Letter to blood

To the Editor:

**Familial risks of primary myeloid leukemia, myelodysplasia and myeloproliferative neoplasms**

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The myeloid malignancies comprising the myeloproliferative neoplasms (MPNs), polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF), and chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are clonal proliferative diseases with shared but diverse phenotype characteristics[1](#_ENREF_1). The etiological basis of most myeloid malignancies is largely unknown. While rare single-gene syndromes and predisposition disorders are associated with AML, MDS and MPNs[2](#_ENREF_2), they do not contribute significantly to the overall disease burden[3](#_ENREF_3). Aside from these rare syndromes, there are limited data on the extent of familial aggregation of AML and MDS, and their relationship to other MPNs. Understanding familial relative risks (FRR) is clinically important as it allows for the discrimination of risk between individuals[2](#_ENREF_2),[4](#_ENREF_4),[5](#_ENREF_5). Additionally, these data are relevant to the design of research to identify susceptibility genes[6](#_ENREF_6). The ability of previous studies to characterise the FRRs of myeloid malignancies has been limited and no comprehensive analysis of the interrelationship between these diseases has been performed[7-10](#_ENREF_7). To address these deficiencies, we have utilised the Swedish Family-Cancer Database to perform the largest population-based study of familial risks of myeloid malignancies to date, which included 93,199 first-degree relatives (FDRs) of 35,037 patients (**Supplementary Table 1**)[11](#_ENREF_11).

The Swedish Family-Cancer Database was created by linking information from the Multi-Generation Register, national censuses, the Swedish Cancer Registry and death notifications[11](#_ENREF_11). The Swedish Cancer Registry, established in 1958, is based on compulsory reporting of all cancers diagnosed in Sweden[12](#_ENREF_12),[13](#_ENREF_13). We analysed all primary cases of myeloid malignancies diagnosed between 1958 and 2015. As MDS and myeloproliferative neoplasms not otherwise specified require ICD-O/2 codes, data for these malignancies could only be ascertained from 1993. Standardised incidence ratios (SIRs), as a measure of FRR, were used to compare the cancer risks in FDR of patients with a myeloid malignancy with the risk in the general population[14](#_ENREF_14). All FDRs were observed from the date of birth, immigration, or the start of cancer-specific registrations in the database. Follow-up ended at diagnosis of cancer, date of death, emigration, or the end date of the registry. The SIRs (indirect standardisation) were calculated as the ratio of observed cases to expected numbers of cases in the FDRs. To calculate the expected numbers of cases in the FDRs age-, sex-, calendar year- and disease-specific incidence rates in the population were multiplied by the corresponding person-years in FDRs. 95% confidence intervals (CIs) were estimated assuming a Poisson distribution.  Tests for trend in SIRs were performed by evaluating the likelihood function in collapsed person-time additive Poisson regression models with and without the inclusion of the variable. The lifetime cumulative risk was calculated based on the average life expectancy in Sweden in 2015 (82 years) and the following calculation: lifelong cumulative rate = sum of all age-specific incident rates; lifelong cumulative risk=1–e–lifelong cumulative rate. To test for anticipation, the phenomenon in which a diseases appears earlier in successive generations, we computed Kaplan-Meier estimates of risk by age and tested for homogeneity of parent and offspring strata using the log-rank test.

Overall we observed an increased risk of all myeloid malignancies in FDRs of patients (1.99, 95% CI 1.81-2.17). The association between family history and increased risk was statistically significant for AML (1.53, 95% CI 1.12-2.04), ET (6.30, 95% CI 3.95-9.54), MDS (6.87, 95% CI 4.07-10.86) and PV (7.66, 95% CI 5.74-10.02). Between the myeloid malignancies the strongest FRRs tended to occur for the same disease although significant associations between diseases were noted (**Table 1**). We next examined FRRs for the same disease by age at diagnosis of the patient. A significantly increased FRR for younger cases when compared to older cases for all MPNs (6.46 vs 4.15), PV (10.90 vs 5.96) and MDS (11.95 vs 3.27) was observed (**Supplementary** **Table 2**). The mean age of a MPN diagnosis was higher in parents of cases as compared to children of cases (70 years vs 54 years, log rank test *P* = 0.05). Whilst we cannot exclude the possibility of anticipation[15](#_ENREF_15), this observation may reflect truncation bias[16](#_ENREF_16). Sibling FRRs were significantly higher than parent-child risks for AML (3.29 vs 1.19; *P* = 2.1 × 10-3) (**Supplementary Table 3**). All 53 familial cases of PV were of a parent-child relationship (*P* = 1.0 × 10-5). We found little evidence that the sex of the patient or FDR had an effect on familial risk (**Supplementary Tables 4 and 5**). We next examined FRRs by the number of affected relatives and found the FRRs of all myeloid malignancies and MPNs were significantly correlated with the number of affected FDRs. The SIRs for FDRs with two or more affected relatives for all myeloid and MPNs were 4.55 (95% CI 2.08-8.64) and 17.82 (95% CI 5.79-24.89), whereas the SIRs for FDRs with one affected relative were 1.96 (95% CI, 1.79-2.15) and 4.83 (95% CI, 4.14-5.60) (**Supplementary Table 6**). Although the FRRs associated with these myeloid malignancies are among the highest known for cancers, these risks do not necessarily translate to a high absolute risk (**Figure 1**). However, markedly elevated cumulative risk estimates were obtained for all myeloid malignancies (4.4%) and MPNs (3.2%) in individuals with two or more affected FDRs (**Supplementary Table 6**).

With more than twice the number of incident cases and 10 years longer follow-up than previous studies of the Swedish population[8](#_ENREF_8),[9](#_ENREF_9), the increased study power has enabled us to demonstrate familial aggregation between different forms of myeloid malignancies. This population-based family cancer registry possesses robust familial relationship data with near complete case registration[12](#_ENREF_12),[13](#_ENREF_13), allowing FRRs to be derived while avoiding biases introduced by case-control study designs. A previous analysis of the Swedish population utilised an additional registry to ascertain <15% MPN cases, which suggests there has previously been an underreporting of MPN cases[8](#_ENREF_8). Potential underreporting has been ameliorated by our extended follow-up and improved statistical power. Although increased surveillance of relatives can bias familial risk estimates, such bias is not likely to occur in the general population over the long time period we have examined. Over recent decades, the diagnosis of hematological malignancies has increasingly relied on molecular tests[1](#_ENREF_1). Future work should therefore refine current risk estimates as well as identify familial risks associated with molecular subgroups.

Our findings indicate that inherited and environmental etiological factors for myeloid malignancies are likely to be shared, and there is heterogeneity in the mechanisms by which such factors may exert their effects on different phenotypes. Consistent with early-onset tumours being more likely to have a genetic predisposition[6](#_ENREF_6), for most of the myeloid malignancies a relationship between familial risk and age at diagnosis was seen. The familial aggregation shown here justifies the continued application of gene-mapping approaches in high-risk families[17](#_ENREF_17). Based on the paradigm of other cancers including some MPNs[6](#_ENREF_6),[18](#_ENREF_18),[19](#_ENREF_19), common genetic variation may also influence the development of the myeloid malignancies.

In summary, our findings provide evidence for genetic susceptibility to most myeloid malignancies as well as a shared genetic susceptibility between these malignancies. Furthermore, our data suggest there are individuals, such as patients diagnosed at a young age and those with multiple affected FDRs, for whom counselling, gene testing and surveillance may be appropriate. Finally, as recently advocated[2](#_ENREF_2), such data may have implications for potential related stem-cell donors.

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**AUTHORSHIP**

**Contribution:** A.S. and K.H. designed the study. K.H. K.S., J.S. provided the data. A.S., S.C. and H.T. performed data extraction and statistical analysis. A.S., R.S.H and K.H. drafted the manuscript. All authors contributed to the manuscript.

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**FIGURE LEGENDS**

**Figure 1: Cumulative risk of myeloid malignancy (A), myeloproliferative neoplasm (B), myelodysplastic syndrome (C) and acute myeloid leukemia (D).** Myeloid malignancies comprise polycythemia vera, essential thrombocythemia, myelofibrosis, myeloproliferative neoplasm NOS, chronic myeloid leukemia, myelodysplastic syndrome, acute myeloid leukemia. Myeloproliferative neoplasm comprise polycythemia vera, essential thrombocythemia, myelofibrosis and myeloproliferative neoplasm NOS.

**TABLES**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Hematological malignancy in first-degree relative** | | | | | | | | | | | | | | | | | |
|  | **Myeloid malignancy** | | **Myeloproliferative neoplasm** | | **Polycythemia vera** | | **Essential thrombocythemia** | | **Myelofibrosis** | | **Myeloproliferative neoplasm NOS** | | **Chronic myeloid leukemia** | | **Myelodysplastic syndrome** | | **Acute myeloid leukemia** | |
| **Individual with hematological malignancy** | | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** | **N** | **SIR (95% CI)** |
|
| **Myeloid malignancy** | | 479 | 1.99 (1.81-2.17) | 265 | 2.86 (2.52-3.22) | 131 | 3.21 (2.69-3.81) | 76 | 2.73 (2.15-3.42) | 25 | 2.49 (1.61-3.67) | 33 | 2.50 (1.72-3.51) | 39 | 1.06 (0.76-1.45) | 59 | 2.31 (1.76-2.98) | 120 | 1.38 (1.15-1.65) |
| **Myeloproliferative neoplasm** | | 267 | 2.79 (2.47-3.15) | 181 | 4.93 (4.24-5.70) | 94 | 5.76 (4.66-7.05) | 54 | 4.97 (3.74-6.49) | 11 | 2.76 (1.38-4.93) | 21 | 4.05 (2.51-6.20) | 20 | 1.37 (0.84-2.12) | 22 | 2.19 (1.37-3.32) | 47 | 1.36 (1.00-1.81) |
| **Polycythemia vera** | | 133 | 3.23 (2.70-3.83) | 94 | 5.92 (4.78-7.24) | 53 | 7.66 (5.74-10.02) | 24 | 5.02 (3.22-7.47) | 7 | 4.00 (1.61-8.24) | 10 | 4.35 (2.08-8.00) | 8 | 1.28 (0.55-2.53) | 7 | 1.57 (0.63-3.23) | 26 | 1.77 (1.15-2.59) |
| **Essential thrombocythemia** | | 78 | 2.65 (2.10-3.31) | 56 | 4.99 (3.77-6.48) | 23 | 4.53 (2.87-6.79) | 22 | 6.30 (3.95-9.54) | 3 | 2.48 (0.51-7.25) | 8 | 5.13 (2.21-10.10) | 5 | 1.12 (0.36-2.62) | 4 | 1.31 (0.36-3.36) | 13 | 1.21 (0.65-2.08) |
| **Myelofibrosis** | | 26 | 2.51 (1.64-3.68) | 11 | 2.75 (1.37-4.92) | 7 | 3.93 (1.58-8.10) | 3 | 2.54 (0.52-7.43) | 0 |  | 1 | 1.79 (0.05-9.95) | 2 | 1.27 (0.15-4.57) | 9 | 8.33 (3.81-15.82) | 4 | 1.08 (0.29-2.76) |
| **Myeloproliferative neoplasm NOS** | | 33 | 2.21 (1.52-3.11) | 21 | 3.87 (2.39-5.91) | 10 | 4.03 (1.93-7.42) | 8 | 5.06 (2.19-9.98) | 1 | 1.72 (0.04-9.61) | 2 | 2.74 (0.33-9.90) | 5 | 2.25 (0.73-5.26) | 3 | 2.16 (0.45-6.31) | 4 | 0.77 (0.21-1.97) |
| **Chronic myeloid leukemia** | | 39 | 1.11 (0.79-1.51) | 20 | 1.47 (0.90-2.27) | 8 | 1.38 (0.60-2.72) | 5 | 1.21 (0.39-2.82) | 2 | 1.34 (0.16-4.85) | 5 | 2.27 (0.74-5.30) | 4 | 0.78 (0.21-1.99) | 5 | 1.25 (0.40-2.91) | 11 | 0.88 (0.44-1.57) |
| **Myelodysplastic syndrome** | | 60 | 2.15 (1.64-2.76) | 21 | 1.96 (1.21-3.00) | 7 | 1.42 (0.57-2.92) | 4 | 1.29 (0.35-3.29) | 8 | 7.02 (3.03-13.83) | 3 | 2.14 (0.44-6.26) | 5 | 1.11 (0.36-2.59) | 18 | 6.87 (4.07-10.86) | 16 | 1.57 (0.90-2.55) |
| **Acute myeloid leukemia** | | 120 | 1.43 (1.19-1.71) | 47 | 1.46 (1.07-1.94) | 26 | 1.87 (1.22-2.73) | 13 | 1.32 (0.70-2.26) | 4 | 1.15 (0.31-2.93) | 4 | 0.86 (0.23-2.19) | 11 | 0.87 (0.43-1.55) | 16 | 1.77 (1.01-2.88) | 46 | 1.53 (1.12-2.04) |

**Table 1: Familial relative risks of myeloid malignancies.** N, number; SIR, Standardised incidence ratios; CI, confidence interval; NOS, not otherwise specified. Myeloid malignancies comprise polycythemia vera, essential thrombocythemia, myelofibrosis, myeloproliferative neoplasm NOS, chronic myeloid leukemia, myelodysplastic syndrome, acute myeloid leukemia. Myeloproliferative neoplasms comprise polycythemia vera, essential thrombocythemia, myelofibrosis and myeloproliferative neoplasm NOS.