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Familial characteristics of autoimmune and hematologic disorders in 8,406 multiple myeloma patients: A population-based case-control study

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A population-based case-control study was conducted to evaluate risk of developing multiple myeloma (MM) associated with personal history of autoimmune diseases and occurrence of autoimmune and selected hematologic disorders in first-degree relatives. Data were obtained for all (*n* = 8,406) MM cases diagnosed in Sweden (1958–1998), with linkable relatives, 16,543 matched controls and first-degree relatives of cases (*n* = 22,490) and controls (*n* = 44,436). Odds ratios (ORs) were calculated to quantify the risk of MM in relation to personal/family history of 32 autoimmune disorders. Familial aggregation of malignancies was evaluated in a marginal survival model using relatives as the cohort. The risk for MM was significantly elevated among subjects with a personal history of pernicious anemia (OR = 3.27; 2.22–4.83) and individuals with a family history of systemic lupus erythematosus (OR = 2.66; 1.12–6.32). Compared with controls, relative risk (RR) of MM was significantly increased (RR = 1.67; 1.02–2.73) in relatives of cases, particularly relatives of probands aged ≥65 at diagnosis (RR = 2.50; 1.19–5.27). Risks were nearly 4-fold elevated among female relatives (RR = 3.97; 1.54–10.2) and among relatives of female probands (RR = 3.74; 1.58–8.83). MM cases had more cases of monoclonal gammopathy of undetermined significance (MGUS) among their relatives than controls, but the numbers were too small to be conclusive. There was generally no increase in risk of MM in probands whose relatives had hematologic malignancies other than MM. These findings do not support a strong association between personal/familial autoimmune diseases and MM. However, MM itself shows significant familial aggregation, implicating the etiologic importance of this type of hematological neoplasm and perhaps MGUS in germ line genes.
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Key words: hematopoietic malignancies; multiple myeloma; autoimmune disease; family history; familial aggregation

Multiple myeloma (MM) is a malignant clonal neoplasm of plasma-cells of B-lymphocyte origin characterized by an overproduction of large amounts of monoclonal immunoglobulins. Clinical symptoms may include bone pain, infections, neurological deficits, cytopenias, hypercalcaemia, renal failure or other abnormalities. Data from the United States Surveillance, Epidemiology and End Results (SEER) program estimated the recent age-adjusted incidence to be 5.6/100,000 overall and 30.4/100,000 for individuals >65 years.[1] Incidence rates in men are 1.5 times higher than in women and 2 times higher in Black than in White Americans. The median age at diagnosis of MM is 71.0 years in Whites and 67.0 in Black Americans.[1]

Although etiological factors are unknown, case-control and cohort studies have shown elevated risks associated with occupational exposure to ionizing radiation following long latency periods in radiologists,[2,3] and unidentified occupational exposures among some, but not all, studies of farmers,[4,5] petrochemical and rubber workers.[6–8] Elevated risk of MM has been associated with lower levels of education, income and socioeconomic status both in case-control[9] and cohort studies,[10] although these results are controversial.[3,11]

On the basis of the consideration of the nature and functioning of the plasma-cell, experimental studies of induced plasmacytoma in mice, clinical reports and limited data from epidemiological studies, investigators have searched for associations between MM and past history of disorders characterized by chronic immune dysfunction. However, there are inconsistencies in the literature on this topic.[12,13] The only study to consider family history of autoimmune diseases reported a significantly increased risk of MM due to a family history of any autoimmune disease.[14]

Familial myeloma, mentioned briefly in the 1920s,[15] has been described in clinical reports, case-control[16–18] and cohort studies,[19–21] with risk estimates ranging from 4- to 5-fold increase, probands with first-degree relatives with MM, including findings from a previous limited analysis of the Swedish Family-Cancer database.[22] Also, multi-generation high-risk families with multiple cases of MM have been described.[23,24]

We have conducted a population-based registry linkage study to test for personal and familial associations of autoimmune diseases with risk of developing MM and examine the broader familial aggregation of hematologic malignancies and MM. The current study has several unique features. The population-based ascertainments included all MM patients (*n* = 8,406) diagnosed in Sweden over a 40-year-period with one or more linkable relatives, frequency-matched controls (*n* = 16,543) from the same population and linked first-degree relatives of all MM cases and controls (*n* > 66,000). For MM cases, controls and relatives, we retrieved hospital medical record discharge diagnoses, including autoimmune conditions, to quantify the risk of MM in relation to a positive personal or family history of 32 defined autoimmune disorders (Table I). In addition, using the relatives as a cohort, we evaluated familial aggregation of the whole spectrum of hematologic malignancies as well as the benign precursor condition monoclonal gammopathy of undetermined significance (MGUS).

Material and methods

Cases and controls

The Swedish Family–Cancer Database has been described previously.[25] Briefly, Sweden maintains a multi-generation register consisting of individuals born in 1932 and later, with links to their parents. The multi-generation registry has been merged with the Swedish Cancer Registry (all cancers 1958–1998) to create the Family–Cancer Database. For these analyses, MM cases (*n* = 8,406), controls (*n* = 16,543) and relatives of cases (*n* = 22,490) and controls (*n* = 44,436) were linked with the Swedish Inpatient Register 1964–2000, which contains individual patient-based hospital medical record discharge diagnoses on patients discharged from inpatient care. This register has population-based (county-wide) coverage that encompassed >90% of Sweden after the mid 1970s and 100% since 1987. We obtained information on all discharges listing MGUS and 32 defined autoimmune disorders (Table I).

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TABLE I – THE RISK OF MULTIPLE MYELOMA IN RELATION TO PERSONAL AND FAMILY HISTORY OF AUTOIMMUNE CONDITIONS

AI condition/category	Personal history				Family history			
	ca	co	OR	95% CI	ca	co	OR	95% CI
Autoantibodies detectable								
Systemic involvement								
Polymyositis/dermatomyositis	34	49	1.38	0.79–2.91	35	69	1.00	0.67–1.51
Rheumatoid arthritis	87	193	0.90	0.69–1.16	58	136	0.85	0.62–1.16
Sjögren's syndrome	2	5	0.80	0.16–4.13	1	9	0.22	0.03–1.75
Systemic lupus erythematosus	8	17	0.94	0.40–2.17	12	9	*2.66*	*1.12–6.32*
Systemic sclerosis	4	15	0.53	0.18–1.60	3	9	0.66	0.18–2.45
Organ involvement								
Addison's disease	2	5	0.80	0.16–4.12	6	5	2.39	0.73–7.83
Amyotrophic lateral sclerosis	3	20	0.30	0.09–1.00	3	1	6.00	0.62–57.71
Autoimmune hemolytic anemia	2	3	1.34	0.23–8.02	2	4	1.00	0.18–5.45
Chronic rheumatic heart disease	17	74	*0.46*	*0.27–0.77*	15	17	1.76	0.88–3.53
Discoid lupus erythematosus	2	4	1.00	0.18–5.44	3	1	5.97	0.62–57.34
Grave's disease	4	15	0.53	0.18–1.60	10	22	0.92	0.44–1.95
Hashimoto's thyroiditis	3	4	1.49	0.33–6.68	0	4	0	$p = 0.3082$
Idiopathic thrombocytopenic purpura	2	3	1.34	0.23–8.03	1	3	0.66	0.07–6.37
Insulin-dependent diabetes	0	0	–		3	9	0.66	0.18–2.45
Localized scleroderma	0	5	0	$p = 0.1763$	0	1	0	$p = 1.000$
Lupoid hepatitis	0	0	–		0	0	–	
Multiple sclerosis	7	29	0.48	0.21–1.10	18	47	0.76	0.44–1.31
Myasthenia gravis	2	2	1.99	0.28–14.12	3	7	0.85	0.22–3.30
Pernicious anemia	67	41	*3.27*	*2.22–4.83*	8	26	0.62	0.28–1.36
Polyarteritis nodosa	2	4	0.99	0.18–5.42	1	5	0.40	0.05–3.41
Primary biliary cirrhosis	3	7	0.86	0.22–3.31	6	8	1.50	0.52–4.32
Wegener's granulomatosis	1	5	0.40	0.05–3.42	2	3	1.33	0.22–7.95
Autoantibodies not detectable								
Ankylosing spondylitis	13	17	1.52	0.74–3.14	10	25	0.80	0.38–1.66
Behcet's disease	0	0	–		1	1	1.99	0.12–31.77
Chorea minor	0	0	–		0	0	–	
Crohn's disease	7	19	0.73	0.31–1.75	36	76	0.94	0.63–1.40
Polymyalgia rheumatica	45	49	*1.84*	*1.22–2.75*	14	30	0.93	0.49–1.76
Psoriasis	30	44	1.36	0.85–2.16	31	64	0.96	0.62–1.47
Reiter's disease	0	0	–		3	5	1.20	0.29–5.02
Rheumatic fever	9	15	1.20	0.53–2.74	11	19	1.15	0.55–2.43
Sarcoidosis	14	20	1.40	0.70–2.76	27	36	1.48	0.89–2.44
Ulcerative colitis	21	35	1.20	0.70–2.06	46	89	1.03	0.72–1.47

ca, cases; co, controls; OR, odds ratio; CI, confidence interval. *p*-values (2-sided) based on the Fisher's exact test are given when cases or controls have zero individuals with the specified condition. ORs for personal history were adjusted for age, calendar time of MM diagnosis, gender and region. ORs for family history were adjusted for age, calendar time of MM diagnosis, gender, region, and personal history of the same disorder. Values in italic have *p*-values <0.05.

Statistical analysis

Personal and family history of autoimmune conditions. We calculated odds ratios (ORs) to assess the associations between personal history of defined autoimmune conditions and MM. ORs were adjusted for the variables used in control sampling (age, gender, calendar period and region) using logistic regression. When the number of subjects with the autoimmune condition or the controls was zero, we presented *p*-values derived using Fisher's exact test. Using logistic regression, we examined the relationship between MM risk and latency, i.e., time from first inpatient discharge listing a defined autoimmune condition (0–1, 2–4, 5–9, 10 or more years). We also analyzed the risk of autoimmune conditions in relation to age of MM onset (in accordance with SEER[1] we used <65 vs. 65 and older as cut-off). Similarly, we measured associations between MM and family history of autoimmune conditions. ORs for family history were adjusted for the variables used in control sampling (age, gender, calendar period and region) as well as for personal history, using logistic regression. Family history of autoimmune conditions was restricted to include only occurrence of autoimmune disorders in case or control relatives, which occurred prior to the diagnosis of MM in the corresponding index case.

Familial aggregation of hematological malignancies and MGUS. In this analysis, we considered the relatives as a cohort and used a marginal survival model with a robust variance estimate to account for familial dependencies of tumors.[26] Here, the age at inclusion, or age at onset of disease in a relative of a proband, is modeled by a proportional hazards model. Familial aggregation for each malignancy is evaluated by testing the hazard ratio of being a relative of a case compared to being a relative of a control. The model (with gender as a covariate) was fitted to the data using the PHREG procedure in SAS v8.02. We use relative risk (RR) to denote the hazard ratio. We considered other factors affecting risk, including type of relative and age of MM onset (<65 vs. 65 and older) in the cancer proband. We tested separately for increased risk of hematologic malignancies (Table II) and MGUS in relatives. As an exploratory analysis, 29 solid tumor sites were also tested.

Results

Autoimmune conditions

Personal history. A significantly increased risk for MM was found among subjects with a personal history of pernicious anemia (OR = 3.27, 95% confidence interval (CI) 2.22–4.83) (Table I). The estimate was virtually the same for total as for late onset MM (OR = 3.14, 95% CI 2.09–4.69); however, a further elevated risk was found for early onset (<65) MM cases (OR = 5.60, 95% CI 1.21–29.71). When the analysis was stratified by latency, the estimate was highly significantly increased (OR = 15.68, 95% CI 6.70–36.69) for risk of MM occurring 0–1 year after diagnosis of pernicious anemia, but not in the other intervals (not shown). A significantly increased risk for MM was observed among subjects with a personal history of polymyalgia rheumatica (OR = 1.84, 95% CI 1.22–2.75), with the strongest effect for early (<65) onset MM (OR = 4.68, 95% CI 1.21–18.14); risks of MM following polymyalgia rheumatica (OR = 3.13, 95% CI 1.60–6.13) were restricted to the occurrence of MM within 0–1 years of diagnosis of poly-

TABLE II – RELATIVE RISKS AND 95% CI FOR DEVELOPMENT OF HEMATOLOGIC MALIGNANCY AND MGUS BASED ON SURVIVAL ANALYSES OF CASE RELATIVES VERSUS CONTROL RELATIVES, WITH STRATIFICATION BY AGE OF PROBAND AT DIAGNOSIS AND GENDER OF PROBAND AND RELATIVE

Condition/category	Number of affected first-degree relatives		RR (95% CI)[1]
	ca	co	
Hematologic conditions			
Multiple myeloma	29	35	*1.67 (1.02–2.73)*
Probands ≥65 years at diagnosis	17	22	*2.50 (1.19–5.27)*
Probands <65 years at diagnosis	12	13	1.56 (0.80–3.07)
Female relatives	15	8	*3.74 (1.58–8.83)*
Male relatives	14	27	1.05 (0.55–2.01)
Female probands	16	8	*3.97 (1.54–10.2)*
Male probands	13	27	0.98 (0.43–2.22)
Non-Hodgkin's lymphoma	46	77	1.19 (0.83–1.72)
Probands ≥65 years at diagnosis	27	31	*1.72 (1.04–2.85)*
Probands <65 years at diagnosis	19	46	0.83 (0.49–1.40)
Hodgkin lymphoma	10	28	0.71 (0.35–1.46)
Chronic lymphocytic leukemia	10	23	0.89 (0.42–1.87)
Waldenström's macroglobulinemia[2]	3	2	2.96 (0.49–17.7)
Acute lymphocytic leukemia	2	5	0.79 (0.15–4.07)
Acute myeloic leukemia	8	15	0.99 (0.43–2.31)
Chronic myeloic leukemia	3	9	0.67 (0.18–2.47)
Polycythemia vera	10	12	1.68 (0.72–3.87)
MGUS[2]	6	4	2.96 (0.83–10.5)

RR, relative risk; 95% CI, 95% confidence interval; ca, cases; co, controls; MGUS, monoclonal gammopathy of undetermined significance.
[1]n = 66,926. –[2]Chi-square statistics applied. All analyses were adjusted for gender. Values in italic have p-values <0.05.

myalgia rheumatica. A significantly decreased risk (OR = 0.46, 95% CI 0.27–0.77) for MM was found among subjects with a personal history of chronic rheumatic heart disease. When the analysis was stratified by latency, the only significantly reduced risk (OR = 0.27, 95% CI 0.11–0.68) occurred for MM diagnosed 10 or more years after diagnosis of rheumatic heart disease. When we stratified for age at diagnosis of MM, the estimate was OR = 0.32 (95% CI 0.17–0.61) among late onset MM subjects, and as expected the early onset category was hampered by small numbers (not shown).

Family history. A significantly increased risk of MM was found among subjects with a family history of systemic lupus erythematosus (SLE) (OR = 2.66, 95% CI 1.12–6.32). When these analyses were stratified by age of MM diagnosis, the strongest association was found for early onset MM (OR = 4.02, 95% CI 1.00–16.09) (versus late onset MM; OR = 1.99, 95% CI 0.64–6.17). However the estimates were based on small numbers.

Familial hematological malignancies and MGUS

Table II shows that compared to relatives of controls, we found a significantly increased risk of MM in relatives of all MM cases (RR = 1.67, 95% CI 1.02–2.73), which was further increased among female relatives (RR = 3.74, 95% CI 1.58–8.83), relatives of probands ≥65 years at diagnosis of MM (RR = 2.50, 95% CI 1.19–5.27) and among relatives of female probands (RR = 3.97, 95% CI 1.54–10.2). Risks of MM in probands did not differ according to whether the affected family members were siblings or offspring of cases, while numbers of parents were too small for statistical calculations (not shown). Risk of other hematologic malignancies was not increased among first-degree relatives, with the exception of an increase in non-Hodgkin lymphoma (RR = 1.72, 95% CI 1.04–2.85) among relatives of probands ≥65 years at diagnosis. Risks of Waldenström's macroglobulinemia and MGUS were nonsignificantly increased, but the risk estimates were based on small numbers of relatives with these other hematological disorders.

Other cancer sites

We looked for aggregation of other solid tumors among relatives of MM probands. We found colon cancer (RR = 1.56, two-sided p = 0.004) and brain cancer (RR = 0.63, two-sided p = 0.01) to be distributed differently in MM than in control relatives, but there were no differences in occurrence for cancers of any other site. After correction for multiple comparison (n = 29), these findings are not statistically significant.

Discussion

Using a large population-based dataset, we observed a 3-fold significantly increased risk of MM among subjects with a personal history of pernicious anemia, which has been found in previous studies.[14,27,28] Underlying pathogenetic mechanisms of this association may include shared genetic and environmental susceptibility of the two conditions; however, it warrants further study. We observed an increased risk of MM subsequent to polymyalgia rheumatica (which was restricted to 0–1 year of latency); however, our explanation of this result is that it is most likely not a true biological finding, but instead reflecting misclassification caused by early MM manifestations mimicking polymyalgia rheumatica.[29] We observed a decreased risk of MM among subjects with a previous personal history of chronic rheumatic heart disease. Although the databases that we used do not provide detailed clinical information other than discharge diagnoses, we have speculated that the observed protective effect (which is confined to subjects ≥65 years and with more than 10 years of latency between chronic rheumatic heart disease and subsequent MM) could reflect the usage of lifelong antibiotic prophylaxis, which is normally given to patients with chronic rheumatic heart disease.[30] It is possible that lifelong prophylactic penicillin leads to significantly decreased occurrence of bacterial infections, resulting in a reduced number of secondary inflammations, which lowers the risk of MM.[3]

We also observed an increased risk of MM among subjects with a family history of SLE. To our knowledge, this association has been found in only one earlier study[14] performed by one of us (MSL) and that investigation was based on very small numbers.

We tested a large number (n = 32) of autoimmune conditions and found very few of them to be associated with an increased risk of MM. None of the autoimmune conditions under study showed both a positive personal and family history (of the same disorder) to be associated with a significantly increased risk of MM. Thus, in this largest study to date, we conclude that genetic factors predisposing to MM are quite likely to be different from those predisposing to autoimmunity.

We found a significantly increased risk of MM among first-degree relatives of MM cases. The observed familial risk of MM

was further elevated among relatives of later onset MM cases, female relatives and relatives of female cases. The reason for the gender differences is not clear and could be due to genetic or environment factors or both, but is consistent with that seen in data from Iceland.[21] In our study, a non-significantly increased risk of MGUS was found in relatives of MM cases, but the numbers were too small to be conclusive.

No significantly increased risk for other hematologic or solid malignancies was observed among relatives of all MM probands or among subgroups, with the exception that relatives of MM probands $\geq$65 years at diagnosis had a significantly increased risk for non-Hodgkin lymphoma. Our findings of greater familial aggregation among relatives of later onset cases is in contrast with recent studies based on selected high-risk families, in which the age of onset of MM was much earlier and the affected offspring had earlier onset than affected parents (anticipation).[23,24] In this study, the average age at MM diagnosis among relatives of cases (61.3 years; range 37–81 years; $n = 30$) and controls (63.2 years; range 39–87 years; $n = 35$) was virtually the same, showing that familial (versus sporadic) MM is not characterized by an earlier age at diagnosis. We also found no evidence of anticipation for MM.[31]

In our study, we used a register-based case-control design, which ruled out recall-bias, ensured a population-based setting and generalizability of our findings. By including all MM cases diagnosed in Sweden during a 40-year-period, with one or more linkable relatives, we were able to conduct the largest study on autoimmunity and subsequent risk of MM to date. Limitations include incomplete number of first-degree relatives, lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, geography and marital status), lack of validation of the register-based data used to define exposure and outcome and lack of clinical data. Other potential limitations of our study were the absence of validation of the diagnoses of autoimmune conditions, which were retrieved from hospital discharge registry listings, and failure to capture those autoimmune disease diagnoses made in outpatient settings. However, because these were assessed among relatives of matched controls, using same hospital discharge registries, the relative risks should not be biased.

In summary, personal and family history of autoimmune conditions were generally not associated with increased risk for MM. We found an elevated risk for personal history of pernicious anemia and family history of SLE; however, because of multiple comparisons these findings should be interpreted with caution. The observed familial aggregation of MM in first-degree relatives implicates the potential etiologic importance of germline genes. Our data suggest that the spectrum of related conditions may include MGUS but not other hematologic neoplasms. These results provide additional support for applying gene mapping and candidate gene approaches in high risk families and case-control studies.

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