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Risk of solid tumors and myeloid hematological malignancies among first-degree relatives of patients with monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common pre-malignant disorders in western countries with a prevalence of 3.2% in the Caucasian general population 50 years of age or older.[1] It is characterized by the presence of a monoclonal immunoglobulin (M-protein) in individuals lacking evidence of multiple myeloma (MM) or other lymphoproliferative malignancies.[2] Long-term follow-up of MGUS patients reveals an average 1% annual risk of developing a lymphoproliferative malignancy.[3,4] Although the etiology of MM and MGUS is unknown, there is emerging evidence to support a role for genetic factors. For example, familial aggregation of both MM and MGUS has been observed.[5] Also racial disparities in incidence patterns for MGUS and MM support a role for germline genes in the etiology of MM.[6] Recently, we found first-degree relatives of MGUS patients to have an increased risk of MGUS, MM, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, and chronic lymphocytic leukemia, supporting a role for shared common germline susceptibility genes in these disorders.[5] Furthermore, in two recent studies an excess of certain solid tumors among blood relatives to MM patients was reported.[7,8]

To improve our understanding in this area, we have, to the best of our knowledge, conducted the first population-based study to evaluate familial aggregation patterns of 27 solid tumors and all myeloid hematologic malignancies among first-degree blood relatives of MGUS patients. Using high-quality population-based data from Sweden, we identified 4,458 MGUS patients and 17,505 controls, as well as all linkable first-degree

Table 1. Characteristics of MGUS patients and matched controls.

	MGUS patients	Controls
Total, n.	4,458	17,505
Gender male/female, %	49.9/50.1	50.0/50.0
Age at dx, median (range)	69 (22-97)	N.A.
Age group, n (%)		
Less than 40	118 (2.7)	471 (2.7)
40-49	328 (7.4)	1,321 (7.5)
50-59	749 (16.8)	3,008 (17.2)
60-69	1,091 (24.5)	4,236 (24.2)
70-79	1,389 (31.2)	5,389 (30.8)
80 and above	783 (17.6)	3,080 (17.6)
Calendar period, n (%)		
1966-1975	33 (0.7)	138 (0.8)
1976-1985	260 (5.8)	1,048 (6.0)
1986-1995	1,866 (41.9)	7,309 (41.7)
1996-2005	2,299 (51.6)	9,010 (51.5)
MGUS isotype, n (%)		
IgG	1,789 (40.1)	N.A.
IgA	482 (10.8)	N.A.
IgM	447 (10.0)	N.A.
IgD	1 (0.02)	N.A.
Unknown/missing	1,739 (39.0)	N.A.
First-degree relatives, n (%)		
Any relative	14,621 (100)	58,387 (100)
Parents	2,811 (19.2)	11,006 (18.9)
Siblings	2,290 (16.7)	8,962 (15.3)
Offspring	9,520 (65.1)	38,419 (65.8)

Table 2. Relative risk of solid tumors and hematologic myeloid malignancies among first-degree relatives of MGUS patients.

Tumor site	Risk among first-degree relatives of MGUS patients			
	Relatives of MGUS patients (n=14,621)	Relatives of controls (n=58,387)	RR (95%CI)[1]	*p* value
Any solid tumor	892	3,201	**1.1 (1.0-1.2)**	0.004
Buccal	13	73	0.7 (0.4-1.3)	0.255
Salivary gland	4	24	0.7 (0.2-1.9)	0.448
Esophageal	7	40	0.7 (0.3-1.6)	0.379
Stomach	26	118	0.9 (0.6-1.3)	0.554
Small intestines	8	20	1.6 (0.7-3.6)	0.259
Colon	80	335	1.0 (0.7-1.2)	0.702
Rectal	57	203	1.1 (0.8-1.5)	0.444
Liver	13	39	1.3 (0.7-2.5)	0.370
Gallbladder	8	46	0.7 (0.3-1.5)	0.338
Pancreas	35	145	1.0 (0.7-1.4)	0.845
Larynx	9	29	1.2 (0.6-2.6)	0.573
Lung	87	280	1.2 (1.0-1.6)	0.078
Renal	36	112	1.3 (0.9-1.9)	0.191
Bladder	60	175	**1.4 (1.0-1.8)**	0.035
Melanoma skin	86	270	1.3 (1.0-1.6)	0.051
Non-melanoma skin	88	330	1.1 (0.8-1.3)	0.599
Brain	50	187	1.1 (0.8-1.5)	0.680
Spinal cord	6	8	**3.0 (1.0-8.6)**	0.033
Thyroid	20	61	1.3 (0.8-2.2)	0.294
Bone	8	21	1.5 (0.7-3.4)	0.309
Connective tissue	9	40	0.9 (0.4-1.9)	0.772
Breast	178	750	1.0 (0.8-1.1)	0.603
Uterus	36	128	1.1 (0.8-1.6)	0.500
Ovary	43	167	1.0 (0.7-1.5)	0.821
Vulva	5	20	1.0 (0.4-2.7)	0.985
Prostate	166	619	1.1 (0.9-1.3)	0.502
Testicular	24	65	1.5 (0.9-2.3)	0.111
Myeloid malignancy				
AML/MDS	18	58	1.2 (0.7-2.1)	0.425
Myeloproliferative disorders[2]	18	61	1.2 (0.7-2.0)	0.534
Chronic myeloid leukemia	5	19	1.1 (0.4-2.8)	0.921

[1]All estimates were adjusted for sex of first-degree relative. [2]Including the following conditions: polycythemia vera, essential thrombocythemia, and myelofibrosis. Statistically significant RRs are shown in bold. MGUS: monoclonal gammopathy of undetermined significance; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; RR: relative risk; CI: confidence interval.

relatives of patients (n=14,621) and controls (n=58,387) (Table 1). We used χ^2 models to calculate relative risks (RR) and 95% confidence intervals (CI) as measures of familial aggregation.

Compared to relatives of controls, first-degree relatives of MGUS patients had a borderline increased risk of any solid tumor (RR=1.1; 95% CI 1.04-1.21; p=0.004). When we assessed individual tumor sites, we found evidence of a significantly increased risk for bladder cancer (RR=1.4; 95% CI 1.02-1.84; p=0.035) and, based on small numbers, a 3.0-fold (95% CI 1.04-8.64; p=0.033) increased risk for spinal cancer. We also found borderline increased risks for malignant melanoma (RR=1.3; 95% CI 1.00-1.62; p=0.051) and lung cancer (RR=1.2; 95% CI 0.98-1.58; p=0.078). No significantly increased risk was found for any of the other solid tumor sites (Table 1). Neither did we find relatives of MGUS patients to have a significantly increased risk for myeloid hematologic malignancies (Table 1). In analyses stratified by MGUS isotype, the risks were essentially the same (*data not shown*).

The observed increased risk for bladder cancer among relatives of MGUS patients agrees with a prior study showing evidence of co-aggregation of MM and bladder cancer.[9] Furthermore, in a study based on patients with a coexisting MGUS and a solid tumor, 24% had bladder cancer.[10] Also in agreement with a previous study by Camp *et al.*,[7] we found first-degree relatives of MGUS cases to have a borderline increased risk of malignant melanoma. These findings are further supported by a prior genotyping study, suggesting that germline mutations in the *CDKN2A* gene may predispose to both MM and malignant melanoma.[11] Our finding of a borderline increased risk of lung cancer among relatives of MGUS patients needs to be confirmed by other studies.

However, one small study found family history of lung cancer to be associated with an increased risk of MM in elderly patients,[12] a finding not observed in our previous Swedish MM study.[6] In contrast to two prior studies focusing on solid cancers in MM families,[7,8] we did not find a significantly increased risk of prostate cancer among MGUS relatives. Based on small numbers, we found excess risk of spinal cancer among MGUS relatives. Because we evaluated a large number of malignancies, it cannot be ruled out that this finding is due to chance. Finally, we did not find an increased risk of myeloid malignancies among first-degree relatives suggesting that myeloid and lymphoid hematologic malignancies have different mechanisms with regard to etiology. Our study has several strengths, including its large size as well as the application of high-quality data. The use of the nationwide register-based case-control design ruled out recall-bias, ensured a population-based setting, and generalizability of our findings. The nature of this study is hypothesis-generating and one has to interpret our findings with caution due to the large number of tested malignancies.

Our findings support a role for a shared susceptibility (genetic, environmental, or both) that predisposes to MGUS and certain solid tumors, supporting the application of gene mapping and candidate gene approaches in high-risk families and case-control studies.

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Key words: MGUS, solid tumors, familial aggregation, susceptibility.

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Cautions and caveats to the treatment of acquired hemophilia A

We thank Pier Mannnucci and Flora Peyvandi for their recent editorial[1] in which they drew attention to and largely concurred with our international recommendations for the diagnosis and treatment of patients with acquired hemophilia A,[2] both published in the April issue of Haematologica. We would, however, like to re-emphasize three important issues relevant to treating patients with autoantibodies to FVIII.

Congenital hemophilia complicated by alloantibodies presents a serious therapeutic challenge in the treatment of bleeding episodes, and several recent studies indeed support the use of rFVIIa in a single large dose (270 mcg/kg) rather than repeated smaller doses in treating hemarthroses in these patients.[3,4] Due to safety concerns, we strongly caution against the use of single high-dose rFVIIa in the typically much older and multi-morbid patient population with considerable thromboembolic risk factors who present with bleeding related to acquired hemophilia.[5,6] Younger acquired hemophilia patients who bleed post-partum may represent a different patient profile. However, we emphasize that so far there has been no experience with single-dose rFVIIa in acquired hemophilia. It is also important to recognize that joint bleeding in acquired hemophilia is unusual, and because most bleeds are soft, they may not respond well to higher single doses of rFVIIa.

The high risk of life-threatening bleeding in acquired hemophilia patients justifies an aggressive therapeutic approach to inhibitor eradication, with the aim of minimizing the time during which the patient may experience