321–30]

Hodgkin lymphoma is a potentially fatal lymphoproliferative malignancy of B cell origin, with an age-adjusted incidence of 2.3–3.1 per 100 000 in the Western world (1). Clues about the etiology of Hodgkin lymphoma have been suggested by the bimodal distribution of age at diagnosis and by higher risks in males, in persons with higher socioeconomic status, and in smaller families. Young adult-onset (15–44 years of age) Hodgkin lymphoma is thought to arise as a consequence of delayed primary infection with Epstein–Barr virus (EBV) or a similar infectious agent (2–5). Family history of Hodgkin lymphoma has been consistently identified as a risk factor based on previous reports of multiplex families and case series (6–8) and on twin (9), case–control (10), and population registry (11–17) studies. Immunosuppressed disease states (e.g., following organ transplantation or in individuals with acquired immunodeficiency syndrome) are characterized by uncontrolled and dysfunctional lymphocyte proliferation, which is reflected in

well-known increased risks of lymphoma, including Hodgkin lymphoma (18,19).

Autoimmune diseases are characterized by dysregulated lymphocyte reactivity against self-antigens and the production of autoantibodies, leading to damage of the targeted tissues, such as joints or skin (20). Previous studies have shown that there is an increased risk of mainly non-Hodgkin lymphoma subsequent to autoimmune conditions including rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus (21–32). Recent studies focusing on underlying pathophysiologic mechanisms related to lymphomagenesis have provided new evidence establishing differences in the risk of non-Hodgkin lymphoma development associated with various autoimmune disorders (33). As a consequence of these efforts to characterize the role of autoimmunity in different subtypes of lymphomas, there has also been an increased focus on the possible role of autoimmunity in Hodgkin lymphoma. Recent studies have observed an association between certain autoimmune diseases and subsequent risk of Hodgkin lymphoma (21,25–28,30,34). However, there is great heterogeneity among the results of these studies that is likely due to differences in study design or referral patterns or to their limited sample sizes.

To understand better the association between autoimmunity and subsequent risk of Hodgkin lymphoma, we conducted a large population-based case–control study using linked registry data from Sweden and Denmark to examine the association between personal and familial histories of autoimmune diseases and Hodgkin lymphoma. We also employed hierarchical regression models (35) that incorporate knowledge about similar biologic characteristics of autoimmune conditions to obtain more accurate and stable estimates of associations with Hodgkin lymphoma risk. The study included 7476 case subjects with Hodgkin lymphoma, 18 573 matched control subjects, and more than 86 000 first-degree relatives of case and control subjects.

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METHODS

Case and Control Subjects and Their First-Degree Relatives

The creation of the databases of Hodgkin lymphoma case subjects, control subjects, and their relatives from Sweden and Denmark has been described previously (17) and is summarized briefly here.

The Swedish Cancer Registry has been in operation since 1958 with near-complete coverage of the Swedish population (36,37). The Swedish Multigenerational Registry (38) includes information on parent–offspring relations for all Swedish citizens born in 1932 or later. Through iterated linkage using this registry, parents, siblings, and offspring of individuals born 1932 or later can be identified. The Swedish Multigenerational Registry has been merged with the Swedish Cancer Registry (all cancers diagnosed in 1958–1998) to create the Familial Cancer Database, which has been described in detail elsewhere (39–41). In the Familial Cancer Database, all individuals registered with a first cancer diagnosis of Hodgkin lymphoma (International Classification of Diseases, 7th Revision [ICD-7], code 201) between 1958 and 1998 were identified as case subjects. For each case subject, information on date of birth, date of diagnosis of Hodgkin lymphoma, and sex was collected. Two control subjects for each case subject were randomly selected from the database. Case and control subjects were matched by sex, year of birth (within 5 years), and county of residence. Case patients and control subjects with no relatives identified from the Multigenerational Registry linkage were removed from the study, as were duplicate control subjects. Thus, using the Familial Cancer Database, we identified Swedish case subjects with Hodgkin lymphoma, matched population-based control subjects, and their first-degree relatives.

A similar database of case patients with Hodgkin lymphoma, population-based control subjects, and relatives was created using the Danish Cancer Registry and the Danish Central Population Registry (CPR) (17,41). The Danish Cancer Registry became a nationwide registry in 1943, but we limited the selection of Hodgkin lymphoma tumor case subjects to those diagnosed after April 1, 1968, because patients with malignant disease who died before that date could not be linked to the CPR. The CPR contains links of offspring to parents (and vice versa) starting with all children born in 1968, as well as linkages (also starting in 1968) among family members who were living at the same address. Thus, all individuals with Hodgkin lymphoma diagnosed between 1968 and 1997 were selected from the Danish Cancer Registry. For each case subject, information on date of birth, date of diagnosis of Hodgkin lymphoma, and sex was collected. Four control subjects were randomly selected for each case subject from the CPR. Cases and controls were matched by sex, year of birth (within 5 years), and county of residence. All first-degree relatives of case subjects and control subjects were identified by linking the individual's identification number to the relatives in the CPR. Case subjects and control subjects with no relatives identified from the linkage were removed from the study, as were duplicate control subjects. Thus, the final sample contained fewer than four control subjects per case subject.

Approval was obtained from the National Institutes of Health (NIH) institutional review board for these studies. Informed consent was waived because we had no contact with study subjects.

Autoimmune Conditions

All Swedish individuals were further linked with the Swedish Inpatient Registry 1964–2000 (36), which contains information on discharge diagnoses and discharge listings from inpatient care (coded according to ICD-7 to ICD-10). The Swedish Inpatient Registry provides population-based coverage that encompassed 50% of the population in the mid-1970s; coverage increased from over time, reaching 100% in 1987 (36,38). Similarly, all Danish individuals were linked with the Danish Inpatient (1977–1997) and Outpatient (1994–1997) Registry. Through this linkage, we collected information on patients whose discharge diagnoses included autoimmune and related conditions. All autoimmune and related conditions were analyzed both individually and by grouping into categories as follows (42,43): conditions with detectable autoantibodies and systemic involvement (group A), conditions with detectable autoantibodies and organ involvement (group B), and conditions without detectable autoantibodies (group C) (see Tables 2 and 3). We included the following 32 autoimmune and related conditions in our analyses (42,43): polymyositis/dermatomyositis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis (group A); Addison disease, amyotrophic lateral sclerosis, autoimmune hemolytic anemia, chronic rheumatic heart disease, discoid lupus erythematosus, Grave disease, Hashimoto thyroiditis, immune thrombocytopenic purpura, insulin-dependent diabetes (see below), localized scleroderma, lupoid hepatitis, multiple sclerosis, myasthenia gravis, pernicious anemia, polyarteritis nodosa, primary biliary cirrhosis, Wegener granulomatosis (group B); ankylosing spondylitis, Behcet disease, chorea minor, Crohn disease, polymyalgia rheumatica, psoriasis, Reiter disease, rheumatic fever, sarcoidosis, and ulcerative colitis (group C).

No code unambiguously delineates diabetes mellitus type I from type II in the hospital discharge listing for either Sweden or Denmark. All case subjects diagnosed with diabetes mellitus before 30 years of age were therefore designated as having insulin-dependent diabetes mellitus, in accord with a previous study (34).

Statistical Analysis

To determine whether it was appropriate to pool data from Sweden and Denmark, we first examined the association between group A, group B, and group C conditions, as well as the most common individual conditions, and risk of Hodgkin lymphoma for Sweden and Denmark separately. Because the risk estimates were similar (data not shown), we combined the two datasets for further analyses. To capture geographic variability in reporting, we defined six regions for Sweden and considered Denmark as a single separate region.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of association between Hodgkin lymphoma and previous personal history of each defined autoimmune condition using unconditional logistic regression, adjusting for year of birth, sex, calendar period of Hodgkin lymphoma diagnosis, and region. To assess the adequacy of these models, we also accounted for the matched design using conditional logistic regression. Because the models yielded similar estimates (data not shown), we present results from the unconditional logistic regression models only. When the number of Hodgkin lymphoma case subjects or control subjects with autoimmune or associated

Table 1. Characteristics of case and control subjects*

Variable	Sweden		Denmark	
	Case subjects	Control subjects	Case subjects	Control subjects
Total number	5047	10 078	2429	8495
Age (y) at HL diagnosis, median (interquartile range)	44 (27–63)		32 (23–44)	
Age group, N (%)				
<15 y	185 (4)	369 (4)	115 (5)	438 (5)
15–24 y	859 (17)	1717 (17)	569 (23)	2083 (25)
25–34 y	835 (17)	1667 (17)	701 (29)	2652 (31)
35–44 y	666 (13)	1332 (13)	440 (18)	1565 (18)
45–54 y	647 (13)	1289 (13)	312 (13)	1010 (12)
55–64 y	725 (14)	1449 (14)	191 (8)	532 (6)
≥65 y	1130 (22)	2255 (22)	101 (4)	215 (3)
Sex, N (%)				
Male	2996 (59)	5977 (59)	1519 (63)	5226 (62)
Female	2051 (41)	4101 (41)	910 (37)	3269 (38)
Calendar year at HL diagnosis, median (interquartile range)	1980 (1971–1989)		1985 (1977–1991)	
First-degree relatives, N (mean number per proband)				
Parents	4318 (0.9)	7686 (0.8)	2126 (0.9)	8252 (1.0)
Siblings	3723 (0.7)	7968 (0.8)	1467 (0.6)	8299 (1.0)
Offspring	7758 (1.5)	16463 (1.6)	3744 (1.5)	14359 (1.7)

*HL = Hodgkin lymphoma.

conditions was zero, we calculated unadjusted *P* values using Fisher's exact test. As a proxy measure of latency, we examined the relationship between the date of the first inpatient discharge listing a defined condition and the date of diagnosis of Hodgkin lymphoma (0–1, 2–4, 5–9, and ≥10 years). Because some descriptive epidemiologic features of and risk factors for Hodgkin lymphoma differ depending on age (44–46), we also conducted analyses separately according to age of diagnosis of Hodgkin lymphoma (15–44 versus ≥45 years). Individuals younger than 15 years were not included in this subanalysis because there were too few case subjects. Similarly, to measure associations between Hodgkin lymphoma and a hospital discharge diagnosis in one or more family members (i.e., family history of autoimmune conditions), we used logistic regression, adjusting for birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region as well as for personal history of that condition.

In addition to analyzing each autoimmune and related disorder in a separate logistic regression model, we also studied the occurrence of all autoimmune and related conditions simultaneously by fitting hierarchical logistic regression models to the data (47). By employing hierarchical regression models, we could study the impact of the associations of all 32 autoimmune and related disorders simultaneously while incorporating information at the group level (i.e., group A, group B, and group C; see Tables 2 and 3). Also, by using hierarchical models we could correct for correlations due to multiple autoimmune conditions in the same individual and thereby increase the precision of the risk estimates for rare conditions (see Appendix). Specifically, we emphasize conditions for which statistically significant associations with Hodgkin lymphoma were seen using both logistic regression and hierarchical logistic regression models. The details of the hierarchical logistic model are described in the Appendix.

Because only a few families (N = 22) had more than one case subject with Hodgkin lymphoma, we did not account for dependence among case subjects when we computed *P* values and confidence intervals. All *P* values and confidence intervals were two-sided. *P* values <.05 were considered statistically significant. Calculations were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

From the Swedish dataset, we obtained 5047 case subjects with Hodgkin lymphoma, 10 078 matched control subjects, and corresponding relatives of case subjects (N = 15 799) and control subjects (N = 32 117). From the Danish dataset, we identified 2429 case subjects with Hodgkin lymphoma, 8495 matched control subjects, and corresponding relatives of case subjects (N = 7337) and control subjects (N = 30 910) (Table 1). In Sweden, 59% of the case patients were males (Table 1). Probands were born between 1879 and 1994 (mean year of birth was 1934). The ages at diagnosis followed a typical bimodal distribution, with a peak among individuals in their early 20s and a second peak among individuals in their early 60s. In Denmark, 63% of the probands were males. Probands were born between 1897 and 1994 (mean year of birth was 1951). The age distribution at diagnosis was unimodal, with a peak among individuals in their early 20s. The age pattern observed in Denmark was attributable to the restriction of case patients to individuals who were diagnosed between 1968 and 1997. In both datasets, approximately 50% of first-degree relatives were offspring. In Sweden, 25% each were parents and siblings; in Denmark, 30% were parents and 20% were siblings.

The total numbers of case subjects and control subjects with a personal history of autoimmune and related conditions were 192 and 178, respectively. Among affected case subjects, the distribution of autoimmune and related conditions per individual was as follows: one condition (87%), two conditions (12%), and three conditions (1%); for control subjects the corresponding percentages were 89%, 10%, and 1%. Subjects with multiple autoimmune or related conditions were neither aggregated together in families nor aggregated in families with more than one case of Hodgkin lymphoma.

Personal History of Autoimmune Conditions

We examined Hodgkin lymphoma risk in relation to personal history of autoimmune and related conditions (Table 2). In the univariate logistic regression analyses, a statistically significantly

Table 2. Risk of Hodgkin lymphoma in relation to personal history of autoimmune and related conditions*

Autoimmune condition/category	Case subjects	Control subjects	Univariate model	Hierarchical model
			OR (95% CI)†	OR (95% CI)†
No autoimmune disease			1.0 (referent)	1.0 (referent)
Autoantibodies detectable				
Systemic involvement, group A	97	76		2.7 (1.9 to 3.8)
Polymyositis/dermatomyositis	15	18	1.7 (0.9 to 3.4)	1.5 (0.8 to 2.8)
Rheumatoid arthritis	61	50	<u>2.7 (1.9 to 4.0)</u>	<u>2.7 (1.9 to 3.8)</u>
Sjögren syndrome	3	0	∞ ($P = .02$)	10.3 (0.9 to 120)
Systemic lupus erythematosus	15	6	<u>5.8 (2.2 to 15.1)</u>	<u>4.0 (1.9 to 8.0)</u>
Systemic sclerosis	1	3	0.6 (0.1 to 6.2)	1.5 (0.4 to 5.6)
Organ involvement, group B	41	55		1.0 (0.6 to 1.7)
Addison disease	1	1	2.0 (0.1 to 31.3)	1.0 (0.6 to 1.7)
Amyotrophic lateral sclerosis	2	0	∞ ($P = .08$)	13.2 (0.4 to 390)
Autoimmune hemolytic anemia	4	1	8.8 (0.97 to 79.5)	4.5 (0.8 to 24.7)
Chronic rheumatic heart disease	8	15	1.2 (0.5 to 2.9)	1.0 (0.7 to 1.7)
Discoid lupus erythematosus	2	0	∞ ($P = .08$)	27.9 (0.6 to 1200)
Grave disease	3	10	0.7 (0.2 to 2.5)	1.0 (0.6 to 1.7)
Hashimoto thyroiditis	2	2	2.0 (0.3 to 14.0)	1.0 (0.6 to 1.7)
Immune thrombocytopenic purpura	5	0	∞ ($P = .002$)	<u>69.2 (1.1 to 4200)</u>
Diabetes mellitus type I	3	7	1.4 (0.4 to 5.5)	1.0 (0.6 to 1.7)
Localized scleroderma	0	0	—	—
Lupoid hepatitis	0	1	0 ($P = 1.00$)	1.0 (0.6 to 1.7)
Multiple sclerosis	4	12	0.8 (0.3 to 2.4)	1.0 (0.6 to 1.7)
Myasthenia gravis	0	1	0 ($P = 1.00$)	1.0 (0.6 to 1.7)
Pernicious anemia	1	5	0.4 (0.1 to 3.3)	1.0 (0.6 to 1.7)
Polyarteritis nodosa	2	0	∞ ($P = .08$)	1.0 (0.6 to .7)
Primary biliary cirrhosis	3	0	∞ ($P = .02$)	23.9 (0.6 to 900)
Wegener granulomatosis	3	0	∞ ($P = .02$)	24.4 (0.6 to 940)
Autoantibodies not detectable, group C	61	62		1.4 (0.9 to 2.3)
Ankylosing spondylitis	2	10	0.5 (0.1 to 2.2)	0.3 (0.1 to 1.1)
Behcet disease	0	0	—	—
Chorea minor	0	0	—	—
Crohn disease	8	13	1.5 (0.6 to 3.7)	1.4 (0.9 to 2.3)
Polymyalgia rheumatica	9	7	<u>2.9 (1.1 to 7.8)</u>	1.8 (0.9 to 3.7)
Psoriasis	7	8	1.8 (0.6 to 4.9)	1.4 (0.9 to 2.3)
Reiter disease	1	2	1.4 (0.1 to 15.6)	1.4 (0.9 to 2.3)
Rheumatic fever	3	6	1.1 (0.3 to 4.2)	1.4 (0.9 to 2.3)
Sarcoidosis	27	5	<u>14.1 (5.4 to 36.8)</u>	<u>12.8 (5.1 to 31.7)</u>
Ulcerative colitis	4	13	0.8 (0.3 to 2.5)	1.4 (0.8 to 2.3)

*OR = odds ratio; CI = confidence interval.

† P values (two-sided) based on Fisher's exact test are given when no case or control subjects have the specified condition. All analyses were adjusted for birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region. Underlined entries have P values < .05.

increased risk for Hodgkin lymphoma was found among subjects with a prior personal history of rheumatoid arthritis (OR = 2.7, 95% CI = 1.9 to 4.0), systemic lupus erythematosus (OR = 5.8, 95% CI = 2.2 to 15.1), polymyalgia rheumatica (OR = 2.9, 95% CI = 1.1 to 7.8), and sarcoidosis (OR = 14.1, 95% CI = 5.4 to 36.8). Furthermore, we found statistically significantly increased risk for Hodgkin lymphoma for the following autoimmune and related conditions for which there were no affected control subjects (OR = ∞): Sjögren syndrome ($P = .02$), immune thrombocytopenic purpura ($P = .002$), primary biliary cirrhosis ($P = .02$), and Wegener granulomatosis ($P = .02$).

When we considered the 32 autoimmune and related conditions jointly in a hierarchical regression model, the results were similar to the results from the individual logistic regression model, but a few conditions were no longer statistically significantly associated with Hodgkin lymphoma (Table 2). Under the hierarchical model, a statistically significantly increased risk of Hodgkin lymphoma was found for a personal history of group A (i.e., systemic) conditions overall (OR = 2.7, 95% CI = 1.9 to 3.8) that was driven mainly by the associations with rheumatoid arthritis and systemic lupus erythematosus (Table 2). No such increased risk for Hodgkin lymphoma was found

for group B (organ involvement) or group C (no detectable autoantibodies) conditions overall. The estimates remained virtually unchanged when the hierarchical model was further adjusted for family history of autoimmune and related conditions (data not shown).

Family History of Autoimmune Conditions

In the logistic regression analyses adjusted for personal history of autoimmune and related diseases, we found statistically significant increases in risk of Hodgkin lymphoma among subjects with a family history of sarcoidosis (OR = 1.8, 95% CI = 1.01 to 3.1) or ulcerative colitis (OR = 1.6, 95% CI = 1.02 to 2.6) and decreases in risk of Hodgkin lymphoma among subjects with a family history of polymyalgia rheumatica (OR = 0.4, 95% CI = 0.2 to 0.98) (Table 3). In a hierarchical model, only family histories of sarcoidosis and ulcerative colitis were associated with a statistically significantly increased risk (Table 3). We observed an increased risk for Hodgkin lymphoma among subjects with a family history of group C conditions overall (OR = 1.4, 95% CI = 1.1 to 1.8) but not for family history of group A or group B conditions (Table 3). In the hierarchical model, estimates of

Table 3. Risk of Hodgkin lymphoma in relation to family history of autoimmune and related conditions*

Autoimmune condition/category	Case subjects	Control subjects	Univariate model	Hierarchical model
			OR (95% CI)†	OR (95% CI)†
No autoimmune disease			1.0 (referent)	1.0 (referent)
Autoantibodies detectable				
Systemic involvement, group A	86	194		1.2 (0.9 to 1.7)
Polymyositis/dermatomyositis	25	36	1.5 (0.9 to 2.4)	1.3 (0.8 to 2.1)
Rheumatoid arthritis	44	131	0.8 (0.5 to 1.1)	0.8 (0.6 to 1.1)
Sjögren syndrome	1	3	0.9 (0.1 to 8.7)	0.9 (0.6 to 1.4)
Systemic lupus erythematosus	7	15	0.9 (0.4 to 2.3)	0.9 (0.6 to 1.4)
Systemic sclerosis	3	5	1.3 (0.3 to 5.4)	0.9 (0.6 to 1.4)
Organ involvement, group B	82	185		1.3 (1.0 to 1.7)
Addison disease	1	7	0.3 (0.1 to 2.5)	0.6 (0.2 to 2.2)
Amyotrophic lateral sclerosis	2	5	0.9 (0.2 to 4.5)	1.3 (0.95 to 1.7)
Autoimmune hemolytic anemia	1	4	0.6 (0.1 to 5.4)	1.3 (0.95 to 1.7)
Chronic rheumatic heart disease	19	36	1.3 (0.7 to 2.2)	1.3 (0.95 to 1.7)
Discoid lupus erythematosus	3	1	7.1 (0.7 to 68.8)	1.8 (0.6 to 6.0)
Grave disease	7	24	0.7 (0.3 to 1.7)	1.0 (0.6 to 1.7)
Hashimoto thyroiditis	3	6	1.3 (0.3 to 5.4)	1.3 (0.95 to 1.7)
Immune thrombocytopenic purpura	2	5	1.1 (0.2 to 5.8)	1.3 (0.95 to 1.7)
Diabetes mellitus type I	15	39	1.3 (0.7 to 2.4)	1.3 (0.95 to 1.7)
Localized scleroderma	0	2	0 (<i>P</i> = 1.00)	1.3 (0.95 to 1.7)
Lupoid hepatitis	0	0	—	—
Multiple sclerosis	20	31	1.6 (0.9 to 2.8)	1.3 (0.95 to 1.7)
Myasthenia gravis	4	3	3.5 (0.8 to 15.9)	2.1 (0.7 to 6.0)
Pernicious anemia	3	12	0.6 (0.2 to 2.0)	0.9 (0.4 to 1.9)
Polyarteritis nodosa	2	4	1.5 (0.3 to 8.1)	1.3 (0.95 to 1.7)
Primary biliary cirrhosis	0	7	0 (<i>P</i> = .20)	0.1 (0.01 to 2.2)
Wegener granulomatosis	2	2	2.7 (0.4 to 19.4)	1.3 (0.95 to 1.7)
Autoantibodies not detectable, group C	105	202		<u>1.4 (1.1 to 1.8)</u>
Ankylosing spondylitis	7	15	1.1 (0.5 to 2.8)	<u>1.4 (1.1 to 1.8)</u>
Behcet disease	0	2	0 (<i>P</i> = 1.00)	0.5 (0.1 to 4.8)
Chorea minor	0	1	0 (<i>P</i> = 1.00)	<u>1.4 (1.1 to 1.8)</u>
Crohn disease	20	36	1.2 (0.7 to 2.1)	<u>1.4 (1.1 to 1.8)</u>
Polymyalgia rheumatica	12	32	<u>0.4 (0.2 to 0.98)</u>	0.4 (0.2 to 1.0)
Psoriasis	12	32	0.8 (0.4 to 1.6)	1.0 (0.6 to 1.7)
Reiter disease	1	4	0.8 (0.1 to 7.2)	<u>1.4 (1.1 to 1.8)</u>
Rheumatic fever	10	16	1.6 (0.7 to 3.6)	<u>1.4 (1.1 to 1.8)</u>
Sarcoidosis	22	30	<u>1.8 (1.01 to 3.1)</u>	<u>1.4 (1.1 to 1.8)</u>
Ulcerative colitis	30	45	<u>1.6 (1.02 to 2.6)</u>	<u>1.4 (1.1 to 1.8)</u>

*OR = odds ratio; CI = confidence interval.

†*P* values (two-sided) based on Fisher's exact test are given when no case or control subjects have the specified condition. All analyses were adjusted for birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region. Underlined entries have *P* values <.05.

Hodgkin lymphoma risk for autoimmune and related diseases with small numbers of case subjects and control subjects were equal to the overall group mean (see Appendix). Thus, the statistically significant odds ratios for family history of group C conditions with small numbers should not be interpreted individually (see Table 3, group C).

Analyses by Age of Hodgkin Lymphoma Onset, Latency, and Sex

We computed risk estimates stratified by age, latency, and sex for those autoimmune and related conditions that were associated with statistically significantly elevated risk of Hodgkin lymphoma in the overall analyses (Tables 2 and 3). When analyses were stratified by age at diagnosis of Hodgkin lymphoma, in total there were 44 (1.1%) and 147 (4.7%) subjects with autoimmune or related conditions out of 4070 and 3106 Hodgkin lymphoma case subjects in strata of ages 15–44 years and ≥45 years at diagnosis, respectively. Personal history of autoimmune and related conditions was associated with increased risk of both young adult- and late-onset Hodgkin lymphoma. As shown in Table 4, two autoimmune conditions were linked with only young age-

onset Hodgkin lymphoma (immune thrombocytopenic purpura) or only late-onset (polymyalgia rheumatica). This pattern is consistent with the typically very young age at occurrence of immune thrombocytopenic purpura (48) and the typically older age at onset of polymyalgia rheumatica (49).

In analyses stratified by time between first hospitalization for autoimmune or related conditions and subsequent diagnosis of Hodgkin lymphoma (i.e., latency period), small numbers resulted, in some instances, in wide confidence intervals (Table 5). For rheumatoid arthritis, we found a statistically significantly increased risk of Hodgkin lymphoma for all latency periods. The odds ratio estimates for sarcoidosis were extremely elevated in the first latency period (0–1 year; OR = 47.4, 95% CI = 6.4 to 350) and the second latency period (2–4 years; OR = 12.7, 95% CI = 1.4 to 110); the calculations for the other two latency periods were hampered by small numbers. A statistically significantly increased risk of Hodgkin lymphoma was found in the first latency period for polymyalgia rheumatica (OR = 7.3, 95% CI = 1.5 to 35.6), immune thrombocytopenic purpura (OR = ∞, *P* = .02), and systemic lupus erythematosus (OR = ∞, *P* <.001).

All results were similar for males and females in analyses stratified by sex (data not shown).

Table 4. Risk of Hodgkin lymphoma in relation to personal and family histories of autoimmune and related conditions, stratified by age at Hodgkin lymphoma diagnosis*

Autoimmune condition/category	Young adult-onset HL (age 15–44 years)			Late-onset HL (age ≥45 years)		
	Case subjects	Control subjects	OR (95% CI)†	Case subjects	Control subjects	OR (95% CI)†
Personal history						
No autoimmune disease			1.0 (referent)			1.0 (referent)
Rheumatoid arthritis	6	9	1.9 (0.7–5.3)	55	41	<u>2.9 (1.9–4.4)</u>
Systemic lupus erythematosus	2	0	∞ (<i>P</i> = .07)	13	6	<u>4.8 (1.8–12.7)</u>
Immune thrombocytopenic purpura	5	0	∞ (<i>P</i> = .001)	0	0	–
Polymyalgia rheumatica	0	0	–	9	7	<u>2.8 (1.03–7.5)</u>
Sarcoidosis	11	3	<u>11.2 (3.1–40.6)</u>	16	2	<u>18.3 (4.2–79.9)</u>
Family history						
No autoimmune disease			1.0 (referent)			1.0 (referent)
Sarcoidosis	11	21	1.4 (0.7–3.0)	10	9	2.2 (0.9–5.5)
Ulcerative colitis	19	28	1.8 (0.97–3.2)	11	16	1.5 (0.7–3.3)

*OR = odds ratio; CI = confidence interval; HL = Hodgkin lymphoma.

†*P* values (two-sided) based on Fisher's exact test are given when no case or control subjects have the specified condition. All analyses on personal history were adjusted for birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region. All analyses on family history were adjusted for personal history of the same autoimmune condition as the one being tested with regard to a positive family history, birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region. Underlined entries have *P* values <.05.

DISCUSSION

In this population-based case-control study, we assessed risks of Hodgkin lymphoma associated with 32 autoimmune and related disorders. We found that a personal history of systemic autoimmune conditions was strongly associated with increased risk of Hodgkin lymphoma, with the most elevated risk estimates seen for rheumatoid arthritis and systemic lupus erythematosus. Both personal and family histories of sarcoidosis were independently associated with elevated risk of Hodgkin lymphoma. We also found that a personal history of immune thrombocytopenic purpura was associated with increased risk of Hodgkin lymphoma, but this result was based on small numbers (five case subjects and no control subjects).

The observed associations between personal history of autoimmune and related conditions and Hodgkin lymphoma risk are consistent with several possible etiologic explanations, including 1) systemic immune stimulation or inflammation arising from autoimmune and related conditions leads to Hodgkin lymphoma, 2) treatment for autoimmune and related conditions increases risk of Hodgkin lymphoma, or 3) shared genetic or environmen-

tal risk factors underlie both conditions. The general lack of familial association of autoimmune conditions with risk of Hodgkin lymphoma argues against the third alternative. The exception was our observation of statistically significant positive effects of both personal and family histories of sarcoidosis with regard to increased risks of Hodgkin lymphoma, which would suggest some shared susceptibility.

Consistent with results of prior studies (27,50), we observed a strong association between Hodgkin lymphoma and personal history of rheumatoid arthritis. In the latency analyses, the estimates were very stable over time. A prior Swedish registry-based study of patients hospitalized with rheumatoid arthritis suggested there might be an increased risk of Hodgkin lymphoma among their young (0–14 years) offspring (five case subjects; standardized incidence ratio = 3.18, 95% CI = 1.03 to 7.42) (26). In contrast, in this larger study that included both the Swedish and Danish populations, we found no evidence for increased risk of Hodgkin lymphoma among subjects with a family history of rheumatoid arthritis. Thus, our study suggests that the underlying cause of the observed association derives from factors associated with rheumatoid arthritis itself. These factors could be related to

Table 5. Risk of Hodgkin lymphoma in relation to personal history of autoimmune and related condition, stratified by time between hospitalization for autoimmune and related conditions and subsequent Hodgkin lymphoma diagnosis*

Autoimmune condition	Autoimmune conditions 0–1 y before HL			Autoimmune condition 2–4 y before HL			Autoimmune condition 5–9 y before HL			Autoimmune condition 10+ y before HL		
	Case subjects	Control subjects	OR (95% CI)†	Case subjects	Control subjects	OR (95% CI)†	Case subjects	Control subjects	OR (95% CI)†	Case subjects	Control subjects	OR (95% CI)†
No autoimmune disease			1.0 (referent)			1.0 (referent)			1.0 (referent)			1.0 (referent)
Rheumatoid arthritis	17	8	<u>4.5 (1.9 to 10.5)</u>	13	13	<u>2.3 (1.1 to 5.1)</u>	13	8	<u>3.7 (1.5 to 9.0)</u>	18	21	<u>1.9 (1.1 to 3.6)</u>
Systemic lupus erythematosus	8	0	∞ (<i>P</i> < .0001)	2	4	1.2 (0.2 to 6.4)	3	0	∞ (<i>P</i> = .02)	2	2	2.3 (0.3 to 16.2)
ITP	3	0	∞ (<i>P</i> = .02)	1	0	∞ (<i>P</i> < .29)	0	0	–	1	0	∞ (<i>P</i> = .29)
Polymyalgia rheumatica	7	2	<u>7.3 (1.5 to 35.6)</u>	1	1	3.4 (0.2–53.8)	0	4	0 (<i>P</i> = .58)	1	0	∞ (<i>P</i> = .29)
Sarcoidosis	19	1	<u>47.4 (6.4 to 350)</u>	4	1	<u>12.7 (1.4 to 110)</u>	1	1	2.6 (0.2 to 42.2)	3	2	3.8 (0.6 to 23.0)

*OR = odds ratio; CI = confidence interval; ITP = immune thrombocytopenic purpura; HL = Hodgkin lymphoma.

†*P* values (two-sided) based on Fisher's exact test are given when no case or control subjects have the specified condition. All analyses were adjusted for birth year, sex, calendar period of Hodgkin lymphoma diagnosis, and region. Underlined entries have *P* values <.05.

systemic inflammation, to immune-modulating treatments for rheumatoid arthritis with drugs such as methotrexate and tumor necrosis factor antagonists (51–53), or to a combination of these factors.

Increasing evidence supports an association between systemic lupus erythematosus and malignancy (21,54). Elevated risk estimates have been observed for several types of hematopoietic tumors, with the most prominent risk for non-Hodgkin lymphoma (33,55). Based on small numbers (15 case subjects and six control subjects), we found a nearly sixfold increased risk of Hodgkin lymphoma among case subjects with a personal history of systemic lupus erythematosus. However, the lack of increased risk for Hodgkin lymphoma among subjects with a family history of this condition (analogous to rheumatoid arthritis, above) again suggests that the association between Hodgkin lymphoma and systemic lupus erythematosus is a consequence of the disordered immune function or of the associated inflammation characterizing systemic lupus erythematosus, its treatment (51,52), or both.

Little is known about lymphoma risk following sarcoidosis (56,57). When we evaluated the risk of Hodgkin lymphoma occurring subsequent to sarcoidosis by latency period, we found highly increased risks of Hodgkin lymphoma among subjects with a personal history of sarcoidosis up to 4 years before the diagnosis of Hodgkin lymphoma. The extremely elevated 47-fold risk for Hodgkin lymphoma in the first (0–1 year) latency period indicates that there could be a certain degree of diagnostic misclassification between sarcoidosis and Hodgkin lymphoma, as has been reported previously (58,59). However, because Hodgkin lymphoma risk remained strongly elevated 2–4 years after a reported hospital discharge with sarcoidosis, we believe that our findings cannot be explained solely by such misclassification. Furthermore, the risk estimates remained elevated for the last two latency periods, although the confidence intervals were wide, due to small numbers. The observed association between family histories of sarcoidosis and Hodgkin lymphoma indicates that the link between the two disorders could be due to some shared predisposition. Both Hodgkin lymphoma and sarcoidosis appear to involve a dysregulated host response against infectious agents. In development of sarcoidosis, very similar to young adult-onset Hodgkin lymphoma (2), putative infectious triggering agents have been proposed to be important (60). Epidemiologic studies have found evidence of geographic and seasonal clusters of sarcoidosis (61,62). Familial clustering of sarcoidosis has also been observed, suggesting that biologic predisposition to sarcoidosis is determined by genetic factors (63). It is also possible that misclassification of Hodgkin lymphoma as sarcoidosis in the past might have affected the finding of familial aggregation of sarcoidosis. However, the relatives diagnosed with sarcoidosis were equally distributed over the study period (not shown), supporting a true familial association.

Family history, but not personal history, of ulcerative colitis was associated with an increased risk of Hodgkin lymphoma. Linkage studies have implicated several genomic regions as likely to contain inflammatory bowel disease susceptibility genes (64), and one could hypothesize that these genes may also be related to Hodgkin lymphoma susceptibility. Because both ulcerative colitis and Hodgkin lymphoma are associated with high socioeconomic status (65,66), underlying factors related to socioeconomic status could also be involved. However, given a lack of association of Hodgkin lymphoma with personal history

of ulcerative colitis (Table 2) and the large number of autoimmune and related conditions that we investigated, the association with family history of ulcerative colitis could be due to chance.

Although the association between immune thrombocytopenic purpura and increased risk of Hodgkin lymphoma was statistically significant, this relationship must be interpreted with caution. Given that the strongest association between immune thrombocytopenic purpura and risk of Hodgkin lymphoma was seen in the first latency interval (0–1 year) and that immune thrombocytopenic purpura has been reported to be a complication of Hodgkin lymphoma (67), it cannot be ruled out that the observed finding is due to reverse causality (i.e., Hodgkin lymphoma could cause immune thrombocytopenic purpura).

Our study is the largest to date, to our knowledge, to assess the association of personal and familial histories of autoimmune and related conditions with risk of Hodgkin lymphoma. Among its strengths is that it included all case subjects with Hodgkin lymphoma diagnosed in Sweden and Denmark during a 40-year period with one or more linkable relatives. The use of a registry-based case-control design minimized recall bias, allowed us to evaluate risk according to age and sex, and provided a very large population-based sample with sufficient power to consider null findings to be statistically meaningful. In hierarchical regression models, we incorporated knowledge about common characteristics of certain conditions under study and tested the impact of autoimmune and related disorders simultaneously. Because the odds ratios from the hierarchical and the conventional logistic models differed only slightly for our principal findings, we feel confident in the results.

Limitations of this study include incomplete ascertainment of first-degree relatives of case and control subjects, lack of information on potential confounders, lack of validation of the hospital discharge registry-based diagnoses for autoimmune and related conditions, and lack of information on subtype of Hodgkin lymphoma and on potentially important characteristics of the Hodgkin lymphoma tumors that may be etiologically relevant, such as EBV status. Although the current investigation is the most comprehensive study of autoimmunity and subsequent risk of Hodgkin lymphoma to date, the lack of outpatient data for most years (in particular, the fact that for Denmark such data were available only for 1994–1997) is a limitation because it presumably led to underascertainment of autoimmune and associated conditions that did not result in hospitalizations. However, because personal and family histories of autoimmune and related disorders were assessed among matched control subjects using the same hospital discharge registries, underdiagnosis of autoimmune and related disorders in subjects or their first-degree relatives should be nondifferential between case subjects and their matched control subjects, and thus, any bias should have been conservative, i.e., toward a null association. Finally, the results of the logistic regression models have to be interpreted with caution due to the large number of tests that were performed. In the hierarchical regression models formulation, however, the focus of the inference is on the three overall group means, resulting in lesser burden of multiple testing. In addition, spurious odds ratio estimates of single conditions are pulled in toward the group-specific mean (see Appendix).

The results of this study, if confirmed by other studies, may have clinical implications for the treatment of patients with autoimmune or related conditions. Given that autoimmunity is a

well-known risk factor for non-Hodgkin lymphoma (29) and that the median age at diagnosis of non-Hodgkin lymphoma is 66 years (1), physicians may currently have a relatively lower threshold for initiating further workup of older (compared with younger) patients with a history of autoimmune disease who suffer from symptoms such as splenomegaly, lymphadenopathy, fever, weight loss, and/or night sweats. However, our observation of elevated risk of Hodgkin lymphoma arising in both young and older adults following certain systemic autoimmune conditions suggests that more aggressive workup should be undertaken for patients of any age with a personal history of autoimmune disease and new onset of symptoms that might be explained by a lymphoma diagnosis. It is particularly important to diagnose young adult-onset Hodgkin lymphoma at an early stage to improve the probability of cure, to avoid unnecessary trauma for the patient, and to minimize risks of secondary complications due to Hodgkin lymphoma treatment. However, one has to keep in mind that the absolute lifetime risk of Hodgkin lymphoma in whites is only 0.26% in males and 0.21% in females (1). Thus, although the relative risk of Hodgkin lymphoma is elevated for individual patients affected by rheumatoid arthritis, systemic lupus erythematosus, immune thrombocytopenic purpura, polymyalgia rheumatica, or sarcoidosis, the public health impact of these findings is small.

In conclusion, our large population-based study assessing risks of Hodgkin lymphoma according to personal and familial histories of a broad range of autoimmune and related diseases provides clues to the role of immune dysregulation and/or inflammation in etiology of Hodgkin lymphoma. We found personal history of specific systemic autoimmune conditions (in particular, rheumatoid arthritis and systemic lupus erythematosus) to be strongly associated with risk of Hodgkin lymphoma. The associations of both personal and family histories of sarcoidosis with increased risk of Hodgkin lymphoma suggest shared susceptibility that may be of importance in the pathogenesis of this disease. It is important to explore whether the observed associations are due to underlying systemic immune stimulation or inflammation, treatment, shared susceptibility, or a combination.

APPENDIX

The general two-stage hierarchical logistic regression model (35) can be formulated as follows. In the first stage, we fitted a logistic regression model of the form $\text{logit}(p) = \alpha + \beta X + \gamma W$, where p is the probability of being a case, X stands for the individual autoimmune disorders, and W denotes other independent variables, i.e., year of birth, sex, calendar period of Hodgkin lymphoma diagnosis, and region. The coefficients β represent the impact of X , the autoimmune conditions of interest, and γ represents the effects of the other covariates. In the second stage, we modeled β using information on the similarity of autoimmune disorders falling into the same broad group. In our application, we assumed (in vector notation) the linear model $\beta = Z\pi + \delta$, where Z denotes the matrix mapping the autoimmune disorders into one of the three Groups A–C defined above. Specifically, the Z matrix consisted of three rows of ones or zeros, that is $Z_{ij} = 1$ if X_j falls into the i th group A–C and $Z_{ij} = 0$ otherwise. Autoimmune disorders falling into the same group are thus assumed to have the same group effect π . For example, autoimmune disorders in group A share the same group mean π_1 . We assume that the disorders within a group are exchangeable and model the δ 's as independent normal random variables with variance τ (the τ is not assumed to be equal for the different components of δ). The δ 's stand for residual effects remaining after accounting for X and Z that may arise, for example,

from differences in the effects of autoimmune disorders within Groups. We also present estimated individual autoimmune disease effects, by combining the fixed and predicted random effects for the individual autoimmune conditions. Models that included both personal and family history of autoimmune conditions were of the form $\text{logit}(p) = \alpha + \beta_1 X + \beta_2 FH + \gamma W$, where both β_1 and β_2 were modeled using a linear model $\beta_i = \pi_i Z_i + \delta_i$, with the same Z matrix as for the personal history model.

In the hierarchical model all variables are fit simultaneously, and therefore, each P value (or confidence interval) is adjusted for all other autoimmune and related conditions present in the model. The models were fitted using PROC GLIMMIX (SAS version 9.1).

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L. Mellekjaer, G. Gridley, J. H. Olsen, K. Hemminki, M. S. Linet, and L. R. Goldin obtained the data. O. Landgren, E. A. Engels, K. F. Kerstann, R. M. Pfeiffer, and W. Wheeler analyzed the data. O. Landgren initiated this work and wrote the report. All authors were involved in the interpretation of the results and read, commented on, and approved the final version of the manuscript. O. Landgren, E. A. Engels, R. M. Pfeiffer, and L. R. Goldin had full access to all the data in the study and take responsibility for the integrity of the data and the

accuracy of the data analysis. Each author declares that he/she has no conflict of interests relevant to this paper.

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