LYMPHOID NEOPLASIA

Risk of familial classical Hodgkin lymphoma by relationship, histology, age, and sex: a joint study from five Nordic countries

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Key Points

- We provide clinically relevant familial risk estimates for classical HL patients by relationship, histology, age at diagnosis, and sex.

We aimed to provide the familial risk of classical Hodgkin lymphoma (HL) by relationship, histology, age at diagnosis, and sex. A cohort of 57 475 first-degree relatives of 13 922 HL patients diagnosed between 1955 and 2009 in 5 European countries was observed for HL incidence. The overall lifetime cumulative risk (CR) of HL in first-degree relatives of a patient with HL was 0.6%, which represents a threefold (standardized incidence ratio [SIR], 3.3; 95% confidence interval [CI], 2.8-3.9) increased risk over the general population risk. The risk in siblings (6.0-fold; 95% CI, 4.8- to 7.4-fold) was significantly higher than in parents and/or children (2.1-fold; 95% CI, 1.6- to 2.6-fold). Very high lifetime risk of HL was found for those with multiple affected first-degree relatives (13-fold; 95% CI, 2.8- to 39-fold) and for same-sex twins (57-fold; 95% CI, 21- to 125-fold). We found high familial risks between some concordant histologic subtypes of HL such as lymphocyte-rich (81-fold; 95% CI, 30- to 177-fold) and nodular sclerosis (4.6-fold; 95% CI, 2.9- to 7.0-fold) and also between some discordant subtypes. The familial risk in sisters (9.4-fold; 95% CI, 5.9- to 14-fold) was higher than in brothers (4.5-fold; 95% CI, 2.9- to 6.7-fold) or unlike-sex siblings (5.9-fold; 95% CI, 4.3- to 8.1-fold). The lifetime risk of HL was higher when first-degree relatives were diagnosed at early ages (before age 30 years). This study provides tangible absolute risk estimates for relatives of HL patients, which can be used as a sex-, age-, and family history-based risk calculator for classical HL by oncologists and genetic counselors. (*Blood*. 2015;126(17):1990-1995)

Introduction

Hodgkin lymphomas (HLs) are lymphoid tumors that represent about 1% of all de novo neoplasms that occur every year worldwide, with more than 65 000 new cases of HLs diagnosed globally per annum.[1,2] HL is one of the most common cancers among young adults in Western countries.[3,4] It is an etiologically and histologically heterogeneous disease. HL has a bimodal age distribution, the first peak being in young adulthood (age 15-35 years) and the second being in those older than age 55 years, although these peaks may vary with geographic area and ethnicity.[5,6] The etiology of HL is largely unknown. However, higher risks have been reported in those with autoimmune diseases, males (except in adolescents and young adults), persons with higher socioeconomic status, smaller families, those with congenital and acquired immunodeficiency, those with family history of HL or other lymphoid neoplasms, and those with increased antibody titers against certain Epstein-Barr virus (EBV) antigens.[7-9] Higher socioeconomic status is associated with older age at EBV infection. In fact, delayed EBV infection in particular increases the risk of EBV-positive (but not EBV-negative) HL, and the influence of age, sex, and socioeconomic status may vary by tumor EBV status.[10] Patients from developing countries were almost twice as likely to have EBV-associated HL compared with individuals from more westernized countries.[11] For EBV-associated HL patients, there is a small peak in incidence in young adults (age 15-24 years) and a second larger peak in older adults. By contrast, HL that is not associated with EBV (EBV-negative HL) accounts for the major part of the young adult incidence peak, after which the incidence of this disease entity declines.[12,13] The exact role of EBV in the development of HL is not clear. Many people are infected with EBV (95% by age 30 years),[14] but very few develop HL (less than 1%).[1] Approximately 30% of HL patients in the developed world have detectable EBV genomes and gene products in their tumor cells. Genetic characteristics as a predisposing factor have been suggested by several studies.[15,16]

Pathologists currently use the World Health Organization modification of the Revised European-American Lymphoma classification for the histologic classification for adult HL.[17,18] Accordingly, HLs are classified as classical HL and nodular lymphocyte-predominant HL. Classical HL includes nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich subtypes. These subtypes have different

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age-specific incidence curves, sex ratio, and racial patterns.[18,19] In our study, we focused on classical HL because nonclassical HL is a separate disease entity.

Family history is a risk factor for which advice and management may bring both psychosocial and medical benefits. However, to provide evidence-based advice, counselors and caregivers along the entire medical referral system chain need to be aware of the true familial risks, particularly for cancers such as HL that are not covered by the current familial risk management guidelines. Some previous studies show a familial clustering of HLs and suggest higher risks at a relatively young age.[15,16,20] Few studies have provided familial risks by sex of the patient and the relative, suggesting gender concordance among sibling pairs with HL.[15,21,22] The rarity of familial classical HL has hampered a detailed analysis of familial clustering by relationship, histology, age, and sex, and it has probably contributed to the variation even in risk estimates for first-degree relatives.

Moreover, most of the previous studies provide only familial relative risk in terms of standardized incidence ratio (SIR) that needs to be translated to a readily understandable estimate such as cumulative risk (CR) for use in clinical practice. This study benefited from the nationwide family cancer data from 5 countries in northern Europe that have unbiased genealogical and high-quality cancer data to systematically quantify the familial risk of all concordant and discordant histologic subtypes of classical HL in relatives of HL patients. Our goal was to provide the familial risks of classical HL in terms of CR stratified by type of relationship, histology, age, and sex of patients and their relatives.

Materials and methods

Our large data set consisted of pooled family cancer data from 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Information on all HL patients in this large data set (n = 13 922) and their relatives (n = 57 475) was used for this study. Nordic countries have population-based registers through which any lymphoma patient can be identified with the cancer status and histology type in their parents, siblings, or children. With the exception of Iceland, which has complete genealogical information for all the participants, sibships could be ascertained only in the offspring generation (those with identified parents). The country-specific inclusion and exclusion criteria are provided in the supplemental Data available at the *Blood* Web site. In addition, the data characteristics of each country are shown in supplemental Table 1. The Lund regional Ethics Committee approved the study protocol. Protocol followed the Declaration of Helsinki.

Statistical analyses

SIRs were used to compare the cancer risks for individuals with identified first-degree relatives and a family history of cancers in their relatives compared with the risk in their counterparts in the general population. The follow-up in the cohort of family members of HL patients was started at birth, immigration, or the country-specific starting year of cancer registration (January 1, 1955, 1961, 1967, and 1968; supplemental Table 1), whichever came latest. The follow-up was terminated at death, emigration, or the closing date of the study (December 31, 2008, 2009, and 2010; supplemental Table 1). More detailed information on follow-up calculation is available in the supplemental Data. The SIRs were calculated as the ratio of observed to expected numbers of cases (indirect method of standardization). The sex-, age- (5-year bands), period- (5-year bands), cancer site-, histology-, and country-specific background population incidence rates provided by the cancer registries were used as the reference groups (strata-specific cancer incidence rate in the background population). The expected numbers were calculated as the strata-specific cancer incidence rate in the background population multiplied by the corresponding person-years for patients who had first-degree relatives with HL. The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. SAS version 9.2 software (SAS Institute Inc., Cary, NC) was used for the data analysis.

The lifetime (assumed to be 0-79 years) cumulative risk was calculated on the basis of the following formulas: age-specific annual incidence rate = number of cases for each 5-year age group divided by person-years for that age group (0-4, ... , 75-79); age-specific cumulative rate = 5 × age group-specific annual incidence rate; lifelong cumulative rate = sum of all age-specific cumulative rates; and lifelong cumulative risk = $1 - e^{(-\text{lifelong cumulative rate})}$. To avoid bias in cumulative risk calculation toward overestimation as a result of ignorance of competing causes of death, exact values for person-years from individual data (not from conventional aggregated data) were used in the calculation of incidences.

Results

Overall familial risk

The overall CR of HL in first-degree relatives of a patient with HL was 0.6%, which represents a threefold increase over the general population risk (SIR, 3.3; 95% CI, 2.8-3.9; n = 149; data not shown).

Familial risk by relationship

In general, the risk in siblings (0.9%; 95% CI, 0.6%-1.1%; Table 1) (6.0-fold; 95% CI, 4.8- to 7.4-fold; Table 2) was significantly higher than in parents and/or children (0.4%; 95% CI, 0.3%-0.5%; Table 1) (2.1-fold; 95% CI, 1.6- to 2.6-fold; Table 2). The separate analyses for those with an affected parent and for those with an affected offspring did not yield any significant difference (all 95% CIs overlapped). Therefore, we did not report the results separately. Very high risk of HL was found for 3 patients with multiple affected first-degree relatives (2.8% [95% CI, 0%-5.9%] to 8.4% [95% CI, 0%-17%]; Table 1) (13-fold; 95% CI, 2.8- to 39-fold; Table 2) and for 6 same-sex twins (13%; 95% CI, 0%-26%; Table 1) (57-fold; 95% CI, 21- to 125-fold; Table 2). There were no affected unlike-sex twins in the data.

Familial risk by histology

CR of HL in first-degree relatives of HL patients by histology subtypes is shown in Table 3. Family history of lymphocyte-rich HL significantly increased CR in close relatives to about 0.9% (95% CI, 0.4%-1.4%) whereas the CR for mixed cellularity and nodular sclerosis was 0.4% (95% CI, 0.2%-0.6%) to 0.5% (95% CI, 0.3%-0.6%), respectively. We found high familial risk of some concordant histologic subtypes of HL such as lymphocyte-rich (SIR, 81; 95% CI, 30-177; n = 6) and nodular sclerosis (SIR, 4.6; 95% CI, 2.9-7.0; n = 22) and also some discordant subtypes (eg, higher risk of nodular sclerosis; SIR, 3.4; 95% CI, 1.1-7.9; n = 5) when a first-degree relative had mixed cellularity (Table 4).

Trend of familial risk by age

The lifetime risk of HL in patients was slightly higher when a first-degree relative was diagnosed with early-onset (before age 30 years) HL, although the 95% CIs overlap (1.1% [95% CI, 0.3%-1.8%] vs 0.8% [95% CI, 0.5%-1.2%]) in late-onset HL in sibling and 0.6% (95% CI, 0.3%-0.8%) vs 0.4% (95% CI, 0.2%-0.5%) among parent-child pairs (Table 1). Lifetime risk of HL was much higher with history of multiple early-onset HL patients in the family (8.4%; 95% CI, 0.0%-17%). Corresponding age-specific SIRs are presented in Table 2. Age-specific familial risks by sex are presented in supplemental Table 2.

Table 1. Cumulative risk of HL in first-degree relatives of HL patients by family relationship and age at diagnosis compared with the population risk

	Cumulative risk % in relatives by relative's age (y)								Lifetime risk (0-79 y)	
HL patients in the family and age at diagnosis (y)	0-9	0-19	0-29	0-39	0-49	0-59	0-69	0-79	95% CI	No.
Sibling										
All	0.0	0.1	0.4	0.5	0.6	0.7	0.9	0.9	0.6-1.1	86
<30	0.0	0.1	0.4	0.6*	0.7	0.7	1.1	1.1	0.3-1.8	49
30-59	0.0	0.1	0.3	0.4	0.6	0.8	0.8	0.8	0.5-1.2	36
Parent/child										
All	0.0	0.1	0.2	0.2	0.3	0.3	0.3	0.4	0.3-0.5	61
<30	0.0	0.2	0.4	0.5	0.5	0.6	0.6	0.6	0.3-0.8	31
30-59	0.0	0.1	0.2	0.2	0.2	0.3	0.3	0.4	0.2-0.5	26
≥60	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.0-0.2	4
Two or more first-degree relatives										
All	1.0	2.8	2.8	2.8	2.8	2.8	2.8	2.8	0.0-5.9	3
<30	3.0†	8.4	8.4	8.4	8.4	8.4	8.4	8.4	0.0-17	3
Same-sex twin										
All	0.0	0.0	4.0	4.0	5.5	5.5	13	13	0.0-26	6
<30	0.0	0.0	6.5	6.5	6.5	6.5	6.5	6.5	0.1-12	4
Population risk	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.3	0.3-0.3	28 732

Only those with at least 3 cases are presented.

*Example 1: The 0-39 y cumulative risk of HL in a person with a family history of early-onset HL (before age 30 years) in his singleton sibling was 0.6%, whereas the correspondent risk in the general population was 0.1% (lifetime risk 1.1% vs 0.3% in the population).

†Example 2: The 0-9 y cumulative risk of HL in a person with a family history of early-onset HL (before age 30 years) in 2 of his first-degree relatives was 3.0%, whereas the correspondent risk in the general population was 0.0% (lifetime risk 8.4% vs 0.3% in the population).

Familial risk by sex

Although the background risk in men (0.3%; 95% CI, 0.3%-0.3%) was slightly higher than in women (0.2%; 95% CI, 0.2%-0.2%), the familial risk in sisters (9.4-fold; 95% CI, 5.9- to 14-fold) was higher than in brothers (4.5-fold; 95% CI, 2.9- to 6.6-fold) or unlike-sex siblings (5.9-fold; 95% CI, 3.6- to 9.1-fold; supplemental Table 3). Significantly high CR (≥1%) was found among sisters (1.1%; 95% CI, 0.5%-1.7%), brothers with early-onset HL (1.9%; 95% CI, 0%-3.9%), and unlike-sex siblings with HL diagnosed at age 30 to 59 years (1.0% [95% CI, 0.3%-1.7%] to 1.2% [95% CI, 0.5%-1.9%]; supplemental Table 2). Very high risk of HL was found for 2 men (3.7%; 95% CI, 0%-8.5%) and 1 woman (1.9%; 95% CI, 0%-5.5%) with multiple affected first-degree relatives (data not shown) and for twin brothers (18%; 95% CI, 0%-36%; supplemental Table 2). Sex-specific SIRs are presented in supplemental Table 3.

Discussion

This multinational family cancer study, which is the largest of its kind, provided the histology-specific risk of HL for relatives of HL patients by age at diagnosis and sex of patients and their relatives. Concordant lymphocytic-rich subtype in relatives showed the highest familial risk. The overall risk of HL in first-degree relatives of a patient with HL showed a 3.3-fold increased risk over the general population risk. The risk in siblings was significantly higher than in parents and/or children. Very high risk of HL was found for a few patients with multiple affected first-degree relatives (2.8% to 8.4%) and for twin brothers (13%). The familial risk in sisters was higher than in brothers or unlike-sex siblings.

We provided HL risk calculations for family members of HL patients on the basis of type of relationship, age at diagnosis, and age

Table 2. SIR of HL in first-degree relatives of HL patients by age at diagnosis in 5 Nordic countries

		HL patient in family											
		One first-degree relative						Two or more first-degree relatives			Same-sex twin		
Age at diagnosis (y)		Sibling			Parent/child								
Patient	Relative	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI
All	All	87	6.0	4.8-7.4	62	2.1	1.6-2.6	3	13	2.8-39	6	57	21-125
	<30	50	5.8	4.3-7.7	23	3.2	2.0-4.8	3	41	8.4-119	4	63	17-161
	30-59	34	6.3	4.4-8.8	34	2.1	1.5-3.0	0			1	26	0.7-146
	≥60	3	5.0	1.0-15	5	0.7	0.2-1.7	0			1	325	8.2-1812
<30	All	49	6.3	4.7-8.4	31	2.5	1.7-3.5	3	49	10-142	4	66	18-168
	<30	34	6.5	4.5-9.0	11	5.1	2.5-9.1	3	158	33-461	4	93	25-239
	30-59	14	5.8*	3.2-9.8	20	2.6	1.6-4.0	0			0		
30-59	All	36	5.9	4.1-8.1	27	2.2	1.4-3.1	0			1	26	0.7-143
	<30	16	5.1	2.9-8.2	12	3.4	1.8-6.0	0			0		
	30-59	19	7.1	4.3-11	12	2.1	1.1-3.7	0			0		
	≥60	1	3.5	0.1-20	3	0.9	0.2-2.7	0			1	1107	28-6166
≥60	All	2	3.0	0.4-11	4	0.8	0.2-2.0	0			1	202	5.1-1123

*Example: Risk of HL in a 40-year-old person with a family history of early-onset HL (before age 30 years) in his/her sibling was 5.8-fold higher than the risk in his/her counterpart in the general population. Only those rows with a significant age-specific SIR in them are presented.

Table 3. Cumulative risk of HL in first-degree relatives of HL patients by histology of HL patient in the family compared with the population risk

	Cumulative risk % in a relative by age (y)							Lifetime risk		
Histology of HL patient in family	0-9	0-19	0-29	0-39	0-49	0-59	0-69	0-79	95% CI	No.
Any HL	0.0	0.1	0.3	0.4	0.4	0.5	0.5	0.5	0.4-0.6	147
Classical	0.0	0.1	0.3	0.4	0.4	0.5	0.5	0.5	0.4-0.6	63
Nodular sclerosis	0.0	0.2	0.3	0.4	0.5	0.5	0.5	0.5	0.3-0.6	42
Lymphocyte-rich	0.0	0.1	0.5	0.7	0.8	0.9	0.9	0.9*	0.4-1.4	12
Mixed cellularity	0.0	0.1	0.2	0.3	0.3	0.4	0.4	0.4	0.2-0.6	12
Population risk	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.3	0.3-0.3	28 732

*Example: The lifetime 0-79 y cumulative risk of HL in a person with a first-degree relative diagnosed with lymphocyte-rich HL was 0.9%, whereas the risk in the general population was 0.3%.

and sex of relatives and patients. These findings are important because relatives of patients with cancer are currently concerned about their own risk of developing the same cancer that occurs in their family; these data provide evidence-based information on risk prediction for concerned individuals by genetic counselors and oncologists. This may also potentially have an impact on clinical practice toward increasing the awareness among relatives of patients with incidental HL about potential HL symptoms. Oncologists might inform their HL patients about the familial risk, encourage counseling of their first-degree relatives for early diagnosis, and provide information on how their first-degree relatives could be managed if they are willing to seek advice. Conversely, a prediction of having a low risk close to the general population risk for some of the first-degree relatives (having a parent affected after age 60 years) may provide reassurance and decrease their anxiety (psychological benefit).

Early detection would help to clarify chronic symptoms and may allow diagnosis at earlier stages and so would potentially affect the prognosis. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results database, 5-year survival rate of HL stages I to III is 80% to 90% and can decrease to 65% to 75% in stage IV. Therefore, early diagnosis would be potentially beneficial for the survival of patients in addition to treatment cost. It is true that there are currently no standard screening tests for HL and that family members of HL patients do not often develop HL; however, they might benefit from knowing about any possible symptoms that may help early diagnosis. According to the American Cancer Society report,[23] the best way to find HL early is to pay attention to possible symptoms. The most common symptom is enlargement of 1 or more lymph nodes, causing a lump or bump under the skin, which is usually not painful. Other symptoms can include unexplained persistent fever, night sweats, unexplained weight loss, and severe and constant itching.

Our findings were in line with previous studies that suggested a familial clustering of HLs and suggest higher risks at a relatively young age.[15,16,20] Higher familial risk for siblings compared with parent-offspring pairs suggests a recessive component or shared childhood environment effects. Our sex-specific findings suggested a tendency for gender concordance among sisters and father-son pairs with HL, which is in line with some previous studies.[15,21,22] Gender concordance among sibling pairs with HL was reported by Grufferman et al.[24] It has been proposed that a gene for HL might reside in either of the 2 pseudoautosomal regions of the sex chromosomes.[25]

In our study, those with a family history of HL diagnosed at a younger age predicted a higher familial risk. There was a modest tendency toward concordant age at diagnosis of HL only among siblings with HL. However, this was not confirmed in all of the subgroup analyses. It has been also proposed that age at onset in offspring is earlier than that in parents, according to the anticipation phenomenon, which postulates an increase in severity of clinical symptoms or a decrease in the age of onset in successive generations, as previous studies have suggested.[26,27]

This study benefited from the population-based data from 5 Nordic countries, with unbiased family history registration and thus is less vulnerable to ascertainment biases that might occur in case-control studies. Combining valid population-based family cancer data sets of 5 Nordic countries with homogeneous cancer registries[28] enabled us to provide clinically useful relevant information on familial risk of histology subtypes of HL, familial associations between different histology subtypes, and the familial risk by age at diagnosis in the HL patients and their affected relatives. Furthermore, we provide all of these risk estimates for each gender. Incidence of HL slightly varies between Nordic countries (world age standardized rate from about 1.5 per 100 000 in Iceland and Sweden to about 2.5 in Norway and Finland), but in general, their incidences are quite similar to the average of developed countries (2.2) and higher than the world's average (0.9).[2] According to our ad hoc analysis plan, in this study, only results of the pooled data set are presented because regional differences of sporadic

Table 4. SIR of HL by histology in a first-degree relative of an HL patient in 5 Nordic countries

	HL patient in the family																	
	Any HL			Any classical			Nodular sclerosis			Lymphocyte-rich			Mixed cellularity			Lymphocyte-depleted		
Relative's histology	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI
Any HL	149	3.3	2.8-3.9	63	3.0	2.3-3.9	42	3.0	2.2-4.1	12	6.2	3.2-11	12	2.6	1.3-4.5	1	2.9	0.1-16
Classical	70	3.9	3.0-4.9	42	3.9	2.8-5.3	26	3.6	2.3-5.2	9	9.8	4.5-19	10	4.3	2.1-8.0	1	6.3	0.2-35
Nodular sclerosis	44	3.8	2.8-5.1	24	3.5	2.2-5.2	22	4.6	2.9-7.0	1	1.7	0.0-9.5	5	3.4*	1.1-7.9	0		
Lymphocyte-rich	11	7.3	3.7-13	9	12	5.7-24	1	2.0	0.0-11	6	81	30-177	2	15	1.8-54	0		
Mixed cellularity	13	3.6	1.9-6.1	7	3.6	1.5-7.5	3	2.2	0.5-6.5	2	14	1.7-49	2	5.0	0.6-18	0		
Lymphocyte-depleted	2	1.4	0.2-5.1	2	1.9	0.2-6.8	0			0			1	3.4	0.1-19	1	40	1.0-225

*Example: Risk of nodular sclerosis HL in a first-degree relative of a patient with diagnosis of mixed cellularity HL was 3.4-fold higher than the risk in his/her counterpart in the general population.

and familial risks of HL in the Nordic countries are subject to random variation (as a result of small sample size).

Our data, to some extent, showed higher risk for some concordant histologic subtypes, which may confirm the correct classification of HL subtypes. However, the histologic subtype for distant periods of time (less specific codes) in such a long follow-up study may not be as accurate as for recent years, which in turn can be the source of bias toward underestimation of SIRs for concordant histologic subtypes. Adjustment for period of diagnosis has been performed to also take into account the change of incidence over time. Of course, the role of the surveillance bias (more intensive diagnostic approach for family members of an affected case that may lead to the overdiagnosis of indolent cancers) could not be ruled out for the weak associations.

Familial aggregation of HL could be justified by genetic or environmental factors or the interaction between these two components. Families usually share the same environmental risk factors such as living in the same area, family size, socioeconomic status, parental education, EBV infection, and so on. Approximately 30% of HLs in developed countries have detectable EBV in their tumor cells.[29,30] Although EBV positivity is more common in mixed cellularity than nodular sclerosis HL, because nodular sclerosis HL is the most common subtype, it may compose the majority of EBV-positive HL (which typically means detectable EBV DNA in their cancer cells). Furthermore, a study of twins by Mack et al[31] strongly implicates genetic susceptibility over environmental effects as the underlying reason for familial HL. A recent study that assessed family history and risk of pediatric and adolescent HL found that there are no discernable patterns for EBV-positive vs EBV-negative HL.[32] In the context of interaction between genetic and environmental factors, the distinction between these two components would be even more difficult. However, the strength of our study is that estimated familial risks could be used in the clinic regardless of the exact underlying reason for them.

Although no major high-penetrant gene has yet been identified for HL so far, linkage analyses in large HL families point out some specific regions, particularly the HLA locus on chromosome 6. Several studies implicate the role of genetic variants that promote B-cell survival and growth with increased risk of lymphoma.[33] Positive associations between a *GSTT1* deletion and risk of Hodgkin and non-Hodgkin lymphoma have been reported.[33] Recent genome-wide association studies (GWAS) of HL have identified associations with genetic variation at both HLA and non-HLA loci[34,35]; however, much of heritable HL susceptibility remains unexplained.[36] A meta-analysis of three HL GWAS identified a novel variant at 19p13.3 associated with HL (rs1860661 located in intron 2 of *TCF3*, also known as *E2A*), a regulator of B- and T-cell lineage commitment known to be involved in HL pathogenesis.[36] They also note associations between previously published loci at 2p16, 5q31, 6p31, 8q24, 10p14, and HL subtypes.[36] GWAS results are not entirely straightforward, since several associations are specific to certain HL subtypes (eg, EBV-positive HL). The discovery of novel susceptibility genes may be accelerated now with the development of new sequencing technologies.

In conclusion, this study provides tangible HL risk estimates for relatives of HL patients, based on sex, age, and family history, that can be used by genetic counselors and oncologists to provide evidence-based advice. In this study, using unbiased population-based family cancer data, we were able to quantify the absolute and relative risk of HL in relatives of patients with HL. We found the highest familial risk in lymphocytic-rich histologic subtype. We also found increased risks for different histologic subtypes of this malignancy, which may show a common oncogene pathway or environmental risk factor for various subtypes of HL. The higher absolute risk of familial HL (more than 1.5%) was found for those with multiple affected first-degree relatives, same-sex twins, or brothers with early-onset HL.

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Authorship

Contribution: E.K., M.F., and K.H. conceived and designed the study; K.S., E.P., L.T., J.H.O., and S.T. provided study materials; E.K. and M.F. assembled and analyzed the data, interpreted the results, and wrote the manuscript; and all authors reviewed and commented on manuscript and approved the final version.

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References

1. Agostinelli C, Pileri S. Pathobiology of hodgkin lymphoma. *Mediterr J Hematol Infect Dis.* 2014; 6(1):e2014040.
2. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013.
3. Curado MP, Edwards B, Shin HR, et al. Cancer Incidence in Five Continents, vol. IX. WHO Press; Lyon, 2008.
4. Mueller N, Grufferman S. Cancer Epidemiology and Prevention. Oxford University Press; New York, 2006.
5. Mueller N. Cancer epidemiology and prevention, Hodgkin's disease. 2nd ed. New York, NY: Oxford University Press; 1996.
6. Peter M, Armitage J, Diehl V, Hoppe R, Weiss L. Hodgkin's Disease. Lippincott Williams & Wilkins; Philadelphia, 1999.
7. Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Hodgkin lymphoma after autoimmune diseases by age at diagnosis and histological subtype. *Ann Oncol.* 2014;25(7): 1397-1404.
8. MacMahon B. Epidemiology of Hodgkin's disease. *Cancer Res.* 1966;26(6):1189-1201.
9. Biggar RJ, Frisch M, Goedert JJ; AIDS-Cancer Match Registry Study Group. Risk of cancer in children with AIDS. *JAMA.* 2000;284(2): 205-209.
10. Chang ET, Zheng T, Lennette ET, et al. Heterogeneity of risk factors and antibody profiles in epstein-barr virus genome-positive and -negative hodgkin lymphoma. *J Infect Dis.* 2004; 189(12):2271-2281.
11. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer.* 1997;70(4):375-382.
12. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. *N Engl J Med.* 2003; 349(14):1324-1332.
13. Jarrett RF. Risk factors for Hodgkin's lymphoma by EBV status and significance of detection of EBV genomes in serum of patients with EBV-associated Hodgkin's lymphoma. *Leuk Lymphoma.* 2003;44(Suppl 3):S27-S32.
14. Cohen JI. Epstein-Barr virus infection. *N Engl J Med.* 2000;343(7):481-492.
15. Goldin LR, Pfeiffer RM, Gridley G, et al. Familial aggregation of Hodgkin lymphoma and related tumors. *Cancer.* 2004;100(9):1902-1908.
16. Chang ET, Smedby KE, Hjalgrim H, et al. Family history of hematopoietic malignancy and risk of

lymphoma. *J Natl Cancer Inst.* 2005;97(19): 1466-1474.

17. Harris NL. Hodgkin's lymphomas: classification, diagnosis, and grading. *Semin Hematol.* 1999; 36(3):220-232.
18. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011; 117(19):5019-5032.
19. Kristinsson SY, Landgren O, Sjöberg J, Turesson I, Björkholm M, Goldin LR. Autoimmunity and risk for Hodgkin's lymphoma by subtype. *Haematologica.* 2009;94(10):1468-1469.
20. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer.* 2005;103(9): 1906-1915.
21. Altieri A, Hemminki K. The familial risk of Hodgkin's lymphoma ranks among the highest in the Swedish Family-Cancer Database. *Leukemia.* 2006;20(11):2062-2063.
22. Horwitz MS, Mealiffe ME. Further evidence for a pseudoautosomal gene for Hodgkin's lymphoma: Reply to 'The familial risk of Hodgkin's lymphoma ranks among the highest in the Swedish Family-Cancer Database' by Altieri A and Hemminki K. *Leukemia.* 2007; 21(2):351.
23. American Cancer Society. Hodgkin Disease. http://www.cancer.org/acs/groups/cid/documents/webcontent/003105-pdf.pdf. Accessed April 5, 2015.
24. Grufferman S, Cole P, Smith PG, Lukes RJ. Hodgkin's disease in siblings. *N Engl J Med.* 1977;296(5):248-250.
25. Horwitz M, Wiernik PH. Pseudoautosomal linkage of Hodgkin disease. *Am J Hum Genet.* 1999; 65(5):1413-1422.
26. Shugart YY. Anticipation in familial Hodgkin lymphoma. *Am J Hum Genet.* 1998;63(1): 270-272.
27. Shugart YY, Hemminki K, Vaittinen P, Kingman A. Apparent anticipation and heterogeneous transmission patterns in familial Hodgkin's and non-Hodgkin's lymphoma: report from a study based on Swedish cancer database. *Leuk Lymphoma.* 2001;42(3):407-415.
28. Lund EM, Clemmensen IH, Storm HH, Engholm G. Survey of the Nordic Cancer Registries. Copenhagen, Denmark: Danish Cancer Society; 2000.
29. Armstrong AA, Weiss LM, Gallagher A, et al. Criteria for the definition of Epstein-Barr virus association in Hodgkin's disease. *Leukemia.* 1992;6(9):869-874.
30. Jarrett AF, Armstrong AA, Alexander E. Epidemiology of EBV and Hodgkin's lymphoma. *Ann Oncol.* 1996;7(Suppl 4):5-10.
31. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med.* 1995;332(7):413-418.
32. Linabery AM, Erhardt EB, Richardson MR, et al. Family history of cancer and risk of pediatric and adolescent Hodgkin lymphoma: A Children's Oncology Group study. *Int J Cancer.* 2015;137(9): 2163-2174.
33. Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. *Haematologica.* 2007; 92(7):960-969.
34. Enciso-Mora V, Broderick P, Ma Y, et al. A genome-wide association study of Hodgkin's lymphoma identifies new susceptibility loci at 2p16.1 (REL), 8q24.21 and 10p14 (GATA3). *Nat Genet.* 2010;42(12):1126-1130.
35. Frampton M, da Silva Filho MI, Broderick P, et al. Variation at 3p24.1 and 6q23.3 influences the risk of Hodgkin's lymphoma. *Nat Commun.* 2013;4: 2549.
36. Cozen W, Timofeeva MN, Li D, et al. A meta-analysis of Hodgkin lymphoma reveals 19p13.3 TCF3 as a novel susceptibility locus. *Nat Commun.* 2014;5:3856.