



Original Contribution

Autoimmune and Atopic Disorders and Risk of Classical Hodgkin Lymphoma

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Initially submitted November 20, 2014; accepted for publication March 26, 2015.

Results from previous investigations have shown associations between the risk of Hodgkin lymphoma (HL) and a history of autoimmune and atopic diseases, but it remains unknown whether these associations apply to all types of HL or only to specific subtypes. We investigated immune diseases and the risk of classical HL in a population-based case-control study that included 585 patients and 3,187 controls recruited from October 1999 through August 2002. We collected information on immune diseases through telephone interviews and performed serological analyses of specific immunoglobulin E reactivity. Tumor Epstein-Barr virus (EBV) status was determined for 498 patients. Odds ratios with 95% confidence intervals were calculated using logistic regression analysis. Rheumatoid arthritis was associated with a higher risk of HL (odds ratio (OR) = 2.63; 95% confidence interval (CI): 1.47, 4.70), especially EBV-positive HL (OR = 3.18; 95% CI: 1.23, 8.17), and with mixed-cellularity HL (OR = 4.25; 95% CI: 1.66, 10.90). HL risk was higher when we used proxies of severe rheumatoid arthritis, such as ever having received daily rheumatoid arthritis medication (OR = 3.98; 95% CI: 2.08, 7.62), rheumatoid arthritis duration of 6–20 years (OR = 3.80; 95% CI: 1.72, 8.41), or ever having been hospitalized for rheumatoid arthritis (OR = 7.36; 95% CI: 2.95, 18.38). Atopic diseases were not associated with the risk of HL. EBV replication induced by chronic inflammation in patients with autoimmune diseases might explain the higher risk of EBV-positive HL.

atopic hypersensitivity; Epstein-Barr virus; Hodgkin lymphoma; primary Sjögren's syndrome; rheumatoid arthritis; systemic lupus erythematosus

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; IgE, immunoglobulin E; NHL, non-Hodgkin lymphoma; OR, odds ratio; RA, rheumatoid arthritis; SCALE, Scandinavian Lymphoma Etiology.

Hodgkin lymphoma (HL), a malignant neoplasm of B-cell origin (1), is among the most common cancers in adolescents and young adults. Few risk factors for HL have been established. This may reflect the fact that HL comprises at least 2 etiologically heterogeneous entities and that the composition of HL cases that are studied therefore might influence observed associations (2). For instance, the 20%–30% of HL cases that harbor the Epstein-Barr virus (EBV) in the malignant cells, a condition referred to as EBV-positive HL, most likely have a different etiology than the 70%–80% of cases that are EBV-negative (2). Thus, infectious mononucleosis, immune suppression, and cigarette smoking all seem to increase the risk of HL, particularly EBV-positive HL (2–5).

Meanwhile, no etiologic factors for EBV-negative HL have been firmly established.

In several previous investigations, it has been suggested that HL risk is higher among patients with autoimmune diseases, including rheumatoid arthritis (RA) (6–12), systemic lupus erythematosus (10, 11, 13–15), sarcoidosis (10, 11), and immune thrombocytopenic purpura (10, 11). Because HL EBV-status has not been available in these investigations, it is not known whether the reported associations are common to both EBV-positive and EBV-negative HL or if they are particular to one or the other. Furthermore, several autoimmune diseases have been strongly associated with a higher risk of non-Hodgkin lymphoma (NHL) (6–8, 15, 16). Because the

delineation between HL and NHL historically has been imprecise (17), the higher HL risk associated with autoimmune disease could theoretically reflect diagnostically misclassified cases of NHL (18). With one exception (12), none of the previous studies in which associations with autoimmune diseases were suggested included a review of tumor material to confirm the HL diagnosis (6–11, 13–15).

Compared with autoimmune diseases, less attention has been paid to the putative association between risk of HL and atopic disorders. In some studies, researchers have reported a lower risk of HL in patients with asthma (19) or hay fever (20); in others, there was a higher risk in patients with history of eczema (21); and in still others, there was no association (22–24). However, it is not known whether the reported associations with atopic disease are common to both EBV-positive and EBV-negative HL or are specific to only one, which makes it critical to know the status of the studied patients. To provide a more detailed understanding of HL epidemiology, we investigated the association between autoimmune and atopic disorders and the risk of HL by tumor EBV-status in a large Danish-Swedish case-control investigation encompassing 585 patients with classical HL and 3,187 population controls.

METHODS

Subjects

The present investigation was part of the Scandinavian Lymphoma Etiology (SCALE) Study, a population-based case-control study of risk factors for malignant lymphomas. The HL study base encompassed the entire Danish population who were 18–74 years of age during the period of June 1, 2000, to August 30, 2002, and the corresponding Swedish population from October 1, 1999, to April 15, 2002 (3, 16, 25). Participants who were recruited in the pilot phase of a Danish regional study starting on November 1, 1999, were also included, as were prevalent cases of HL diagnosed after January 1, 1999, in either country. The patients were identified through a rapid case ascertainment system that included data from 157 hospital clinics in the 2 countries. Continuous collaboration with the Danish National Pathology Registry in Denmark and the 6 regional cancer centers in Sweden ensured complete reporting through the network. The estimated coverage of the Danish National Pathology Registry and the Swedish cancer registers is close to 100% (25). In both countries, the source population was further restricted to persons who had sufficient knowledge of the Danish or Swedish language to participate in a telephone interview and no known history of organ transplantation, infection with human immunodeficiency virus, or history of other hematopoietic malignancies.

Controls

Controls were randomly sampled from the entire Danish and Swedish populations using continuously updated computerized population registers. A subset of controls was sampled every 6 months during the study period and frequency-matched to controls within each country on the expected age

(in 10-year strata) and sex distributions of the combined group of HL and NHL patients. Among eligible subjects, the participation rates were 91% in patients and 71% in controls (3).

Ethics

The present study was approved by the Danish Data Protection Agency and by relevant scientific ethics committees according to the Helsinki declaration in both countries. Informed consent was obtained from all participants.

Classification of cases, histology, and EBV status

The procedure for histopathologic review of cases has been described in detail previously (25). Tumor biopsies from participating HL patients were retrieved from pathology departments for diagnostic validation and EBV analysis. Cases from whom tumor material could not be retrieved were classified according to the original histopathologic description. Combining these 2 approaches resulted in 64 cases that could not be classified beyond unspecified classical HL. Because nodular lymphocytic predominant HL is believed to constitute a unique subgroup (1), cases with this type of HL were omitted from the analyses ($n = 33$). The tumor biopsies that we retrieved were analyzed for the presence of EBV in the neoplastic Hodgkin-Reed-Sternberg cells using immunohistochemical staining for EBV latent membrane protein-1 and/or in situ hybridization for EBV-encoded small RNAs, as has been previously described (3). Tumor EBV status was available for 498 (85%) of 585 cases.

Exposure information

Information on suspected risk factors for malignant lymphoma was obtained through standardized telephone interviews that were identical in the 2 countries and conducted by trained interviewers. Recorded information included family characteristics (number of siblings and birth order), parental and personal educational levels, childhood housing conditions, tobacco smoking history, history of infectious mononucleosis, and history of an array of autoimmune and atopic disorders (3, 16, 26). In particular, using both lay and medical terminology, specific questions were asked to assess history of RA, Sjögren's syndrome, systemic lupus erythematosus, celiac disease, Crohn's disease, ulcerative colitis, psoriasis, and sarcoidosis as diagnosed by a doctor, as well as history of diabetes mellitus. These questions were followed by additional queries regarding age at diagnosis or onset of symptoms and treatment when relevant, as has been previously described (16). Accordingly, participants with a self-reported history of RA were further questioned about disease duration, RA-related surgeries, and constraints on daily life. We obtained information on hospital discharges for RA before lymphoma diagnosis from nationwide population-based hospital discharge registers in each country (27, 28) and used that data as a surrogate for more severe disease. We also assessed history of allergic rhinitis, atopic eczema in childhood, and medically confirmed asthma, as well as age at onset of symptoms and treatment for allergic rhinitis and asthma (16, 26).

Laboratory analyses

Participants in the SCALE Study were asked to provide blood samples. Patients were asked to provide samples before initiation of treatment whenever possible, and controls were asked as soon as possible after interview (26). To supplement data self-reported history of allergic disease, we carried out serological analyses for specific immunoglobulin E (IgE) reactivity against common inhalant allergens using an enzyme-linked immunosorbent assay (ImmunoCAP Phadiatop test, Phadia, Uppsala, Sweden) (29).

Statistical analyses

We used unconditional multiple logistic regression to calculate odds ratios, with 95% Wald test-based confidence intervals, as estimates of the relative risk of HL in association with studied exposures. A reported diagnosis of autoimmunity was excluded if symptoms began less than 2 years before the lymphoma diagnosis (or 2 years before the interview for controls) to avoid inclusion of autoimmune phenomena due to incipient lymphoma (30). We considered the association of HL with history (ever vs. never) of each of the individual autoimmune diseases separately. For RA, we further carried out detailed analyses to characterize the association with HL according to measures of disease severity.

The association between HL risk and atopy was assessed using both self-reported exposure and results from the serological analyses. Regarding the latter, a negative test for atopy was defined according to the manufacturer's recommendations (cutoff <0.36 kU/L) (29). To evaluate possible effects of HL treatment, supplementary analyses were carried out that were stratified according to whether blood had been sampled before or after initiation of treatment. Here, we also compared levels of IgE reactivity between HL patients. Finally, we evaluated the association between HL risk and self-reported history of hay fever corroborated by serologic IgE reactivity in pretreatment samples.

We analyzed the risk of all types of classical HL combined and EBV-positive and EBV-negative HL separately. In keeping with HL classification tradition and to retain comparability with previous reports (1), we also analyzed HL by histological subtype, that is, nodular sclerosis, mixed-cellularity, and "other" HL, with the last group including lymphocyte-depleted ($n = 2$), lymphocyte-rich ($n = 8$), and unclassifiable ($n = 64$) HL, and by age at diagnosis, that is, younger (18–44 years of age; $n = 384$) and older (45–74 years of age; $n = 201$).

The statistical significance of independent variables was tested using the likelihood ratio test. We tested for homogeneity of the associations between exposures and different outcomes by tumor EBV status or histological subtype in a polytomous logistic regression model using the likelihood ratio test. Potential confounders were considered based on prior knowledge of risk factors for HL within the SCALE Study (3, 16). Thus, all statistical analyses were adjusted for the matching variables of age (in 10-year categories), sex, and country, as well as cigarette smoking, number of younger and older siblings, history of infectious mononucleosis, mother's age at participant's birth, and country-specific measures of mother's level of education. All statistical tests were

2-sided, and P values less than 5% were considered statistically significant.

RESULTS

There were slightly more male cases ($n = 305$; 52%) than female cases ($n = 280$; 48%) (Table 1). The prevalence of autoimmune diseases was higher among cases ($n = 21$; 3.6%) than among controls ($n = 88$; 2.8%). Serological classification of atopy as determined by IgE testing was available for 510 patients with HL (87% of case patients) and 2,086 control subjects (65% of controls). As previously reported, 50% of cases with mixed-cellularity HL and cases with 22% of nodular sclerosis HL were EBV positive (3).

Autoimmune diseases

Self-reported RA was associated with a more than 2-fold higher risk of HL overall (odds ratio (OR) = 2.63, 95% confidence interval (CI): 1.47, 4.70) (Table 2). The difference in risk was statistically significant for EBV-positive HL (OR = 3.18, 95% CI: 1.23, 8.17) but not for EBV-negative HL (OR = 1.60, 95% CI: 0.64, 4.01). However, the 2 risk estimates were not statistically significantly different (P for homogeneity = 0.38). The higher risk with RA applied to mixed-cellularity HL but less so to nodular sclerosis HL (Table 2), as well as the small combined group of other subtypes (data not shown). Risk estimates for HL overall were similar in younger (OR = 2.89, 95% CI: 0.47, 17.82) and older (OR = 2.64, 95% CI: 1.42, 4.88) adults.

Systemic lupus erythematosus was reported by 2 patients and 2 controls, and primary Sjögren's syndrome was reported by 1 patient and 2 controls; due to the low numbers, we did not estimate the individual associations of the 2 conditions with HL.

Self-reported history of type I diabetes mellitus (Table 2), psoriasis (Table 2), ulcerative colitis (3 patients and 18 controls), celiac disease (1 patient and 10 controls), sarcoidosis (2 patients and 12 controls), and Crohn's disease (0 patients and 6 controls) were not associated with HL risk, although except for psoriasis, there were few subjects with these autoimmune diseases (data not shown).

Rheumatoid arthritis characteristics

We carried out analyses of HL risk by detailed characteristics of RA disease in an attempt to disentangle the mechanisms underlying the observed associations between the 2 conditions; however, these results should be interpreted cautiously because of the low numbers of subjects (21 patients with RA in total). Here, HL risk appeared to be more elevated among those who had ever received daily medication for RA (including treatment with disease-modifying antirheumatic drugs), had a longer RA duration, had undergone surgery for RA, had more disease-related constraints on daily activities, or had been hospitalized for RA (Table 3). Again, risk estimates were highest for EBV-positive cases (Table 3).

Atopic diseases

Self-reported history of allergic rhinitis was associated with a nonsignificantly lower risk of HL overall (OR = 0.81,

Table 1. General and Disease Characteristics of Cases With Hodgkin Lymphoma and Controls, Scandinavian Lymphoma Etiology Study, 1999–2002

Characteristic	No. of Control Subjects (n = 3,187)	Total No. of HL Cases ^a (n = 585)	No. With Nodular Sclerosis HL (n = 409)	No. With Mixed-Cellularity HL (n = 102)	No. of Other and Unclassified HL (n = 74)	No. With EBV-Positive HL (n = 142)	No. With EBV-Negative HL (n = 356)
Age, years							
18–34	312	277	211	41	25	58	182
35–54	861	171	121	25	25	37	112
55–74	2,014	137	77	36	24	47	62
Sex							
Male	1,767	305	202	66	37	91	166
Female	1,420	280	207	36	37	51	190
Country							
Denmark	1,186	247	170	40	37	64	144
Sweden	2,001	338	239	62	37	78	212
Rheumatoid arthritis ^b							
No	3,073	559	395	93	71	134	345
Yes	88	21	11	7	3	8	7
Psoriasis ^b							
No	3,002	555	390	97	68	135	338
Yes	150	25	17	3	5	7	14
Type I diabetes ^b							
No	3,021	577	405	100	72	141	351
Yes	140	6	3	1	2	1	4
Allergic rhinitis ^b							
No	2,340	429	294	79	56	107	261
Yes	815	150	111	21	18	34	91
Childhood eczema ^b							
No	2,935	521	360	96	65	129	318
Yes	202	58	43	6	9	12	35
Asthma ^b							
No	2,896	534	376	92	66	131	325
Yes	275	50	32	10	8	11	30
IgE reactivity ^b							
Negative	1,714	388	264	73	51	92	238
Positive	372	122	91	19	12	29	75
IgE reactivity before treatment or in controls ^b							
Negative	1,714	131	87	27	17	26	86
Positive	372	53	36	11	6	12	35
IgE reactivity during treatment or in controls ^b							
Negative	1,714	158	117	27	14	40	98
Positive	372	41	33	5	3	9	25
Self-reported hay fever and positive IgE reactivity before treatment or in controls ^b							
Negative	1,834	146	97	30	19	30	96
Positive	233	37	25	8	4	8	25

Abbreviations: EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; IgE, immunoglobulin E.

^a Diseases with fewer than 5 cases are not presented.^b Numbers do not add up to the total number of participants because some questions were left unanswered or, for IgE reactivity analyses, not all participants gave a blood sample (75 cases, 1,101 controls).

Table 2. Relative Risk^a of Hodgkin Lymphoma, by Histological Subtype and Tumor Epstein-Barr Virus Status, in Association With Previous Autoimmune Diseases or Allergic Conditions, Scandinavian Lymphoma Etiology Study, 1999–2002

Exposure	All HL (n = 585)		Nodular Sclerosis HL (n = 409)		Mixed-Cellularity HL (n = 102)		EBV-Positive HL (n = 142)		EBV-Negative HL (n = 356)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Rheumatoid arthritis ^b										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	2.63	1.47, 4.70	2.10	0.96, 4.58	4.25	1.66, 10.9	3.18	1.23, 8.17	1.60	0.64, 4.01
Psoriasis ^b										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.93	0.54, 1.60	0.78	0.39, 1.56	0.82	0.25, 2.69	1.12	0.46, 2.70	0.90	0.45, 1.79
Type I diabetes ^b										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.55	0.22, 1.40	N/A ^c	N/A ^c	N/A ^c	N/A ^c	N/A ^c	N/A ^c	N/A ^c	N/A ^c
Allergic rhinitis										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.81	0.64, 1.03	0.86	0.65, 1.14	0.68	0.39, 1.16	0.85	0.55, 1.33	0.77	0.57, 1.04
Childhood eczema										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.82	0.56, 1.20	0.83	0.54, 1.27	0.50	0.19, 1.31	0.81	0.40, 1.63	0.70	0.44, 1.11
Asthma										
No	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Yes	0.81	0.54, 1.20	0.77	0.48, 1.25	0.99	0.47, 2.09	0.77	0.38, 1.56	0.85	0.52, 1.39
IgE reactivity										
Negative	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive	0.88	0.65, 1.21	0.93	0.65, 1.32	0.78	0.42, 1.44	0.82	0.48, 1.41	0.88	0.61, 1.27
IgE reactivity before treatment or in controls										
Negative	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive	0.97	0.64, 1.49	0.87	0.52, 1.45	1.35	0.59, 3.09	1.23	0.54, 2.80	0.92	0.55, 1.53
IgE reactivity during treatment or in controls										
Negative	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive	0.85	0.54, 1.32	0.92	0.56, 1.51	0.53	0.17, 1.66	0.70	0.29, 1.69	0.84	0.49, 1.43
Self-reported hay fever and positive IgE reactivity before treatment or in controls										
Negative	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Positive	0.95	0.58, 1.54	0.88	0.49, 1.62	1.30	0.51, 3.26	1.19	0.47, 3.00	0.95	0.54, 1.67

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; HL, Hodgkin lymphoma; IgE, immunoglobulin E; N/A, not applicable; OR, odds ratio.

^a Relative risks are presented as odds ratios. Results were adjusted for age, sex, country, current cigarette smoking, number of younger and older siblings, history of infectious mononucleosis, mother's age at participant's birth, and maternal socioeconomic status.

^b Subjects were excluded if symptoms began less than 2 years before the lymphoma diagnosis or interview.

^c Values were not calculated because fewer than 3 cases and controls were exposed.

95% CI: 0.64, 1.03; $P = 0.09$) (Table 2) and EBV-negative HL (OR = 0.77, 95% CI: 0.57, 1.04; $P = 0.09$) (Table 2). Childhood eczema was not associated with the risk of HL, whether overall or for any of the subgroups considered. Self-reported history of asthma was not associated with risk of HL overall or with any of the HL subgroups (Table 2).

A comparison of self-reported hay fever with corresponding results from IgE reactivity tests showed that controls were

8 times (OR = 8.46, 95% CI: 6.61, 10.82) more likely to be seropositive than were controls without hay fever. Overall, atopy status determined by serological analysis was also not statistically significantly associated with HL risk, whether overall or by subgroup (Table 2). Analyses in which we considered the timing of blood sampling suggested that treatment status interfered with IgE reactivity, because in analyses adjusted only for matching factors (age, sex, and country),

Table 3. Relative Risk^a of Hodgkin Lymphoma in Relation to Characteristics of Rheumatoid Arthritis, Scandinavian Lymphoma Etiology Study, 1999–2002

Exposure	No. of Controls	All HL			EBV-Positive HL			EBV-Negative HL			Nodular Sclerosis HL			Mixed-Cellularity HL		
		No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI
History of RA																
No	3,073	559	1.00	Referent	134	1.00	Referent	345	1.00	Referent	395	1.00	Referent	93	1.00	Referent
Yes	88	21	2.63	1.47, 4.70	8	3.18	1.23, 8.17	7	1.60	0.64, 4.01	11	2.10	0.96, 4.58	7	4.25	1.66, 10.9
Treatment >4 weeks ^b																
No RA	3,073	559	1.00	Referent	134	1.00	Referent	345	1.00	Referent	395	1.00	Referent	93	1.00	Referent
Never ^c	35	5	0.86	0.23, 3.23	1	0	0	2	0.36	0.04, 3.36	2	0.33	0.04, 3.04	2	1.72	0.22, 13.7
Ever	52	16	3.98	2.08, 7.62	7	5.86	2.19, 15.7	5	2.90	1.09, 7.71	9	3.78	1.64, 8.67	5	6.13	2.15, 17.5
Disease duration, years																
No RA	3,073	559	1.00	Referent	134	1.00	Referent	345	1.00	Referent	395	1.00	Referent	93	1.00	Referent
2–5	16	3	2.87	0.73, 11.2	0	0	0	1	1.63	0.20, 13.5	1	1.39	0.16, 11.7	1	3.47	0.38, 31.7
6–20	34	13	3.80	1.72, 8.41	7	8.98	3.00, 26.9	4	2.06	0.59, 7.23	8	3.70	1.39, 9.81	4	6.89	1.89, 25.1
>20	38	5	1.50	0.52, 4.30	1	1.09	0.14, 8.65	2	1.10	0.21, 5.82	2	0.92	0.18, 4.72	2	2.76	0.59, 13.0
Surgery for rheumatoid arthritis																
No RA	3,073	559	1.00	Referent	134	1.00	Referent	345	1.00	Referent	395	1.00	Referent	93	1.00	Referent
Never	75	15	2.07	1.04, 4.12	6	2.51	0.82, 7.68	4	0.86	0.24, 3.08	9	1.90	0.79, 4.58	4	2.40	0.68, 8.47
Ever	13	6	5.47	1.87, 16.0	2	7.00	1.23, 39.8	3	5.77	1.49, 22.3	2	3.12	0.63, 15.4	3	15.4	3.66, 64.7
Constraints of daily life																
No RA	3,073	559	1.00	Referent	134	1.00	Referent	345	1.00	Referent	395	1.00	Referent	93	1.00	Referent
No restraints	45	8	1.73	0.73, 4.07	1	0.77	0.10, 6.20	4	1.64	0.52, 5.22	4	1.26	0.39, 4.03	2	2.20	0.48, 10.1
Little/some	31	9	4.91	2.11, 11.4	5	10.2	3.15, 33.0	2	2.22	0.50, 9.85	5	3.99	1.30, 12.2	3	8.81	2.34, 33.1
A lot	9	3	2.44	0.44, 13.6	1	3.63	0.33, 40.0	1	0	0	2	3.38	0.41, 27.9	1	5.92	0.64, 54.4
Hospital discharge with rheumatoid arthritis																
No	3,038	576	1.00	Referent	139	1.00	Referent	352	1.00	Referent	405	1.00	Referent	98	1.00	Referent
Yes	15	9	7.36	2.95, 18.4	3	9.80	2.21, 43.5	4	6.48	1.92, 21.9	4	5.47	1.60, 18.7	4	15.7	4.35, 56.8

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; IgE, immunoglobulin E; HL, Hodgkin lymphoma OR, odds ratio; RA, rheumatoid arthritis.

^a Relative risks are presented as odds ratios. Results were adjusted for age, sex, country, current cigarette smoking, number of younger and older siblings, history of infectious mononucleosis, mother's age at participant's birth, and maternal socioeconomic status. History of rheumatoid arthritis was excluded if symptoms began less than 2 years before the diagnosis or interview.

^b Includes any daily tablet treatment for more than 4 weeks.

^c The "never treated" group includes participants who used local corticosteroid injections and/or had irregular use of nonsteroidal antiinflammatory drugs.

patients whose blood samples were taken before treatment were statistically significantly more likely to be IgE reactive than were patients whose blood samples were taken after treatment (OR = 1.73, 95% CI: 1.02, 2.92). This difference between subsets of patients was also apparent in analyses that were adjusted similarly to the case-control comparisons, only they were no longer statistically significant (OR = 1.57, 95% CI: 0.91, 2.71). This variation was to some extent also reflected in the associations with HL risk (Tables 1 and 2). In combination, self-reported hay fever accompanied by pretreatment IgE reactivity was not associated with HL risk (Table 2).

DISCUSSION

In the present investigation, we found that HL risk was higher in patients with a self-reported history of RA and that the risk increase tended to correlate with proxy measures for severity of disease. Self-reported history of allergic rhinitis was associated with a lower risk of HL that was of borderline statistical significance, but this inverse association was not borne out by any other questionnaire-based measures of atopic disease or by serological analyses for IgE reactivity.

Our findings add further credence to the previously reported theory that the association between RA and HL is causal in nature thanks to a number of study strengths. Specifically, unlike the present investigation, several of the earlier studies on autoimmune diseases and HL (6, 7, 9) exclusively included hospitalized patients. This subset of patients might constitute a biased subset of the autoimmune disease patient population who have a particularly higher risk of lymphoma (31) either because they suffer from more aggressive autoimmune disease, in which high inflammatory activity promotes HL development (31), or because they receive lymphoma-inducing treatment for autoimmune disease. Indeed, a higher occurrence of HL in patients treated with disease-modifying antirheumatic drugs has been reported (8, 32). Also, in contrast to the present study, the majority of previous studies have been register-based (6–11, 13–15) and therefore have not included control for risk factors common to both HL and autoimmune diseases, for example, smoking and socioeconomic status (3, 4, 6–11, 13–15, 33–35).

The observed association between HL and RA resembles those reported between a variety of autoimmune diseases, including RA and NHL (6–8, 15, 16, 23). Therefore, in theory, misclassified cases of NHL could contribute to the observed relation between RA and HL. However, because tumor biopsies were reviewed by expert hematopathologists for more than 90% of the patients in our study, we consider this as an unlikely explanation for our observations.

Meanwhile, the use of self-reported rather than validated histories of autoimmune diseases is a potential source of bias. As described in a previous investigation of NHL in the same study population, the prevalence of RA among the controls was in the upper range of what has been reported for the general population elsewhere (36). This excess might reflect selection bias among the controls or, more likely, misclassification of RA. However, such misclassification of RA would only contribute to the observed association if it were more extreme among HL patients than among controls. Because the results

of our analyses are congruent with those from register-based analyses in which an association between RA and HL was demonstrated (6–11, 13–15), we find this an unlikely scenario, especially because all participants were unaware of the hypothesis under study.

Absent obvious methodological explanations, our analyses therefore indicate that patients with RA—particularly those with severe disease—truly have a higher risk of HL. This excess risk appeared higher for cases with EBV-positive HL than for cases with EBV-negative HL, although no formally significant heterogeneity was noted. Patients with autoimmune diseases have elevated anti-EBV antibody titers (35, 37), but it is unclear whether EBV reactivation causes autoimmune disease or whether the elevated EBV antibodies are a consequence of the autoimmune disease (35). In prospective studies, however, autoimmune diseases appear to be associated with B-cell activation (e.g., leading to self-reactive antibodies) and with increased EBV replication in infected B cells (37). Thus, our findings are compatible with a model in which autoimmune disease activates EBV replication and thereby increases the risk of EBV-positive HL (35, 37). A stronger correlation of RA with EBV-positive HL than with EBV-negative HL was suggested in 2 register-based studies in which the strongest association was observed for mixed-cellularity HL, which is typically more often EBV-positive than is nodular sclerosis (1, 11, 38), as was also the case in our study. In our analyses, we did not rule out the possibility that the risk of EBV-negative HL might also be higher in RA patients, which means that there are potentially other mechanisms that link autoimmune disease with HL risk, for example, treatment and shared genetic susceptibility (2, 5).

Regarding atopic conditions, it has been speculated that atopy might be associated with a higher risk of HL, particularly among younger adults (21). In the present study, the prevalence of self-reported atopic diseases was lower among HL patients than among controls, albeit not statistically significantly so. Although the prevalence of overall serological evidence of atopy was also lower among HL patients than among controls, stratified analyses indicated that this could be explained to some extent by treatment. Indeed, self-reported hay fever and IgE reactivity in pretreatment samples also were not associated with HL risk. Atopic diseases and HL risks might both be related to correlates of socioeconomic affluence in childhood, such as number of siblings, housing density, and childhood infections (3, 39, 40), for which we controlled in our study. The findings with a lower prevalence of self-reported atopic diseases in HL patients are similar to observations in studies of NHL (26). However, for NHL, we previously found evidence of reverse causality, because analyses of prospectively sampled sera indicated that the inverse relationship with specific IgE reactivity arose only shortly before lymphoma diagnosis (26). On the whole, our observations are therefore entirely compatible with there being no association between atopic disease and HL risk.

Our investigation has a number of strengths and weaknesses. The strengths include the population-based setting, rapid case ascertainment, histopathologic review of more than 90% (3) of the cases in connection with EBV typing, classification of all HL cases according to the World Health Organization system, a high participation rate among cases

(90%), and relatively high participation rate among controls (70%).

Study weaknesses include potential participation bias and exposure misclassification. Accordingly, although we have no reason to assume this to be the case, we cannot fully exclude the possibility that participating controls differ from nonparticipants with respect to prevalence of the exposures under study that contributed to the observed associations. Autoimmune and atopic disease histories were self-reported and not validated. However, for most exposures, participants were asked specifically about medically confirmed diagnoses and, when relevant, about age at onset and treatment. Because autoimmune diseases are rare, the number of conditions that could be analyzed individually was limited.

In conclusion, we observed a statistically significantly higher prevalence of RA among patients who had been diagnosed with HL. Because the association was seemingly restricted to patients with EBV-positive tumors, we propose that chronic inflammation induces EBV replication, with an associated increased risk of EBV-positive HL.

ACKNOWLEDGMENTS

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This study was supported by the National Institutes of Health (grant 5 ROI CA-69269), Nordic Cancer Union (grant 16-02-D), and Plan Danmark. P.H. was further supported by the Uppsala-Örebro Regional Research Council. I.G. was further supported by the Swedish Society of Medicine and the Swedish Society for Medical Research. H.-O.A. was supported by the distinguished Professor Award from Karolinska Institutet (Dnr: 2368/10-221).

Conflict of interest: none declared.

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