

Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden

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There are emerging data to suggest a role for genetic factors in the pathogenesis of multiple myeloma (MM). Based on small numbers, certain solid tumors have been reported to occur more frequently among blood relatives of patients with MM. Using population-based data, we assessed risks for hematologic malignancies, monoclonal gammopathy of undetermined significance (MGUS), and solid tumors among first-degree relatives of patients with MM. We included 13,896 patients with MM and 54,365 matched controls. Also we identified first-degree relatives of patients with MM ($n = 37,838$) and controls ($n = 151,068$). Using a marginal survival model, we estimated relative risks (RRs) and 95% confidence intervals (CIs) for hematologic and solid tumors among family members of patients with MM and controls as measures of familial aggregation. Compared with relatives of controls, relatives of patients with MM had an increased risk of developing MM (RR = 2.1; 95% CI 1.6–2.9), MGUS (2.1; 1.5–3.1), acute lymphoblastic leukemia (ALL) (2.1; 1.0–4.2), any solid tumor (1.1; 1.0–1.1) and bladder cancer (1.3; 1.0–1.5). No significantly increased risk was found for other hematologic or solid malignancies. Our findings support a role for a shared susceptibility (genetic, environmental or both) that predisposes to MM, MGUS, ALL and bladder cancer.

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Multiple myeloma (MM) is a malignant B-cell disorder characterized by the proliferation and accumulation of malignant plasma cells in the bone marrow, which is coupled with the overproduction of monoclonal proteins in serum or urine.¹

MM has an age-adjusted incidence rate of 2.5–8.0 per 100,000 in Western countries,^{2,3} and the median age at diagnosis of around 70 years.² Males and African Americans are known to be more frequently affected.⁴ A personal history of the precursor condition, monoclonal gammopathy of undetermined significance (MGUS), is associated with an increased risk of developing MM.⁵

Although the etiology of MM and MGUS is unknown, there is evidence to support a role for genetic factors, including studies showing familial aggregation of MM^{6–14} and familial aggregation of MGUS.¹⁵ In addition, racial disparities in incidence patterns for MGUS and MM support a role for germline genes in the etiology of MM.¹⁶ In a recent study, we found first-degree relatives of patients with MGUS to have an increased risk of MGUS, MM, lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (WM) and chronic lymphocytic leukemia (CLL), supporting the operation of shared common germline susceptibility genes in these disorders.¹⁵ However, no study has defined the risk of MGUS among relatives of patients with MM. Furthermore, 2 recent studies reported certain solid tumors (including malignant melanoma and prostate cancer) to coaggregate among blood relatives to patients with MM, suggesting an overlap in the etiology of MM and other types of cancer.^{1,12}

Given the implications for future studies aimed at uncovering underlying susceptibility genes, it is important to define the spec-

trum of tumors associated with MM. We conducted a comprehensive study designed to evaluate familial aggregation patterns of hematologic malignancies, MGUS and solid tumors among first-degree blood relatives of patients with MM. Using high-quality population-based data from Sweden, we were able to identify 37,838 first-degree relatives of 13,896 patients with MM and 151,068 first-degree relatives of 54,365 matched population-based controls.

Material and methods

Central registries, patients, controls and first-degree relatives

Sweden provides universal medical health care for the entire population, which is currently ~9 million people. In contrast to many other countries, patients with lymphoproliferative malignancies in Sweden are typically diagnosed, treated and followed clinically by physicians at hospital-based hematology or oncology centers.

Since 1958, all physicians and pathologists/cytologists in Sweden are required by law to report each case of cancer they diagnose or treat to the centralized nationwide Swedish Cancer Registry, which has a very high rate of completeness and diagnostic accuracy.^{17,18}

Using the Swedish Cancer Registry, we identified all patients with MM diagnosed between 1958 and 2005. For each patient with MM, 4 population-based controls (matched by sex, year of birth and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive at the time of MM diagnosis for the corresponding case and with no previous hematologic cancer at the date of the corresponding case's diagnosis. Using the Swedish Multigenerational Registry,¹⁹ we obtained information on all first-degree relatives (parents, siblings and offspring) of patients with MM and controls. All patients with MM and controls without linkable relatives were removed from the study. As a final step, we conducted record-linkages with the Swedish Cancer Registry, a nationwide MGUS cohort established from a national hospital network including patients with MGUS ($N = 4,458$) diagnosed in Sweden 1967–2005; described elsewhere²⁰), a nationwide LPL/WM cohort (described elsewhere²⁰), and a nationwide myeloproliferative disorders (MPD) cohort (described elsewhere²¹) to obtain information on malignancies and MGUS among first-degree relatives of patients with MM and controls.

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TABLE I – RELATIVE RISK OF HEMATOLOGIC DISORDERS AMONG FIRST-DEGREE RELATIVES OF MULTIPLE MYELOMA PATIENTS

	Relatives of multiple myeloma patients (<i>n</i> = 37,838)	Relatives of multiple myeloma controls (<i>n</i> = 151,068)	RR (95%CI) ¹	<i>p</i> -value
Lymphoid disorders				
MGUS	42	79	2.1 (1.5–3.1)	<0.001
Multiple myeloma	94	178	2.1 (1.6–2.9)	<0.001
Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia	10	29	1.4 (0.7–2.8)	0.65
Chronic lymphocytic leukemia	38	130	1.1 (0.8–1.7)	0.25
Non-Hodgkin lymphoma	104	390	1.1 (0.9–1.4)	0.34
Hodgkin lymphoma	28	119	0.9 (0.6–1.4)	0.73
Acute lymphoblastic leukemia	12	23	2.1 (1.0–4.1)	0.02
Myeloid malignancies				
Acute myeloid leukemia/Myelodysplastic syndrome	27	134	0.8 (0.5–1.2)	0.30
Chronic myeloproliferative disorders	31	113	1.1 (0.7–1.6)	0.65
Chronic myeloid leukemia	6	48	0.5 (0.2–1.2)	0.10

¹All estimates were adjusted for sex of first-degree relative.—Statistically significant RRs are shown in bold.—MGUS, Monoclonal gammopathy of undetermined significance; RR, relative risk; CI, confidence interval; n.s., not significant.

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

Statistical analysis

The statistical approach is based on a model proposed by Liang²² and described in detail elsewhere.²³ We classified relatives as “affected” if they had a primary cancer registration with the tumor of interest (examining up to 5 cancer registrations). Here, the age or age at onset of disease in a relative of a proband is modeled by a proportional hazards model. Familial aggregation for each condition is evaluated by testing the hazard ratio of being a relative of a case compared with being a relative to a control. The model was fitted to the data using the PHREG procedure in SAS v8.02. We use relative risk (RR) to denote the hazard ratio defined above, with 95% confidence intervals (CI). Since we have complete ascertainment of cases, every case is a “proband” and thus families with more than 1 case appear twice in the dataset. The robust sandwich covariance matrix accounts for dependencies among family members, including dependence due to the overlapping family clusters.²³ We tested separately for increased risk for MM, MGUS, LPL/WM, non-Hodgkin lymphoma (NHL) (*i.e.*, NHL excluding LPL/WM), chronic lymphocytic leukemia (CLL), Hodgkin lymphoma (HL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), MPD, chronic myeloid leukemia (CML) and 27 different solid tumors. Because cases and control probands were matched (see earlier section), the relatives should be generally well matched. However, because they cannot be individually matched, we adjusted for sex in all analyses.

Results

A total of 13,896 patients with MM [mean age at diagnosis 68 years (range 19–96), 56% males], 54,365 matched controls and corresponding first-degree relatives of patients (*n* = 37,838) and controls (*n* = 151,068) were identified.

Familial risks for hematologic disorders

As shown in Table I, first-degree relatives of patients with MM had a significantly increased risk of developing MM (RR = 2.1; 95% CI 1.6–2.9), MGUS (RR = 2.1; 95% CI 1.5–3.1) and ALL (RR = 2.1; 95% CI 1.0–4.2). However, we found no significantly

increased risk of developing NHL (RR = 1.1; 95% CI 0.8–1.7), CLL (RR = 1.1; 95% CI 0.8–1.7), LPL/WM (RR = 1.4; 95% CI 0.7–2.8), HL (RR = 0.9; 95% CI 0.6–1.4), MPD (RR = 1.1; 95% CI 0.7–1.6), AML/MDS (RR = 0.8; 95% CI 0.5–1.2) or CML (RR = 0.5; 95% CI 0.2–1.2).

When we assessed the risk of hematologic disorders in relation to type of first-degree relative (parent, sibling, offspring), age at diagnosis for the probands (above/below 65 years) and sex of the first-degree relative, the estimates for first-degree relatives of patients with MM were very similar (data not shown).

Familial risks for solid tumors

First-degree relatives of patients with MM had an increased risk of developing “any solid tumor” (RR = 1.1; 95% CI 1.0–1.1) and bladder cancer (RR = 1.3; 95% CI 1.0–1.5) (Table II). We also found borderline increased risks for prostate cancer (RR = 1.1; 95% CI 1.0–1.2; *p* = 0.06). No significantly increased risk was found for any other solid tumor.

Discussion

In this population-based case-control study including over 13,000 patients with MM and their almost 40,000 first-degree relatives, we made several important and novel observations. Given the large sample size, we were able to conduct the most comprehensive evaluation of MGUS, hematologic and solid tumors among first-degree relatives of patients with MM and controls to date.

Compared to first-degree relatives of controls, we found that first-degree relatives of patients with MM had a 2-fold higher risk of developing MM. This pattern is consistent with prior studies.^{9–14} We also found, that first-degree relatives of patients with MM had a 2-fold increased risk of MGUS. This finding is consistent with our recent investigations showing that first-degree relatives of patients with MGUS are at increased risk of developing both MGUS and MM.¹⁵ Also a recent study from the Mayo Clinic found relatives to patients with MM and MGUS to have 2- and 3.3-fold increased risks of MGUS.²⁴ Compared to first-degree relatives of controls, we also found first-degree relatives of patients with MM to have a 2-fold increased risk of developing ALL. A positive familial aggregation for ALL and MM has not been reported previously in any large study; however, it has been observed in a prior single high-risk MM family.²⁵ Because we evaluated a large number of malignancies, it cannot be ruled out that this finding is due to chance. In contrast to our previous studies showing overlapping excess familial risks for various types of

TABLE II – RELATIVE RISK OF SOLID TUMORS AMONG FIRST-DEGREE RELATIVES OF MULTIPLE MYELOMA PATIENTS

Tumor site	Risk among first-degree relatives of MM patients			
	Relatives of multiple myeloma patients (n = 37,838)	Relatives of multiple myeloma controls (n = 151,068)	RR (95%CI) ¹	p-value
Any solid tumor	2,118	8,042	1.1 (1.0–1.1)	0.001
Buccal	45	145	1.1 (0.8–1.5)	0.59
Salivary gland	9	33	1.1 (0.5–2.3)	0.83
Esophageal	22	85	1.0 (0.6–1.7)	0.84
Stomach	64	260	1.0 (0.8–1.4)	0.95
Small intestines	11	62	0.7 (0.4–1.3)	0.31
Colon	213	845	1.0 (0.9–1.2)	0.83
Rectal	143	526	1.1 (0.9–1.3)	0.30
Liver	31	98	1.3 (0.9–1.9)	0.22
Gallbladder	24	77	1.3 (0.8–2.0)	0.32
Pancreas	63	261	1.0 (0.7–1.3)	0.94
Larynx	17	75	0.9 (0.5–1.5)	0.74
Lung	175	746	0.9 (0.8–1.1)	0.52
Renal	70	264	1.1 (0.8–1.4)	0.63
Bladder	137	443	1.3 (1.0–1.5)	0.02
Melanoma skin	224	815	1.1 (0.9–1.3)	0.25
Nonmelanoma skin	166	780	0.8 (0.7–1.0)	0.13
Brain	115	503	0.9 (0.7–1.1)	0.37
Spinal cord	9	27	1.3 (0.6–3.0)	0.51
Thyroid	50	164	1.2 (0.9–1.7)	0.23
Bone	14	59	0.9 (0.5–1.7)	0.84
Connective tissue	30	115	1.0 (0.7–1.5)	0.97
Breast	596	2,263	1.0 (0.9–1.1)	0.33
Uterus	92	346	1.1 (0.8–1.3)	0.62
Ovary	128	446	1.1 (0.9–1.4)	0.20
Vulva	16	69	0.9 (0.5–1.6)	0.80
Prostate	400	1473	1.1 (1.0–1.2)	0.06
Testicular	34	145	0.9 (0.6–1.4)	0.71

¹All estimates were adjusted for sex of first-degree relative.–RR, relative risk; CI, confidence interval; n.s., not significant.–Statistically significant RRs are shown in bold.

lymphomas,^{20,26–28} with the exception of ALL, we found no increased risk for other hematologic malignancies among MM relatives.

To our knowledge, there are only limited data available on familial aggregation of solid tumors and MM. Recently, 1 case report and 1 registry-based study reported evidence of an excess occurrence of malignant melanoma¹² and prostate cancer^{11,12} among relatives of patients with MM. Given the implications for future studies aimed to uncover underlying susceptibility genes, we were motivated to evaluate a broad range of a solid tumors (n = 27) among first-degree relatives of patients with MM and controls. We found a significantly increased risk for any solid tumor and bladder cancer among relatives of patients with MM. Although this could be a chance finding due to screening a large number of tumors, there is 1 prior study showing evidence of coaggregation of MM and bladder cancer.²⁹ In the 2 previously mentioned studies,^{11,12} a significantly increased risk of prostate cancer among MM relatives was found. In our study, we found only a borderline increased risk, suggesting there might be shared susceptibility in MM and prostate cancer. The reason for the discrepancy between our results and previous studies might, at least in part, be due to selection mechanisms. In this study, we applied a population-based study design based on all patients with MM diagnosed in Sweden over the past 4 decades. For relatives of patients with MM and their matched controls, we obtained information on incident

cancers through record linkage with the Swedish Cancer registry. In contrast, the study by Lynch *et al.*¹¹ was based on a single high-risk MM family (including 5 MM cases) seen at a research center specialized in familial disease. The study by Camp *et al.*¹² was based on 2.5 million persons with genealogic data linked to the Utah Surveillance, Epidemiology, and End Results (SEER) cancer registry including a total of 1354 patients with MM, and their 13,288 first-degree relatives, 45,575 second-degree relatives and 118,363 third-degree relatives.

Although long-term follow-up studies from the Mayo Clinic have shown that patients with MGUS have an increased risk of developing MM,⁵ until recently, it has been unknown whether all patients with MM are preceded by MGUS, or if MM can occur *de novo*. In a recent prospective nationwide US cancer screening trial enrolling 77,469 healthy adults, a total of 71 individuals were identified who developed MM during the course of the study in whom serially-collected (up to 6) prediagnostic serum samples obtained (up to 10 years) before MM diagnosis were available. In that study, asymptomatic MGUS stage preceded the diagnosis of MM in almost all patients with MM.³⁰ Importantly, the findings from our present familial MM study, as well as the observations from the aforementioned prospective screening study, link MM and MGUS closely together and establish a key role for MGUS in the pathway to MM. This is of relevance for investigations designed to uncover pathogenetic mechanisms in MM, for the identification of novel molecular targets and ultimately for future preventive trials.^{31,32} In particular, the observed familial aggregation patterns in the present study support a role for shared common susceptibility genes in MM and MGUS.¹¹ Consequently, our results support the application of gene mapping and candidate gene approaches in high risk families and case-control studies.

Our study has several strengths, including its large size as well as the application of high-quality data, including a large MGUS cohort, from Sweden in a stable population with access to standardized universal medical health care during the entire study period. The use of the nationwide register-based case-control design ruled out recall-bias, ensured a population-based setting and the generalizability of our findings. Limitations include lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age and geography), and lack of detailed clinical data. Also, because of the nature of this hypothesis-generating study, one has to interpret our findings with some caution due to the large number of tested malignancies.

In summary, compared to first-degree relatives of matched controls, we found an increased risk of developing MM, MGUS, ALL and bladder cancer among first-degree relatives of patients with MM. These results support a role for some shared susceptibility (genetic, environmental or both) that predisposes to these malignancies. Our study provides novel information supporting the application of gene mapping and candidate gene approaches in high risk families and case-control studies.

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