Familial risk for haematological malignancies – Swedish insights

In reference to
Sud et al. Blood.
2019;134(12):960-969
https://doi.org/10.1182/blood.2019001362

Haematological malignancies are characterized by a distinctive clinical phenotype reflective of differences in cells of origin and underling biology. The lymphomas, B- and T-cell leukaemias, and myeloma are of lymphoid origin, arising at differing stages of maturation. Acute and chronic myeloid leukemia (CML), myelodysplastic syndrome, and the myeloproliferative diseases are all derived from a myeloid progenitor. Although individually rare they contribute significantly to the overall cancer burden in the population.

Aside from exposure to DNA-damaging agents and the association between Epstein-Barr virus, HIV, human T-cell lymphotropic virus, and Helicobacter pylori with specific lymphoma subtypes, the etiological basis of most haematological malignancies is poorly understood. Epidemiological observational studies and reports of families segregating haematological malignancies over the years have supported the role of inherited factors in disease aetiology.

Recent genome-wide association studies have provided evidence for a heritable basis to sporadic forms of acute lymphoblastic leukaemia, Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), primary central nervous system lymphoma, follicular lymphoma (FL), marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and the myeloproliferative neoplasms (MPNs).

To gain insight into the familial risk for the different haematological malignancies and their possible inter-relationship Sud et al. (Blood. 2019; 134(12):960-969) evaluated cases from 1958-2015 using Swedish Family-Cancer Database covering over 16.1 million entries. They identified 153.115 patients diagnosed with a primary haematological malignancy and quantified familial relative risks (FRRs) by calculating standardized incident ratios (SIRs) in 391.131 of their first-degree relatives. FRR were defined as the ratio of the number of observed cases of a given haematological malignancy in first-degree relatives of patients to the expected number of cases in first-degree relatives. As such, SIRs as a measure of FRR were used to compare the risk for haematological malignancies in first-degree relatives of patients (i.e., parent, sibling, or child) with that of the general population.

Detailed analysis of the FRRs of the myeloid malignancies revealed 1.5-, 6.8-, 6.9-, and 7.7-fold increases in FRRs for acute myeloid leukemia (AML), essential thrombocythemia, myelodysplastic syndrome (MDS), and polycythemia vera (PV) in Swedish population. For the B-cell tumors, a range of FRRs was observed, with two-fold increases for DLBCL, FL, and MM and 5.6-, 8.3-, 9.8-, 13.3-, 15.8-, and 16.7-fold increases for CLL, hairy cell leukemia, nodular sclerosis HL, mantle cell lymphoma, LPL/WM, and mixed cellularity HL. There was no evidence to support familial clustering of CML, myelofibrosis, and the T-cell neoplasms.

Analysis of FRRs of the lymphoid diseases by age at diagnosis, sex, and type of familial relationship revealed that familial risks were significantly higher for relatives of cases diagnosed young for all HL (5.76 vs 3.36) and CLL (6.99 vs 4.83). The FRRs were significantly higher in siblings when compared with that of parent-offspring relationships for non-HL (1.97 vs 1.69), HL (7.45 vs 3.09), and CLL (7.80 vs 5.36). In contrast, parent-offspring RRs were significantly higher for LPL/WM (21.88 vs 5.56).

There was no evidence of gender differences in FRR. FRRs were significantly higher for relatives with two or more affected first degree relatives when compared with relatives with one affected first degree relative for all haematological malignancies (2.08 vs 1.31) and CLL (27.13 vs 5.36). Familial risks were significantly higher for relatives of cases diagnosed young for all MPNs (6.46 vs 4.15), PV (10.91 vs 5.96), and MDS (11.95 vs 3.27). Sibling relative risks were higher than parent-child relative risks for AML (3.08 vs 1.09), and all 53 familial cases of PV were of a parent-child relationship. Familial relative risks were significantly higher for relatives with two or more affected first-degree relatives for all myeloid malignancies (4.55 vs 1.96) and all MPNs (17.82 vs 4.83).

The majority of haematological malignancies showed increased FRRs for the same tumor type, with the highest FRRs observed for mixed cellularity Hodgkin lymphoma (SIR, 16.7), lymphoplasmacytic lymphoma (SIR, 15.8), and mantle cell lymphoma (SIR, 13.3). There was also evidence for pleiotropic relationships i.e. chronic lymphocytic leukaemia was associated with an elevated familial risk for other B-cell tumors and myeloproliferative neoplasms.

Familial cases represented 4.1% of all haematological malignancy diagnoses, which was higher than cancers of the nervous system (1.8%), kidney (2.8%), and pancreas (3.0%), but lower than breast (8.5%), colorectal (10.1%), and prostate cancers (15.3%). Almost all of the haematological malignancies showed statistically significant increased familial risks for the same tumor type.

Although the strengths of this study were the large sample size and unbiased assessment of cancer status in relatives, it did not contain information concerning possible risk factors for malignancies that may be correlated within families. These findings also may only apply to Western countries and may not therefore be applicable to economically developing countries that have different tumor incidence rates. These data provide evidence for shared etiological factors for many haematological malignancies that can help to identify individuals with increased risk, as well as boost future gene discovery initiatives.

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