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Familial aggregation of early-onset haematological malignancies

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Summary

Population-based studies on familial aggregation of haematological malignancies (HM) have rarely focused specifically on early-onset HMs. We estimated standardized incidence ratios (SIR) and cumulative risks of relatives with Hodgkin lymphoma (HL), non-Hodgkin lymphomas (NHL), acute lymphoblastic leukaemia/lymphoma (ALL/LBL) and acute myeloid leukaemia (AML) when index persons and relatives were diagnosed with early-onset HM. A total of 8791 patients aged ≤40 years and diagnosed with primary HM in Finland from 1970 to 2012 were identified from the Finnish Cancer Registry and their 75 774 family members were retrieved from the population registry. SIRs for concordant HMs were elevated among first-degree relatives in all of the most common HMs of children and adolescents and young adults (AYA). The risk was highest among siblings with HL (SIR 9·09, 95% confidence interval 5·55–14·04) and AML (8·29, 1·00–29·96). HL also had the highest cumulative risk for siblings at ≤40 years of age (0·92% vs. 0·11% in the population). In conclusion, significantly elevated SIRs indicate a role of shared aetiological factors in some families, which should be noted in the clinical setting when caring for patients with early-onset HMs.

Keywords: haematological malignancies, leukaemia, lymphomas, epidemiology, aetiology, genetics.

Introduction

Haematological malignancies (HM) originate from an interplay of inherited and acquired (somatic) genetic changes in haematopoietic cells. Somatic alterations may arise from, for example, ionizing radiation or carcinogenic chemicals. Although the role of germline mutations in the development of solid malignancies has been recognized for decades, in HMs we have only begun to scratch the surface of deciphering the impact of hereditary predisposition.[1–4]

Haematological malignancies represent a significant entity in childhood and adolescent and young adulthood (AYA) cancers. Among different HMs, acute lymphoblastic leukaemia/lymphoma (ALL/LBL) is the most common in childhood, whereas Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) and acute myeloid leukaemia (AML) are

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the major diagnoses in the AYA group (15–40 years of age).[5–8] Epidemiological register studies have found an approximately two-fold familial relative risk of HMs for first-degree relatives of HM patients.[9,10] Specifically, the risk has been reported to be three- to eight-fold for HL, two-fold for NHL, and three- to seven-fold for ALL. The risk for AML has been from 1·5- to six-fold and the risk for myelodysplastic syndrome (MDS) over six- to eleven-fold, depending on the age at onset and type of family relation.[9–25] Siblings seem to be at greater risk compared to other first-degree relatives.[10,15,22,23,25] The risk appears higher if HM is diagnosed at a young age or if there is more than one affected relative in the family, which are established characteristics of inherited predispositions.[10,15,25,26] Some recent studies show that germline mutations also contribute to myeloid malignancies and HMs affecting older patients.[3,27–29] Yet, varying age at onset, untypical clinical phenotypes and lack of known family history complicate detection of individuals with causal mutations.[30–33] So far, the largest registry study from Sweden reported familial aggregation of HMs and investigated associations between different HMs, suggesting their possibly shared aetiology.[10] Population-based registry studies on familial clustering, however, have rarely focused specifically on early-onset HMs.

Our aim in this study was to evaluate familial relative and cumulative risks of early-onset concordant and discordant HMs when index persons and family members were diagnosed at a young age (≤40 years).

Material and methods

Data on incident cancers were retrieved from the Finnish Cancer Registry (FCR) and family data from the Digital and Population Data Services Agency (DVV, previously known as the Central Population Register). The FCR registers all cancers diagnosed in Finland since 1953, with high coverage for solid cancers (96%), and HMs ranging from 86% in adults to 97% in children.[34,35] The DVV records data on all citizens permanently residing in Finland, including personal IDs and family relations.

We ascertained 8791 early-onset primary HM patients aged ≤40 years, called probands (Table SI), diagnosed in Finland between 1st of January 1970 and 31st of December 2012, and their 75 774 family members forming the familial cohort (Table I). Family members included the proband's mother, father, siblings and children and siblings' children. Additionally, the spouses of probands and siblings were retrieved based on shared children at the time of linkage (2012). No family members were found for 262 (3·0%) probands, and information on one or both parents was missing for 5·7% and 11·5% of the probands, respectively, due to historical linkage issues in the 1970s when the population registration was made electronic. The design and methods have been described in more detail previously[36] and in the supplementary material (Figure S1 and Data S1).

The follow-up of the familial cohort started at the date of birth or 1st of January 1953 and ended at the date of HM diagnosis, death or emigration or 31st of December 2017, whichever came first. Immortal periods, that is, periods when by study design HM could not be diagnosed or periods before registration of cancers began in 1953, were removed from the analysis (Figure S1).

The World Health Organization (WHO) International Classification of Diseases and Related Health Problems (ICD-10) was used to classify HMs as follows: HL (C81), NHL (C82–85), ALL/LBL (C91.0, C83.51–2, C83.59), AML (C92.0) and all other HMs (C81–96, D45–47, D76). NHLs were grouped by the 2008 WHO Classification of Lymphomas,

Table I. Characteristics of the families with early-onset haematological malignancies by diagnosis.

Diagnosis	Families with a young proband (≤40 years) and family data available	Family members (≤40 years) of probands		Number of families by number of affected family members with an early-onset (≤40 years) concordant cancer				Early-onset concordant familial cancers	
		Number	Person-years	None* (only proband)	One family member	Two family members	Three family members	Total number of familial cancer cases	Number of families with familial cancer (%)
HL	2571	22 969	438 948	2537	33	1	0	35	34 (1·3)
NHL	2274	21 918	410 831	2254	20	0	0	20	20 (0·9)
ALL/LBL	2037	16 070	321 194	2027	10	0	0	10	10 (0·5)
AML	792	7100	147 200	788	4	0	0	4	4 (0·5)
Other	855	7717	160 046	855	0	0	0	0	0 (0)
Total	8529	75 774	1 478 219	8387	138†	3†	1†	147†	142 (1·7)†

ALL/LBL, acute lymphoblastic leukaemia/lymphoma; AML, acute myeloid leukaemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma. Other diagnoses include chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), myeloproliferative neoplasms (MPN), plasma cell dyscrasias (PCD), leukaemia not otherwise specified, T-cell large granular lymphocytic leukaemia, malignant mastocytosis, malignant histiocytosis, Langerhans cell histiocytosis, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia and hairy cell leukaemia.

*The analyses exclude families where proband has no family members.

†The total includes both concordant and discordant familial cancers.

and morphology was based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3).[37] Histological subtypes of NHL and HL, as well as diagnoses such as MDS and essential thrombocythemia (ET), were systematically available after 2007.

Statistical methods

We estimated familial relative risk of early-onset HM by calculating the standardized incidence ratio (SIR) and life-time risk until ≤40 years of age by cumulative risk. The SIR compares observed HMs with expected ones by sex, age and period indicating the calendar year. The expected numbers are calculated based on person-years from the familial cohort multiplied by the sex, age and period-specific incidence rates of the population. We calculated SIRs for concordant (same) and discordant (different) HMs by type of relatedness separately and for all first-degree relatives combined. A Poisson distribution was assumed when calculating SIRs and 95% confidence intervals (CI). Cumulative risks were estimated using standard methods until ≤40 years of age only for the probands' siblings in HL, NHL, ALL/LBL, AML and all HMs combined. Probands with no family data available were excluded from the analyses. More details on statistical methods are given in Data S1. We used R software, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) packages Epi, version 2.35 and popEpi, version 0.4.7 for data analysis.

The study was approved by the National Institute for Health and Welfare (permit no. THL/1006/5.05.00/2017). Informed consent was deemed unnecessary as this was a registry-based study that required no contact with patients or their families.

Results

We found 147 familial HMs (concordant or discordant) appearing until ≤40 years of age among 75 774 family members in 8529 families (i.e. 1·7% of the early-onset HMs were familial) (Table I). Altogether, 69 of the early-onset familial HMs were concordant. Aggregation of concordant early-onset cases was observed in HL, NHL, ALL/LBL and AML. Among other HMs, there were no concordant early-onset cases in this cohort. Familial concordant early-onset HMs were more prominent in families with HL compared to families with acute leukaemias or NHL (1·3% vs. 0·5–0·9% respectively). There was only one family with two familial early-onset HL cases in addition to the proband. In other HMs, there were no families with multiple concordant early-onset HMs. Ninety-four of any familial early-onset HMs (concordant or discordant) were found among first-degree relatives, of whom 64 were siblings (Table II and Table SII). For concordant early-onset HMs, there were 48 cases in any first-degree relatives, of which 37 were in siblings.

Table II. Number and SIR (95% CI) for concordant and discordant haematological malignancies (HM) for siblings of probands both at ≤40 years of age.

	Early-onset haematological malignancies in siblings (≤40 years)									
	Any HM		HL		NHL		ALL/LBL		AML	
Proband's diagnosis	*N*	SIR (95% CI)	*N*	SIR (95% CI)	*N*	SIR (95% CI)	*N*	SIR (95% CI)	*N*	SIR (95% CI)
Any HM	64	2·37* (1·82–3·02)	23	2·85* (1·81–4·28)	18	2·52* (1·49–3·98)	8	2·19* (0·95–4·32)	6	2·58* (0·95–5·61)
HL	30	4·12* (2·78–5·88)	20	9·09* (5·55–14·04)	7	3·46* (1·39–7·12)	1	1·44 (0·04–8·03)	2	3·19 (0·39–11·54)
NHL	13	2·01* (1·07–3·43)	2	1·11 (0·13–4·01)	8†	4·61* (1·99–9·08)	0	0·00 (0·00–5·01)	0	0·00 (0–6·58)
ALL/LBL	14	1·73 (0·95–2·91)	1	0·38 (0·00–2·11)	1	0·50 (0·01–2·78)	7	4·42* (1·78–9·10)	1	1·47 (0·04–8·18)
AML	4	1·46 (0·40–3·74)	0	0·00 (0·00–4·73)	1	1·35 (0·03–7·52	0	0·00 (0·00–10·74)	2	8·29* (1·00–29·96)

ALL/LBL, acute lymphoblastic leukaemia/lymphoma; AML, acute myeloid leukaemia; CI, confidence interval; HL, Hodgkin lymphoma; HM, haematological malignancy; SIR, standardized incidence ratio.

*The 95% confidence interval (CI) does not include 1·00 and *P*-value is <0·05.

†The histological types of familial non-Hodgkin lymphomas (NHLs) were scrutinized in original Finnish Cancer Registry notifications and pathology reports. Familial NHLs were of B-cell lineage, mostly diffuse large B-cell lymphoma (n = 3, 38% of the cases), except for two pairs of probands and sibling with early-onset concordant T-cell lymphoma.

Familial relative risks

The SIR of any early-onset HM was 2·37 (95% CI 1·82–3·02) in siblings and 1·67 (95% CI 1·35–2·04) in any first-degree relatives (Table II and Table SII). In siblings, we detected a statistically significant aggregation of concordant cases in all of the most common early-onset HMs (HL, NHL, ALL/LBL and AML) with SIRs ranging from 4·42 (95% CI 1·78–9·10) in ALL/LBL to 9·09 (95% CI 5·55–14·04) in HL. The second highest SIR for siblings was seen in AML (8·29, 95% CI 1·00–29·96) (Table II).

The risk of familial, early-onset HM was lower among first-degree relatives other than siblings. HL probands' children had an elevated risk of HL with an SIR of 3·18 (95% CI 1·03–7·42). SIRs for spouses were all at population level (data not shown). There was a male predominance among HM probands (Table SI), but males were not overrepresented among affected family members.

Cumulative risks

The cumulative risks for siblings until ≤40 years of age for HL, NHL, ALL/LBL and AML are presented in Fig 1. Among the studied early-onset HMs, HL showed the highest cumulative risk of 1/100 (0·92%) for siblings, in contrast to the population cumulative risk of 1/1000 (0·11%). There was an approximately same-level cumulative risk of 1/200 for siblings of NHL and ALL/LBL probands (0·47% and 0·48% respectively) compared to the population cumulative risk of approximately 1/1000 or less (0·10% in NHL and 0·08% in ALL/LBL). The excess risk of ALL/LBL was reached by adolescence, whereas the cumulative risk of NHL steadily increased until the cut-off age of ≤40 years. The cumulative risk of AML for siblings was 1/300 (0·26%) compared to the population risk of only 1/3000 (0·03%).

Discordant familial HMs

Significantly elevated familial SIRs for early-onset HMs were predominantly seen in concordant HM diagnoses, but some elevated risks of discordant HMs between lymphomas among first-degree relatives were noted as well (Table II and Table SII). Siblings of HL probands had an increased risk of NHL (SIR 3·46, 95% CI 1·39–7·12). There was also a trend towards an increased risk of NHL for first-degree relatives of HL probands (SIR 2·11, 95% CI 0·91–4·16, $P = 0·056$).

Discussion

Our study demonstrated familial aggregation in all of the most common HMs of children and AYA among families with at least one case of early-onset HM. The increased familial relative and cumulative risks were seen mostly among siblings with concordant cancers. Amid different haematological diagnoses, HL was the one that, expectedly, aggregated most, but the familial risk of acute leukaemias was almost comparable to lymphomas. We also detected a risk of discordant, albeit lymphatic, HMs, notably between HL and NHL.

Siblings of HL probands had the highest familial risk of concordant early-onset HM with an SIR of 9·09. The risk for any first-degree relatives was over five-fold. Also, the cumulative risk of HL in siblings until ≤40 years of age was much higher than in the population (0·92% vs. 0·11%). Our findings are in line with the results from other population-based register studies, although our results rank at the higher end of the previously reported range.[9–16] Accordingly, in the literature, when stratified by age at onset, familial risk has been more prominent in early-onset HL cases.[11,13,15,18]

First-degree relatives of NHL probands had a significantly increased risk of NHL and the risk was again highest (over 4·5-fold) for siblings. The familial NHLs in siblings were most often diffuse large B-cell lymphomas (DLBCL). In our study, the risk for NHL probands' children was not statistically significantly elevated. In comparison, previous studies have shown a two- to three-fold risk of familial NHL for first-degree relatives and siblings.[10,11,17–21] We think that our results, showing a higher risk, may reflect the age focus of our study with both young probands and relatives of ≤40 years of age. In previous studies, the cut-off age between early and late-onset NHL has mostly been higher than in our study (50–60 years) or absent. However, in one large Nordic registry study, a SIR of 1·5 for NHL was reported in first-degree relatives of early-onset NHL patients of ≤30 years.[19]

Acute leukaemias demonstrated high risks of early-onset concordant cancer for siblings. In ALL/LBL the risk was over four-fold, and in AML over eight-fold, although the number of AML cases in siblings was small. Affected siblings with familial early-onset ALL/LBL were all children (aged 2–14 years) whereas siblings with AML were mainly diagnosed in young adulthood (at 20–40 years). High familial risk of childhood ALL in monozygotic twins is thought also to be explained by shared blood circulation and placenta.[38] In our study, there was only one pair of twins with ALL. Unfortunately, information on zygosity is not recorded in the DVV and, therefore, we cannot carry out a sensitivity analysis on this. Previous register-based research on familial clustering of acute leukaemias is sparse compared to lymphomas.[10,22–25] One previous study from Sweden and Finland demonstrated a slightly lower SIR of 3·2 compared to our results in childhood ALL/LBL for siblings.[22] Also, Goldin *et al.* have reported familial aggregation of early-onset AML.[24] Our study indicated that the familial risk for siblings in early-onset acute leukaemias was comparable to that of lymphomas and supports the recent findings on a germline-predisposed disease in a subset of acute leukaemia patients.[3,4,27,28]

We found some elevated risks of discordant early-onset HMs within the B-cell lymphatic malignancies in first-degree relatives. Siblings of probands with HL had an over three-

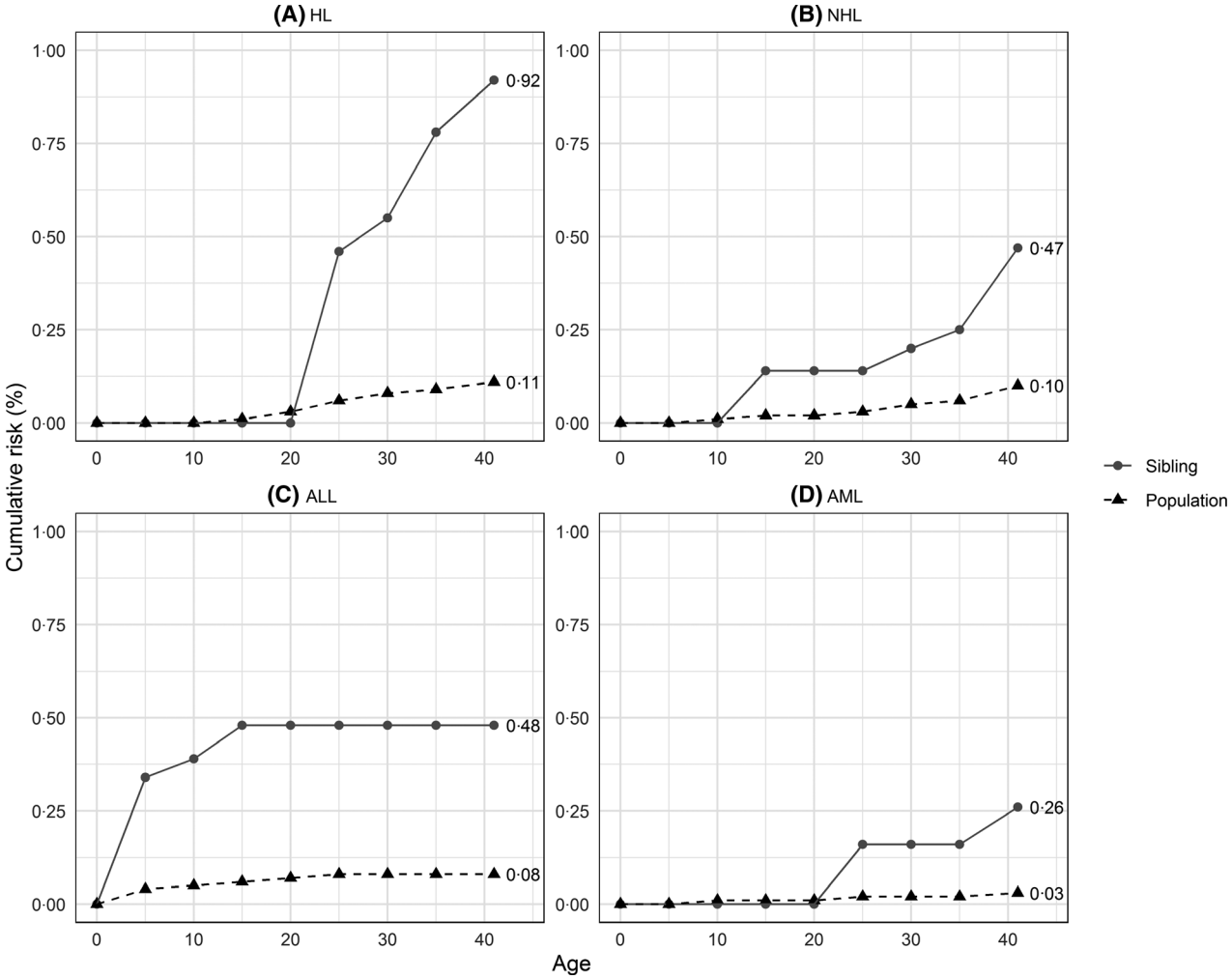

Fig 1. Cumulative risks for siblings until ≤40 of age in early-onset Hodgkin lymphoma, non-Hodgkin lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia.

fold risk of NHL. First-degree relatives of HL probands had a two-fold increased non-significant risk of NHL, which is in line with previous study findings.[10,16] Lymphatic malignancies aggregating in families tend to be of B-cell lineage, whereas we and others have not detected respective phenomena in T-cell diseases.[10,17,18] In our study, there were early-onset probands with T/natural killer cell malignancies but no concordant cancers in relatives. Although, pathology reports of familial NHLs revealed two pairs of probands and siblings both with T-cell lymphoma. Some studies and clinical experience suggest that HMs of both lymphatic and myeloid origin can cluster in the same families.[9,10,39] However, aetiological research of cross-lineage clustering, or even the entity of lymphoproliferative malignancies, has been problematic because of the heterogeneity of the diseases and evolving understanding of their genetic background.[40]

Here, we present a large familial cohort consisting of 75 774 family members of 8529 probands. To our knowledge, this is the largest population-based, prospective registry study concentrating specifically on familial clustering of early-onset HMs until ≤40 years of age. The follow-up is long and complete with no losses to follow-up. The probands and their family members are retrieved from high quality national registers with personal ID linkage. The distribution of HM diagnoses and the probands' characteristics represent, plausibly, early-onset HMs in the Finnish population. Since this is a registry study, recall bias is not relevant, unlike in many familial studies with interview data. The SIR compares familial risks to the risk in population and considers both age and calendar year (period) in the analyses. This method takes into consideration changes in diagnostics, treatment and survival.

Some limitations may explain why our results reflect the minimum familial risk of HMs. First, the cancer cases in the population also include the familial cases in the SIR analyses. Second, as we here chose to focus on early-onset HMs, fewer

patients with a typically late-onset haematological diagnosis were included in the cohort. Based on earlier register and genetic studies, familial clustering of some HMs with median age at onset above 60 years, such as chronic lymphocytic leukaemia (CLL), myeloproliferative neoplasms (MPN) and plasma cell dyscrasias (PCD), is also acknowledged.[4,10,25,41–49] Our decision to include only families with at least one family member diagnosed at ≤40 years of age resulted in underestimating the familial clustering of the above-mentioned HMs. This choice, however, was made as familial aggregation is most prominent at a young age, according to previous epidemiological data.[26] Additionally, the incidence and survival in older age groups with HM may be more affected by other aspects beyond germline genetics (e.g. comorbidities, poorer tolerance of cancer treatment, environmental exposures). Moreover, the follow-up in our study does not yet cover well enough ages >40 years. It is also worth noting that familial cohort members without HM who had not reached the age of 40 at the end of follow-up may reduce the statistical power, but do not introduce bias in the proper time-to-event (SIR) analysis.

The completeness of the FCR data is excellent for childhood HMs and good for adults.[34,35] The relatively recent start of registration of MDS and ET in the FCR (year 2007) might partly explain the lack of probands with MDS or ET in our study population. It is also estimated that approximately 8% of MDS is registered only when it transforms into AML.[50] Lymphomas are generally well covered in the FCR, but frequent changes in classification of NHLs over the years cause fragmentation of time series and difficulties in evaluating concordance of malignancies. Histological subtypes of NHL and HL were systematically registered only after 2007. Thus, we were not able to investigate reliably the familial clustering within or between different NHL and HL subtypes.

Elevated familial risks for siblings have been reported in HMs typical for children and AYA, whereas some other HMs seem to aggregate by parent-child relationship.[10] The historically poor survival and the lowered fertility among early-onset HM survivors could be one of the reasons why familial aggregation was seen almost exclusively among siblings. In acute leukaemias particularly, the survival was very poor in the 1970s but has improved significantly since then.[51] In our study, despite the comparable number of HL and ALL/LBL probands, HL patients had 10 times more children. HL was the only HM showing an elevated risk for offspring. The decrease in fecundity is well documented in childhood leukaemia survivors and after haematopoietic stem cell transplantation.[52–54] HL patients, on the other hand, have been treated with less toxic and fertility preserving chemotherapy since the 1970–1980s.[55] It has also been speculated that probands with a less severe and possibly less heritable disease could be selected. Mutagenic genetic effects of cancer treatment for offspring of young cancer survivors are not supported by studies, although a trend towards higher risk among leukaemia patients has been established.[56]

We included spouses as a control group because they are unrelated to the probands and represent the cancer risk in a population excluding shared early-life environmental effects. Indeed, the spouses' risk was at population level, which suggests that early-onset HMs probably do not result from a pure environmental exposure in adulthood. Probands' siblings, on the other hand, share both genetic background and potential early-life environmental exposures.

Acknowledging the possibility of germline predisposition in HMs is of importance, given its relevance, for example, in choosing family members for donors of haematological stem cells. Also, genetic counselling should be an integral part of families with an identified germline mutation. The absolute risk of HM in the population aged ≤40 years remains small. However, in clinical decision making the risk should be evaluated case by case and based on comprehensive sequencing studies.

In conclusion, our study, which to our knowledge is the largest population-based study focusing specifically on early-onset HMs, showed increased familial aggregation in all of the most common HMs in this age group. SIRs for siblings were higher than previously reported, which could be attributed to the younger age focus of our study. Significantly elevated SIRs indicate a role of shared aetiological factors in some families, such as rare early exposures and/or germline genetics. Importantly, our data imply that germline contribution to the disease onset should be considered not only in children, but also in AYA patients with HMs.

Author contributions

RR performed the research and wrote the first draft. EH worked on the data and carried out statistical analysis. NM and OK revised the manuscript. JP designed the research study, provided guidance for statistical analysis and revised the manuscript. UWK provided guidance for haematological clinical interpretation of the results and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Probands' characteristics. All probands were diagnosed with primary haematological malignancy (HM) at ≤40 years of age. The total number of haematological probands, distribution of diagnoses, number (proportion) of males and females and median age-at-onset (by gender).

Table SII. Number and SIR (95% CI) for concordant and discordant haematological malignancies (HM) for 1st degree relatives of probands both at ≤40 years of age.

Fig S1. A Lexis diagram of the ascertainment and follow-up of the early-onset primary haematological malignancy familial cohort.

Data S1. Statistical methods.

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