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

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Running head:
Familial classical Hodgkin lymphoma risk assessment

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

The rarity of familial Hodgkin lymphoma (HL) has hampered detailed analyses of familial clustering. We aimed to provide the familial risk of 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 five European countries was followed for HL incidence. Standardized incidence ratios (SIRs) were calculated using histology-, age-, sex-, period-, and country-specific incidence rates as the reference. The lifetime cumulative risks (CR) were also calculated.

The overall CR of HL in first-degree relatives of a patient with HL was 0.6%, which represents a 3-fold (SIR=3.3, 95%CI=2.8–3.9) increased risk over the general population risk. The risk in siblings (6.0-fold; 4.8–7.4) was significantly higher than in parents/children (2.1-fold; 1.6–2.6). Very high lifetime risk of HL was found for those with multiple affected first-degree relatives (13-fold; 2.8–39) and for same-sex twins (57-fold; 21-125). We found high familial risks between some concordant histological subtypes of HL [lymphocyte-rich (81-fold, 30–177) and nodular sclerosis (4.6-fold, 2.9–7.0)] and also between some discordant subtypes. The familial risk in sisters (9.4-fold; 5.9–14) was higher than in brothers (4.5-fold; 2.9–6.7) or unlike-sex siblings (5.9-fold; 4.3–8.1). The lifetime risk of HL was higher when first-degree relatives were diagnosed at early ages (before age 30).

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 Hodgkin lymphoma by oncologists and genetic counselors.

Key words: Hodgkin lymphoma; classical Hodgkin lymphoma; familial risk; histology; population-based study; age at onset
Introduction

Hodgkin lymphomas (HLs) are lymphoid tumors that represent about 1% of all de novo neoplasms that occur every year worldwide, with over 65,000 new cases of HLs diagnosed globally per annum.\textsuperscript{1,2} HL is one of the most common cancers among young adults in Western countries.\textsuperscript{3,4} It is an etiologically and histologically heterogeneous disease. HL has a bimodal age distribution; the first peak being young adulthood (age 15–35) and the second being in those over 55 years old, although these peaks may vary with geographic area and ethnicity.\textsuperscript{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.\textsuperscript{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, gender and socioeconomic status may vary by tumor EBV status.\textsuperscript{10} Patients from developing countries were also almost twice as likely to have EBV-associated HL compared with individuals from more westernized countries.\textsuperscript{11} For EBV-associated HL cases, there is a small peak in incidence in young adults (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.\textsuperscript{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),\textsuperscript{14} but very few develop HL (less than 1%).\textsuperscript{1} Around 30% of HL patients in the developed world have detectable EBV genomes and gene products in their tumor cells. Genetic factors as a predisposing factor have been suggested by several studies.\textsuperscript{15,16}

Pathologists currently use the World Health Organization (WHO) modification of the Revised European-American Lymphoma (REAL) classification for the histologic classification for adult
Hodgkin lymphoma (HL). 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 age-specific incidence curves, sex ratio and racial patterns. In our study we focused on classical HL as non-classical 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, in order 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. Few studies have provided familial risks by sex of the patient and the relative, suggesting gender concordance among sibling pairs with HL. 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 only provide familial relative risk in terms of standardized incidence ratio (SIR) that needs to be translated to a readily understandable estimate, such as cumulative risk, for use in clinical practice. The present study benefited from the nationwide family-cancer data from five countries in northern Europe, with unbiased genealogical and high quality cancer data, to systematically quantify the familial risk of all concordant and discordant histological subtypes of classical HL in relatives of HL patients. Our goal was to provide the familial risks of classical HL also in terms of cumulative risk stratified by type of relationship, histology, age, and sex of patients’ and their relatives’.
Materials and methods

Our large dataset consisted of pooled family-cancer data from five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). Information on all HL patients in this large dataset (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, with complete genealogical information for all the participants, sibships could only be ascertained in the offspring generation (those with identified parents). The country-specific inclusion/exclusion criteria are presented in the supplementary materials (online only). In addition, the data characteristics of each country are shown in the Supplementary Table S1 (online only). The Lund regional Ethics Committee approved the study protocol. Protocol followed the Declaration of Helsinki.

Statistical analyses

Standardized incidence ratios (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 to 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 (1st of January of 1955/1961/1967/1968; Suppl. Table S1), whichever came latest. The follow-up was terminated at death, emigration or the closing date of the study, (31 Dec 2008/2009/2010; Suppl. Table S1). More detailed information on follow-up calculation is available in the section “Starting date of follow-up” in the online supplementary material. 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 subjects with HL in their first-degree relatives. 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. SAS software (SAS Institute Inc., Cary, NC, USA) version 9.2 was used for the data analysis.

The lifetime cumulative risk (assumed to be 0–79 years) was calculated based on 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 – exp (– lifelong cumulative rate). To avoid bias in cumulative risk calculation toward over-estimation due to 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 3-fold 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=4.8–7.4), Table 2] was significantly higher than in parents/children [0.4% (95% CI=0.3–0.5%), Table 1; 2.1-fold (95% CI=1.6–2.6), 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 three subjects 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=2.8–39), Table 2] and for six same-sex twins [13% (95% CI=0–26%), Table 1; 57-fold (95% CI=21–125), Table 2]. There were no affected unlike-sex twins in the data.
Familial risk by histology

Cumulative risk 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%), while 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 histological subtypes of HL [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 [e.g. 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 subjects were slightly higher when a first-degree relative was diagnosed with early-onset (before age 30) HL, although the 95% CIs overlap [1.1% (95% CI=0.3–1.8%) versus 0.8% (95% CI=0.5–1.2%) in late-onset HL in sibling and 0.6% (95% CI=0.3–0.8%) versus 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 Suppl. Table S2 (online only).

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=5.9–14) was higher than in brothers (4.5-fold, 95% CI=2.9–6.6) or unlike-sex siblings (5.9-fold, 95% CI=3.6–9.1; Suppl. Table S3). 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 30-59 [1.0% (95% CI=0.3–1.7%) to 1.2% (95% CI=0.5–1.9%); Suppl. Table S2]. Very high risk of HL was found for two men (3.7%, 95% CI=0–8.5%) and one 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%; Suppl. Table S2). Sex-specific SIRs are presented in Suppl. Table S3.

Discussion

This multi-national family cancer study, which is the largest of its kind, provided the histology-specific risk of HL for relatives of HL patients by patients’ and their relatives’ age at diagnosis and sex. 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/children. Very high risk of HL was found for few subjects with multiple affected first-degree relatives (2.8-8.4%) 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 based on type of relationship, age at diagnosis and age and sex of relatives and patients. These findings are important as relatives of cancer patients are currently concerned about their own risk of developing the same cancer that occur in their family; these data provide evidence-based information on risk prediction for concerned individuals by genetic counselors and oncologists. This may also potentially impact 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 and 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. On the other hand, a prediction of being low risk close to population risk for some of the first-degree relatives
(having a parent affected after age 60 years) may provide assurance 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 National Cancer Institute’s SEER database, 5-year survival rate of HL in stage I-III is 80-90% and can decrease to 65-75% in stage IV. Therefore, early diagnosis would be potentially beneficial for the survival of patients in addition to treatment cost. It is true that currently there are 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 the best way to find HL early is to pay attention to possible symptoms. The most common symptom is enlargement of one 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 suggesting a familial clustering of HLs and suggest higher risks at a relatively young age. Higher familial risk for siblings compared to parent–offspring pairs suggest 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. Gender concordance among sibling pairs with HL was reported by Grufferman et al. It has been proposed that a gene for HL might reside in either of the two pseudoautosomal regions of the sex chromosomes.

In our study, those with a family history of HL diagnosed at 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 suggested.\textsuperscript{26,27}

The present study benefited from the population-based data from five 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 datasets of five
Nordic countries with homogenous cancer registries,\textsuperscript{28} enabled us to provide clinically useful
relevant information on familial risk of histology subtypes of HL, familial associations between
different histology subtypes, 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 standardize rate from about 1.5/100,000 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).\textsuperscript{2}

According to our \textit{ad hoc} analysis plan, in this paper, only results of the pooled dataset are presented
as regional differences of sporadic and familial risks of HL in the Nordic countries are subject to
random variation (due to small sample size).

Our data, to some extent, showed higher risk for some concordant histological subtypes, which may
confirm the correct classification of HL subtypes. However, the histological 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 under-estimation of SIRs for
concordant histological subtypes. Adjustment for period of diagnosis has been performed to also
take into account the change of incidence over time. Of course, role of the surveillance bias (more
intensive diagnostic approach for family members of an affected case that may lead to the over-
diagnosis of indolent cancers) could not be ruled out for the weak associations.
Familial aggregation of HL could be justified by genetic, environmental, 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, etc. About 30% of HLs in developed countries have detectable EBV in their tumor cells. Although EBV positivity is more common in mixed cellularity than nodular sclerosis HL, because nodular sclerosis HL is the most common subtype, it may comprises the majority of EBV-positive HL (which typically means detectable EBV DNA in their cancer cells). Furthermore, a study on twins by Mack et al. strongly implicates genetic susceptibility over environmental effects as the underlying reason for familial HL. Moreover, a recent study, which assessed family history and risk of pediatric and adolescent HL, found that there are no discernable patterns for EBV-positive versus EBV-negative HL. 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. Positive associations between a GSTT1 deletion and risk of Hodgkin and non-Hodgkin lymphoma have been reported. Recent genome-wide association studies (GWAS) of HL have identified associations with genetic variation at both HLA and non-HLA loci; however, much of heritable HL susceptibility remains unexplained. A meta-analysis of three HL GWAS identify 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. They also note associations between previously published loci at 2p16, 5q31, 6p31, 8q24 and 10p14 and HL subtypes. GWAS results are not entirely straightforward, since several associations are specific to certain HL subtypes (e.g., 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, which can be used by genetic consolers and oncologists to provide evidence-based advice. In this study, using an 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 histological subtype. We also found increased risks for different histological 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.

Contributions
Conception and design: Elham Kharazmi, Mahdi Fallah, Kari Hemminki
Provision of study materials: Kristina Sundquist, Eero Pukkala, Laufey Tryggadottir, Jörgen H. Olsen, Steinar Tretli
Assembly of data and analysis, interpretation of results and writing the manuscript: Elham Kharazmi, Mahdi Fallah
Reviewing and commenting on manuscript and approval of the final version: All authors

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Disclosure
The authors have declared no conflicts of interest.

References
Table 1: Cumulative risk of Hodgkin lymphoma (HL) in first-degree relatives of HL patients by family relationship and age at diagnosis compared to the population risk

<table>
<thead>
<tr>
<th>HL patient(s) in the family†</th>
<th>Cumulative risk (%) in relatives by relative’s age</th>
<th>CI and N for lifetime risk (0−79 years)</th>
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</thead>
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<tr>
<td></td>
<td>0−9 0−19 0−29 0−39 0−49 0−59 0−69 0−79</td>
<td>95% CI N</td>
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<tr>
<td>Relationship</td>
<td>Age at diagnosis</td>
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<tr>
<td>Sibling</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0 0.1 0.4 0.5 0.6 0.7 0.9 0.9</td>
<td>(0.6−1.1) 86</td>
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<tr>
<td></td>
<td>&lt;30</td>
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</tr>
<tr>
<td></td>
<td>0.0 0.1 0.4 0.6* 0.7 0.7 1.1 1.1</td>
<td>(0.3−1.8) 49</td>
</tr>
<tr>
<td></td>
<td>30-59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0 0.1 0.3 0.4 0.6 0.8 0.8 0.8</td>
<td>(0.5−1.2) 36</td>
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<tr>
<td>Parent/Child</td>
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<tr>
<td></td>
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<td>(0.3−0.5) 61</td>
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<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0 0.2 0.4 0.5 0.5 0.6 0.6 0.6</td>
<td>(0.3−0.8) 31</td>
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<td></td>
<td>30-59</td>
<td></td>
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<tr>
<td></td>
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<td>(0.2−0.5) 26</td>
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<tr>
<td></td>
<td>≥60</td>
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<tr>
<td></td>
<td>0.0 0.0 0.0 0.0 0.0 0.1 0.1 0.1</td>
<td>(0.0−0.2) 4</td>
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<tr>
<td>≥2 First-degree relatives</td>
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<tr>
<td></td>
<td>1.0 2.8 2.8 2.8 2.8 2.8 2.8 2.8</td>
<td>(0.0−5.9) 3</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0** 8.4 8.4 8.4 8.4 8.4 8.4 8.4</td>
<td>(0.0−17) 3</td>
</tr>
<tr>
<td>Same-sex twin</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0 0.0 4.0 4.0 5.5 5.5 13 13</td>
<td>(0.0−26) 6</td>
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<tr>
<td></td>
<td>&lt;30</td>
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<td></td>
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<td>Population risk</td>
<td>0.0 0.0 0.1 0.1 0.1 0.2 0.2 0.3</td>
<td>(0.3−0.3) 28732</td>
</tr>
</tbody>
</table>

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

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

Only those with at least 3 cases are presented.
Table 2: Standardized incidence ratio (SIR) of Hodgkin lymphoma (HL) in first-degree relatives of HL patients by age at diagnosis, Nordic countries

<table>
<thead>
<tr>
<th>HL patient in family →</th>
<th>1 First-degree relative</th>
<th>≥2 First-degree relatives</th>
<th>Same-sex twin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Relative</td>
<td>Sibling</td>
<td>Parent/child</td>
</tr>
<tr>
<td>All</td>
<td>All</td>
<td>87</td>
<td>6.0 (4.8–7.4)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>All</td>
<td>50</td>
<td>5.8 (4.3–7.7)</td>
</tr>
<tr>
<td>30-59</td>
<td>All</td>
<td>34</td>
<td>6.3 (4.4–8.8)</td>
</tr>
<tr>
<td>≥60</td>
<td>All</td>
<td>3</td>
<td>5.0 (1.0–15)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>All</td>
<td>49</td>
<td>6.3 (4.7–8.4)</td>
</tr>
<tr>
<td>30-59</td>
<td>All</td>
<td>34</td>
<td>6.5 (4.5–9.0)</td>
</tr>
<tr>
<td>30-59</td>
<td>All</td>
<td>14</td>
<td>5.8* (3.2–9.8)</td>
</tr>
<tr>
<td>≥60</td>
<td>All</td>
<td>36</td>
<td>5.9 (4.1–8.1)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>All</td>
<td>16</td>
<td>5.1 (2.9–8.2)</td>
</tr>
<tr>
<td>30-59</td>
<td>All</td>
<td>19</td>
<td>7.1 (4.3–11)</td>
</tr>
<tr>
<td>≥60</td>
<td>All</td>
<td>1</td>
<td>3.5 (0.1–20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>3.0 (0.4–11)</td>
</tr>
</tbody>
</table>

*Example: Risk of HL in a 40-year old person with family history of early-onset (before age 30) HL 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 SIR in them are presented.
Table 3: Cumulative risk of Hodgkin lymphoma (HL, any histology) in first-degree relatives of HL patients by histology compared to the population risk

<table>
<thead>
<tr>
<th>Histology of Hodgkin lymphoma patient in family</th>
<th>Cumulative risk (%) in a relative by age (years)</th>
<th>CI and N for lifetime risk (0−79 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0−9 0−19 0−29 0−39 0−49 0−59 0−69 0−79</td>
<td>95% CI  N</td>
</tr>
<tr>
<td>Hodgkin lymphoma, any</td>
<td>0.0 0.1 0.3 0.4 0.4 0.5 0.5 0.5</td>
<td>(0.4−0.6) 147</td>
</tr>
<tr>
<td>Classical</td>
<td>0.0 0.1 0.3 0.4 0.4 0.5 0.5 0.5</td>
<td>(0.4−0.6) 63</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>0.0 0.2 0.3 0.4 0.5 0.5 0.5 0.5</td>
<td>(0.3−0.6) 42</td>
</tr>
<tr>
<td>Lymphocyte-rich</td>
<td>0.0 0.1 0.5 0.7 0.8 0.9 0.9 0.9</td>
<td>0.9* (0.4−1.4) 12</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>0.0 0.1 0.2 0.3 0.3 0.4 0.4 0.4</td>
<td>(0.2−0.6) 12</td>
</tr>
<tr>
<td>Population risk</td>
<td>0.0 0.0 0.1 0.1 0.1 0.2 0.2 0.3</td>
<td>(0.3−0.3) 28,732</td>
</tr>
</tbody>
</table>

*Example: The lifetime (0−79 years) 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%.
Table 4: Standardized incidence ratio (SIR) of Hodgkin lymphoma (HL) by histology in a first-degree relative of a HL patient, Nordic countries

<table>
<thead>
<tr>
<th>Relative's histology ↓</th>
<th>Hodgkin lymphoma, any</th>
<th>Classical, any</th>
<th>Nodular sclerosis</th>
<th>Lymphocyte-rich</th>
<th>Mixed cellularity</th>
<th>Lymphocyte-depleted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N SIR (95% CI)</td>
<td>N SIR (95% CI)</td>
<td>N SIR (95% CI)</td>
<td>N SIR (95% CI)</td>
<td>N SIR (95% CI)</td>
<td>N SIR (95% CI)</td>
</tr>
<tr>
<td>Hodgkin lymphoma, any</td>
<td>149 3.3 (2.8–3.9)</td>
<td>63 3.0 (2.3–3.9)</td>
<td>42 3.0 (2.2–4.1)</td>
<td>12 6.2 (3.2–11)</td>
<td>12 2.6 (1.3–4.5)</td>
<td>1 2.9 (0.1–16)</td>
</tr>
<tr>
<td>Classical</td>
<td>70 3.9 (3.0–4.9)</td>
<td>42 3.9 (2.8–5.3)</td>
<td>26 3.6 (2.3–5.2)</td>
<td>9 9.8 (4.5–19)</td>
<td>10 4.3 (2.1–8.0)</td>
<td>1 6.3 (0.2–35)</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>44 3.8 (2.8–5.1)</td>
<td>24 3.5 (2.2–5.2)</td>
<td>22 4.6 (2.9–7.0)</td>
<td>1 1.7 (0.0–9.5)</td>
<td>5 3.4* (1.1–7.9)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte-rich</td>
<td>11 7.3 (3.7–13)</td>
<td>9 12 (5.7–24)</td>
<td>1 2.0 (0.0–11)</td>
<td>6 81 (30–177)</td>
<td>2 15 (1.8–54)</td>
<td>0</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>13 3.6 (1.9–6.1)</td>
<td>7 3.6 (1.5–7.5)</td>
<td>3 2.2 (0.5–6.5)</td>
<td>2 14 (1.7–49)</td>
<td>2 5.0 (0.6–18)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte-depleted</td>
<td>2 1.4 (0.2–5.1)</td>
<td>2 1.9 (0.2–6.8)</td>
<td>0</td>
<td>0</td>
<td>1 3.4 (0.1–19)</td>
<td>1 40 (1.0–225)</td>
</tr>
</tbody>
</table>

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

Elham Kharazmi, Mahdi Fallah, Eero Pukkala, Jørgen H. Olsen, Laufey Tryggvadottir, Kristina Sundquist, Steinar Tretli and Kari Hemminki