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General MM

What is the familial risk of developing a hematological malignancy?

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This article provides a summary of a study recently published in *Blood* by Amit Sud, Institute of Cancer Research, London, UK and the German Cancer Research Center, Heidelberg, DE, and colleagues. The study aimed to investigate the familial risks in hematological malignancies using a large database registry in Sweden.

Background

Hematological malignancies differ by their clinical phenotype depending on whether the progenitor cell was of lymphoid origin or myeloid origin. Examples of malignancies of lymphoid origin include; lymphomas, B-cell and T-cell leukemias and multiple myeloma (MM), whilst the myeloid malignancies include; acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPNs).

Aside from some established risk factors, such as exposure to DNA-damaging agents, the etiological basis of most hematological malignancies is poorly understood. It is possible that there are inherited factors involved in this process, with some types of hematological malignancies linked to hereditary factors in recent genome-wide association studies.

A better understanding of familial risk in hematological malignancy may allow healthcare professionals to identify patients at a higher risk, and will enhance knowledge of genetic susceptibility of the disease.

Study design

Using the Swedish Family-Cancer Database of 16.1 million individuals, 153,115 patients diagnosed with a primary hematological malignancy were identified between 1958 and 2015. The authors of the study aimed to quantify the familial relative risk (FRR), which was defined as the ratio of the number of observed cases of a hematological malignancy in first-degree relatives (FDRs) of patients, to the expected number of cases in FDRs of patients. To do this, they calculated standardized incident ratios (SIR) in 391,131 FDRs to compare the risk of developing a hematological malignancy compared to the general population. Statistical analysis was conducted, and a two-sided p value of 0.05 was determined to indicate statistical significance.

The study included patients diagnosed with; all hematological malignancies, all myeloid malignancies, MPNs, AML, acute lymphoblastic leukemia (ALL), Hodgkin lymphoma (HL), nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Burkitt lymphoma (BL), small lymphocytic leukemia (SLL), hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), MM, mature T-cell lymphoma (MTCL), anaplastic T-cell lymphomas (ATCL) and cutaneous T-cell lymphoma (CTCL).

Results

Nearly all hematological malignancies analyzed showed a statistically significant increase in the risk of a family member developing the same malignancy (**Table 1**).

Table 1. Increase in FRR of the same disease, by hematological malignancy

Hematological malignancy	**Increase in FRR (-fold)**
AML	1.5
DLBCL	2
FL	2
MM	2
CLL	5.6
ET	6.8
MDS	6.9
PV	7.7
HCL	8.3
NSHL	9.8
MCL	13.3
LPL/WM	15.8
MCHL	16.7

The investigators subsequently analyzed the FRR by age at diagnosis, type of relationship, and number of affected FDRs (**Table 2**). In several malignancies, this demonstrated a significantly increased risk for family members of patients diagnosed at a younger age, siblings, and those with a higher number of affected FDRs.

Table 2. Malignancies found to have statistically significantly higher FRR by age at diagnosis, type of familial relationship and number of affected FDRs

Hematological malignancy	**SIR**		***P* value**
Age at diagnosis (years)	**Younger**	**Older**	
HL (≤28 *vs* >28)	5.76	3.36	7.3×10^{-3}
CLL (≤63 *vs* >63)	6.99	4.83	1.1×10^{-3}
MPNs (≤59 *vs* >59)	6.46	4.15	4×10^{-3}
PV (≤59 *vs* >59)	10.91	5.96	0.03
MDS (≤68 *vs* 68)	11.95	3.27	8.8×10^{-3}
Relationship	**Sibling**	**Parent/offspring**	
NHL	1.97	1.69	Not available (NA)
HL	7.45	3.09	NA
CLL	7.8	5.36	NA
AML	3.08	1.09	NA
LPL/WM	5.56	21.88	NA

Number of affected FDRs	≥**2**	**1**	
All	2.08	1.31	2.1×10^{-12}
CLL	27.13	5.36	1.34×10^{-8}
All myeloid	4.55	1.96	0.02
All MPNs	17.82	4.83	0.01

Lifetime risk

Example: in CLL, the lifetime risk for the generation population is 0.4%, so an FRR of 6.99 for a patient whose relative was diagnosed at the age of 63 or under, increases this risk to 2.2%.

This low overall lifetime risk therefore has limited clinical value.

Shared risk across the malignancies

The authors examined FRR between all hematological malignancies and found that whilst the strongest connections were disease-specific, some patterns of familial risk were identified. Most were cell-lineage specific, for example CLL had associated familial risk with nearly all B-cell tumors. Other risk associations were cross-lineage, for example HL, DLBCL, MCL, CLL and MM shared risk with myeloid malignancies.

Advantages and limitations of the study

Table 3. Advantages and limitations of the study

Advantages	**Limitations**
Large sample size	Advances to the classification system would further refine FRR estimates
Swedish Family Cancer Database contains near complete case registration for nearly all cases of hematological malignancies, avoiding bias	No information available about other risk factors within families such as shared environmental risk factors that may increase FRR
Long-term follow-up	Potential that misclassification impacted these calculations

	Study may only be applicable to Western populations
	Limited power for malignancies recorded after 1993
	The absolute risk of developing a hematological malignancy remains small, so these data are of limited clinical significance

Conclusion

This study has shown significantly elevated risks in FDRs for the same malignancy, particularly in patients with relatives who were diagnosed at a younger age, or who have multiple affected FDRs. The increased FRR by age of onset may indicate that genetic predisposition is involved in disease risk.

The FRR was also found to be increased across different hematological tumors. Therefore, it may be inferred that there are shared etiological factors between these malignancies, both within the same hematopoietic lineage at different stages of differentiation, and also across lineages.

This large, retrospective, population-based analysis may help to inform future studies that investigate the etiology of hematological malignancies. It also provides the basis of a rationale to provide counselling and genetic testing to family members of patients diagnosed with a hematological malignancy, in order to accurately stratify patients by individual risk.

References

1. Sud A. *et al.*, Analysis of 153,115 patients with hematological malignancies refines the spectrum of familial risk. Blood. 2019 Aug 08. DOI: 10.1182/blood.2019001362