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ORIGINAL REPORT

Familial Aggregation of Acute Myeloid Leukemia and Myelodysplastic Syndromes

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ABSTRACT

Purpose
Apart from rare pedigrees with multiple cases of acute myeloid leukemia (AML), there is limited data on familial aggregation of AML and myelodysplastic syndromes (MDSs) in the population.

Patients and Methods
Swedish population-based registry data were used to evaluate risk of AML, MDS, and other malignancies among 24,573 first-degree relatives of 6,962 patients with AML and 1,388 patients with MDS compared with 106,224 first-degree relatives of matched controls. We used a marginal survival model to calculate familial aggregation.

Results
AML and/or MDS did not aggregate significantly in relatives of patients with AML. There was a modest risk ratio (RR, 1.3; 95% CI, 0.9 to 1.8) in myeloproliferative/myeloid malignancies combined. The risks for any hematologic or any solid tumor were modestly but significantly increased. Relatives of patients with MDS did not show an increased risk for any hematologic tumors. In contrast, we found a significantly increased risk (RR, 6.5; 95% CI, 1.1 to 38.0) of AML/MDS and of all myeloid malignancies combined (RR, 3.1; 95% CI, 1.0 to 9.8) among relatives of patients diagnosed at younger than age 21 years.

Conclusion
We did not find evidence for familial aggregation of the severe end of the spectrum of myeloid malignancies (AML and MDS). The risks of myeloproliferative neoplasms were modestly increased with trends toward significance, suggesting a possible role of inheritance. In contrast, although limited in sample size, relatives of young patients with AML were at increased risk of AML/MDS, suggesting that germline genes may play a stronger role in these patients. The increased risk of all hematologic malignancies and of solid tumors among relatives of patients with AML suggests that genes for malignancy in general and/or other environmental factors may be shared.

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INTRODUCTION

The molecular underpinnings of the development of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDSs) are unclear. Known exogenous risk factors for AML include exposure to ionizing radiation, occupational exposure to benzene and other chemicals, and cytotoxic chemotherapy, especially with alkylating agents and topoisomerase II inhibitors.[1-5] Lifestyle factors such as smoking, obesity, and diet may contribute to risk.[4] There is emerging evidence that autoimmune, infectious, and inflammatory conditions are associated with an excess risk for subsequent AML or MDS[6,7] suggesting that disturbances in the immune system may contribute to risk.

Several single-gene syndromes are associated with AML/MDS including bone marrow failure syndromes, Li-Fraumeni syndrome, and Down syndrome,[1,7] although the various genes identified for these syndromes do not seem to contribute to susceptibility of sporadic disease. Mutations in the *RUNX1* gene have been described in familial platelet disorder with propensity to develop AML.[8-11] Mutations in *CEBPA* have been identified in families with AML segregating in an autosomal dominant pattern.[8] Interestingly, somatic *CEBPA* mutations are found in patients who also have germline mutations.[12] Aside from the rare syndromes identified and rare pedigrees published with multiple patients with AML, there are limited data on the extent of familial aggregation of AML/MDS in the population. Early

studies found increased risk of leukemia among relatives of patients with all types of leukemia but this was largely accounted for by chronic lymphocytic leukemia (CLL).[13] Two studies in the Utah Population database found significant familial clustering of AML, although CLL showed substantially more familial clustering.[14,15]

Germline genes with smaller effects may also contribute to susceptibility to AML. Since chemical exposures and radiation are associated with risk of AML, genes involved in detoxification, DNA repair, and genome stabilization pathways could be involved. There have been some studies of these pathways in patients with AML compared with normals, and some associations have been found.[3,16] A recent meta-analysis of the glutathione-*S*-transferases found that *GSTM1* and *GSTT1* null genotypes were associated with risk of AML.[17] However, the number of studies and genes examined are limited, and findings have not been consistently replicated. A mutation in *TERT* has also been found to be associated with AML and other hematologic malignancies.[18] Clearly, a better understanding of the role for genetic factors in the causation of AML/MDS is of major importance for patients and their families, health care professionals, and scientists.

Taking advantage of high-quality data from Sweden, we conducted the largest population-based study to date, which included 20,579 first-degree relatives of 6,962 primary patients with AML and 3,994 first-degree relatives of 1,388 primary patients with MDS compared with relatives of matched controls. The aim of our study was to quantify familial aggregation for AML/MDS as well as other hematopoietic and solid tumors.

PATIENTS AND METHODS

Registries, Patients, Controls, and Relatives

Details of the study population have been described previously.[19,20] From the Swedish Cancer Registry, we identified all patients with AML who were diagnosed from January 1, 1958, through December 31, 2004. MDS was not reported to the Cancer Registry until 1993, so we included all patients with MDS in the Cancer Registry from January 1, 1993, through December 31, 2004. To minimize risk for bias in this study, we excluded patients with another cancer diagnosed before their AML or MDS diagnosis. For each patient with AML or MDS, four population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All control individuals had to be alive at the time of AML/MDS diagnosis for their corresponding case patient and without a hematologic malignancy at the date of AML/MDS diagnosis for their corresponding case patient. We obtained information from the Swedish Multigenerational Registry,[21] which includes information on parent-sibling-offspring relations for all Swedish citizens who were born in the year 1932 and later, on all first-degree relatives (parents, siblings, and offspring) of cases and controls.

The statistical approach is described in detail elsewhere.[22] We classified relatives as "affected" if they had a cancer registration with the tumor of interest (examining up to three cancer registrations). Here, the age or age at onset of disease in a relative is modeled by a proportional hazards model.[22] Familial aggregation for each condition is evaluated by testing the hazard ratio of being a relative of a case compared with being a relative of a control. The model was fitted to the data by using the PHREG procedure in SAS v9.1 (SAS Institute, Cary, NC). We used risk ratio (RR) to denote the hazard ratio, with 95% CIs provided. We adjusted for sex in all analyses. The robust sandwich covariance matrix accounts for the dependence of the family members. We have previously shown that the marginal model sometimes overestimates the variance of the hazard ratio because of the matching of case and control probands and that a bootstrap procedure can accommodate this matching.[22] The bootstrap procedure was used to confirm the size of the confidence intervals. We also tested for departure from the proportional hazards assumption. Since AML occurring in young people may be etiologically distinct from the more commonly occurring AML in older adults, we also tested familial aggregation among relatives of patients with onset in childhood through adolescence (younger than age 21 years).

Approval for this study was obtained from the Karolinska Institutional Review Board. Informed consent was waived because we had no contact with study participants. An exemption from institutional review board review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Table 1. Characteristics of Primary Patients With AML or MDS and Matched Controls With Available Relatives

Variable	AML (n = 6,962)		Controls (n = 27,827)		MDS (n = 1,388)		Controls (n = 5,312)	
	No.	%	No.	%	No.	%	No.	%
Median age at diagnosis, years	64				76			
Males		53.6		54.0		56.0		55.2
Age group, years								
< 21	534	7.7			14	1.0		
21-39	722	10.4			19	1.4		
40-49	674	9.7			30	2.2		
50-59	950	13.6			100	7.2		
60-69	1,555	22.3			233	16.8		
70-79	1,672	24.0			532	38.3		
≥ 80	855	12.3			460	33.1		
Year of diagnosis								
< 1976	949	13.6			0			
1976-1985	1,638	23.5			0			
1986-1995	2,388	34.3			300	21.6		
1995-2004	1,987	28.6			1,088	78.4		

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

RESULTS

A total of 6,962 patients with AML and 1,388 patients with MDS could be linked to first-degree relatives. These patients were matched to 27,827 and 5,312 population-based controls, respectively. As depicted in Table 1, 53.6% of the patients with AML and 56.0% of the patients with MDS were male; the median age at diagnosis was 64 years and 76 years for patients with AML or MDS, respectively.

Table 2 depicts the risk of specific myeloid and lymphoid malignancies in 20,579 relatives of patients with AML compared with 90,406 relatives of matched controls and 3,994 relatives of patients with MDS compared with 15,818 relatives of matched controls. AML and/or MDS did not aggregate in relatives of patients with AML or MDS.

Myeloproliferative neoplasms (MPNs) showed a modest increase among relatives of patients with AML, which was mostly accounted for by the increased risk of polycythemia vera. The combination of all MPNs and all myeloid malignancies was also modestly increased although not significant. Lymphoid malignancies showed a modest but nonsignificant increased risk in relatives of patients with AML with a borderline significantly increased risk of CLL. The risk for "any hematologic malignancy" was significantly increased among relatives of patients with AML (RR, 1.2; 95% CI, 1.0

Table 2. Risk of Myeloid, Lymphoid, and Solid Malignancies in Relatives of Patients With AML or MDS

Outcome in Relatives	AML (n = 20,579)	Controls (n = 90,406)	RR	95% CI	MDS (n = 3,994)	Controls (n = 15,818)	RR	95% CI
Myeloid								
AML	15	70	0.9	0.5 to 1.9	3	11	1.1	0.30 to 3.8
MDS	4	10	1.8	0.6 to 5.7	2	2	4.0	0.4 to 43.1
AML/MDS	19	80	1.0	0.6 to 1.9	5	13	1.5	0.5 to 4.8
CML	9	29	1.3	0.6 to 2.9	1	2	2.0	0.2 to 21.6
Any myeloid malignancy*	28	109	1.1	0.7 to 1.8	6	15	1.6	0.6 to 4.5
PV	13	25	**2.3**	**1.2 to 4.5**	1	5	0.8	0.1 to 6.7
ET	5	22	1.0	0.4 to 2.6	0	3		
MF	4	17	1.0	0.4 to 3.1	1	3	1.3	0.1 to 12.6
MPD NOS	3	12	1.1	0.3 to 3.9	2	0		
Any myeloproliferative malignancy†	25	75	1.5	0.9 to 2.3	4	10	1.6	0.50 to 5.0
Any myeloid or myeloproliferative malignancy	53	182	1.3	0.9 to 1.8	10	24	1.6	0.7 to 3.6
Lymphoid								
NHL	67	287	1.0	0.8 to 1.3	8	46	0.7	0.3 to 1.4
CLL	25	70	**1.6**	**1.0 to 2.5**	2	16	0.5	0.1 to 2.1
HL	20	64	1.3	0.8 to 2.2	2	10	0.8	0.2 to 3.6
MM	26	117	1.0	0.6 to 1.5	4	23	0.7	0.2 to 2.0
Any lymphoproliferative malignancy	140	539	1.1	0.9 to 1.4	16	95	0.7	0.4 to 1.1
ALL	7	26	1.2	0.5 to 2.7	1	2	2.0	0.2 to 21.3
Any hematologic malignancy	197	742	**1.2**	**1.0 to 1.4**	27	120	0.9	0.6 to 1.3
Any solid tumor	2,087	8,476	**1.1**	**1.0 to 1.1**	381	1,412	**1.1**	**1.0 to 1.2**

NOTE. Bolded entries indicate that risk ratio (RR) is significantly different from 1.0.
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ET, essential thrombocythemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; MPD, myeloproliferative disorder; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; PV, polycythemia vera.
*Any myeloid malignancy includes AML, MDS, and CML.
†Any myeloproliferative malignancy includes PV, ET, MF, and MPD NOS.
‡Any lymphoproliferative malignancy includes NHL, HL, CLL, and MM.

to 1.4). The risk for "any solid tumor" was also significantly increased (RR, 1.1; 95% CI, 1.0 to 1.1). However, both of these increased relative risks were modest and the significance levels were borderline. First-degree relatives of patients with MDS had no significantly increased risk of any malignancy, but the sample size was smaller than that for the AML analysis. The risk of MDS appears to be higher, but the number of affected relatives is so small that no conclusions can be made. As with the AML sample, the risk of solid tumors was modestly increased (RR, 1.1; 95% CI, 1.0 to 1.2).

Table 3 details the risks in relatives of younger patients (diagnosed before age 21 years) compared with relatives of controls. Although numbers were small (1,951 relatives of patients with AML compared with 9,790 relatives of matched controls), relatives of these younger patients with AML had a significantly increased risk of all AML/MDS and a three-fold (and significantly) increased risk for all myeloid malignancies combined. Among lymphoid malignancies, there was a significantly increased risk of multiple myeloma, but the numbers were small. The risks for "any hematologic malignancy" and "any solid tumor" were modestly but non-significantly increased.

Finally, we tested the validity of the assumption of proportional hazards by introducing interaction terms of the main effects with the time-dependent age variable. None of these interaction terms were statistically significant, indicating that the application of the proportional hazards model was valid in our study. In addition, applying a bootstrap procedure made little difference in the size of the confidence intervals and did not change any conclusions about the significance of the risk estimates.

DISCUSSION

Many patients worry about their family members having a potentially increased risk of developing AML or MDS and, on the basis of our clinical experience, many clinicians are of the opinion that there is a small but significant familial pathogenic component. In this largest population-based study to date, including all age groups of patients with AML or MDS, we found no significant familial aggregation for AML or MDS. We found a small increased risk of MPNs (which was significant for polycythemia vera only) and of all myeloid disorders combined, but the increased risk did not reach statistical significance. However, given the size of the risks and the trend toward significance, we cannot rule out a small role for inherited factors in determining the risk for myeloid disorders. There was also a small increased risk for lymphoid malignancies which was not significant, except for CLL. Relatives of patients with AML were at a modest but statistically significant increased risk for "any hematologic malignancy." The risk for "any solid tumor" was also significantly increased. Relatives of patients with MDS showed similar trends for myeloid malignancies but the sample size was much smaller and the risks were not significantly increased. However, the risk of solid tumors was modestly increased and borderline significant.

The absence of increased risk for the most severe malignancies, AML and MDS, among relatives and the modest increased risks for

Table 3. Risk of Myeloid, Lymphoid, and Solid Malignancies in Relatives of Patients With AML Diagnosed at Age 20 Years or Younger

Outcome in Relatives	AML (n = 1,951)	Controls (n = 9,790)	RR	95% CI	P
Myeloid					
AML	3	0			**.005**
MDS	0	2			
AML/MDS	3	2	**6.5**	**1.1 to 38.0**	
CML	2	5	1.8	0.3 to 9.0	
Any myeloid malignancy*	5	7	**3.1**	**1.0 to 9.8**	
Any myeloproliferative malignancy†	1	3	1.5	0.2 to 14.3	
Any myeloid or myeloproliferative malignancy	6	10	**2.6**	**1.0 to 7.2**	
Lymphoid					
NHL	5	20	1.0	0.4 to 2.7	
CLL	3	4	3.6	0.8 to 16.5	
HL	1	7	0.6	0.1 to 5.2	
MM	4	4	**4.3**	**1.1 to 16.9**	
Any lymphoproliferative malignancy‡	13	35	1.6	0.8 to 2.9	
ALL	0	4			
Any hematologic malignancy	18	49	1.6	0.9 to 2.6	
Any solid tumor	151	607	1.1	0.9 to 3.2	

NOTE. Bolded entries indicate that risk ratio (RR) is significantly different from 1.0.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

*Any myeloid malignancy includes AML, MDS, and CML.

†Any myeloproliferative malignancy includes polycythemia vera, essential thrombocythemia, myelofibrosis, and myeloproliferative disorder.

‡Any lymphoproliferative malignancy includes NHL, HL, CLL, and MM.

combined myeloproliferative and myeloid malignancies can be contrasted with previous findings of ours from the same population showing highly increased risks for other lymphoid malignancies[23-26] and for myeloproliferative neoplasms[27] among relatives with those conditions. The increased risk to first-degree relatives ranged from 2.0 to eight-fold or more depending on the particular subgroups analyzed. In fact, relatives of patients with MPNs had a more than five-fold increased risk for MPNs compared with relatives of controls.[27] The sample sizes in many of these other studies are similar to our sample size of patients with AML and their relatives in this study, making lack of power an unlikely possibility for explaining the failure to find an increased risk of AML/MDS in relatives.

Interestingly, we found significant familial aggregation patterns among first-degree relatives of young (age < 21 years) patients with AML compared with their matched controls. Despite the much smaller sample sizes, first-degree relatives of these younger patients had significantly increased risks for AML/MDS as well as a three-fold risk for any myeloid malignancy. They were also at borderline increased risk for any lymphoid malignancy, and the risk of multiple myeloma was significantly increased. The risks for "any hematologic malignancy" and "any solid tumor" were similar to those of the whole sample of AML relatives but were not significantly increased.

In summary, our findings suggest that, overall, there is not a strong specific genetic predisposition to AML or MDS. The modest increase in risk of MPNs, all myeloid malignancies combined, and "any hematologic malignancy" suggests that relatives may share some germline genes predisposing them to hematologic malignancies in general or even malignancy in general, given the increased risk for "any solid tumor." One could argue that finding more solid tumors in relatives of patients with AML and MDS might be due to increased surveillance in relatives because of the diagnosis of the index case. When we tested for increased risk of solid tumors in relatives of patients with AML restricted to only those tumors that occurred before the AML diagnosis of the index case, the risk was unchanged. We also examined the risk of all solid tumors combined in relatives of patients with other hematologic malignancies (specifically CLL, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's lymphoma) that we have previously reported and found that they were also modestly but significantly increased (data not shown). Thus, the modest increase in solid tumors among relatives of patients with AML may not be specific to AML since we see it in other hematologic malignancies. The underlying causes may be shared etiologic factors (including germline susceptibility genes and environmental exposures) that affect the risk of nonspecific cancer, and there may also be an effect of increased surveillance or it may be a combination of these factors. Future studies are needed to characterize underlying mechanisms of our findings.

On the basis of small numbers, we found evidence of familial aggregation of AML/MDS as well as combined categories of tumors among first-degree relatives of patients with AML who were diagnosed when they were younger than age 21 years, which supports the existence of genes with stronger effects that predispose to AML/MDS susceptibility in the young. Since this subgroup was small, further studies are needed to confirm this stronger association among young patients.

Recent candidate gene studies have identified potential associations of gene variants with AML and more will be identified as high throughput genotyping methods are applied to AML and MDS populations. Sequencing of tumors has also allowed identification of somatic genetic changes in AML and related malignancies which may also provide clues to the germline genes involved.[28] The observed differences by age provide additional support that there may be age-related etiologic/molecular heterogeneity in AML/MDS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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