Prior cancer and risk of monoclonal gammopathy of undetermined significance: a population-based study in Iceland and Sweden

Sæmundur Rögnvaldsson,[1,2] Sigrun Thorsteinsdóttir,[1,3] Elisavet Syriopoulou,[4,5] Ingigerdur Sverrisdottir,[1,6] Ingemar Turesson,[7] Elias Eythorsson,[1,2] Jon Thorir Oskarsson,[1] Thorir Einarsson Long,[1,7] Brynjar Vidarsson,[2] Pall Torfi Onundarson,[1,2] Bjarni A. Agnarsson,[1,2] Margret Sigurdardottir,[2] Isleifur Olafsson,[2] Ingunn Thorsteinsdottir,[2] Thor Aspelund,[1] Gauti Kjartan Gislason,[1] Andri Olafsson,[1] Jon Kristinn Sigurdsson,[1] Malin Hultcrantz,[8] Brian G. M. Durie,[9] Stephen Harding,[10] Magnus Bjorkholm,[4,11] Ola Landgren,[12] Thorvardur Jon Love[1,2] and Sigurdur Yngvi Kristinsson[1,2]

[1]Faculty of Medicine, University of Iceland, Reykjavík, Iceland; [2]Landspítali – The National University Hospital of Iceland, Reykjavík, Iceland; [3]Rigshospitalet, Copenhagen, Denmark; [4]Karolinska Institutet, Stockholm, Sweden; [5]Red Door Analytics AB, Stockholm, Sweden; [6]Sahlgrenska University Hospital, Gothenburg, Sweden; [7]Skåne University Hospital, Lund, Sweden; [8]Myeloma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [9]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA, USA; [10]Binding Site Group Ltd., Birmingham, UK; [11]Karolinska University Hospital, Stockholm, Sweden and [12]Myeloma Program, Department of Medicine, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL, USA

Correspondence: S. Rögnvaldsson
srognvald@hi.is

Received: September 25, 2023.
Accepted: January 4, 2024.
Early view: January 11, 2024.

https://doi.org/10.3324/haematol.2023.284365

Abstract

There is some evidence that a prior cancer is a risk factor for the development of multiple myeloma (MM). If this is true, prior cancer should be associated with a higher prevalence or increased progression rate of monoclonal gammopathy of undetermined significance (MGUS), the precursor of MM and related disorders. Those with a history of cancer might therefore constitute a target population for MGUS screening. This two-part study is the first study to evaluate a relationship between MGUS and prior cancers. First, we evaluated whether prior cancers were associated with having MGUS at the time of screening in the Iceland Screens Treats or Prevents Multiple Myeloma (iStopMM) study that includes 75,422 individuals screened for MGUS. Next, we evaluated the association of prior cancer and the progression of MGUS to MM and related disorders in a population-based cohort of 13,790 Swedish individuals with MGUS. A history of prior cancer was associated with a modest increase in the risk of MGUS (odds ratio=1.10; 95% confidence interval: 1.00-1.20). This excess risk was limited to prior cancers in the year preceding MGUS screening. A history of prior cancer was associated with progression of MGUS, except for myeloid malignancies which were associated with a lower risk of progression (hazard ratio=0.37; 95% confidence interval: 0.16-0.89; *P*=0.028). Our findings indicate that a prior cancer is not a significant etiological factor in plasma cell disorders. The findings do not warrant MGUS screening or different management of MGUS in those with a prior cancer.

Supplementary table 1: The international classification of diseases (ICD) 10 and 9 diagnostic codes used to define prior cancer and its subtypes.

Category	ICD 10	ICD 9	ICD 7
Myeloproliferative	D45, D473, D475, D471, D475, D46, C929, C93, C94, C92	45, 2091, 473, 2089, 475, 2090, 471, 475, 2081, 46, 2059, 929, 2052, 2060, 93, 207, 94, 92, 2051	2079, 209, 2071, 2059, 2050, 2073, 2072, 2051
Non-melanoma skin cancer	C44	44, 173	191
Solid cancer			
Bone and soft tissue	C40, C41, C49	40, 41, 49, 170, 171	196, 197
Breast	C50	50, 174, 175	170
Central nervous system	C71, C70, C72, D33, D32	71, 191, 70, 1923, 72, 33, 32	1930, 1930, 1939
Female reproductive	C51, C52, C57, C58, C53, C54, C55, C56	51, 52, 57, 58, 181, 184, 53, 180, 54, 55, 179, 182, 56	176, 1751, 1759, 1994, 171, 172, 174, 1750
Gastrointestinal	C15, C16, C17, C18, C19, C20, C21	15, 150, 16, 151, 17, 152, 18, 19, 20, 153, 1541, 1540, 21, 1542, 1590	150, 151, 152, 153, 1540, 1541, 1539
Head and neck	C0, C10, C11, C12, C13, C14, C30, C31, C32, C69	10, 11, 12, 13, 14, 14, 30, 31, 160, 32, 161, 69, 190	14, 160, 161, 192
Hepatic, biliary, and pancreatic	C22, C23, C24, C25	22, 155, 23, 24, 156, 25, 157	1550, 1551, 1552, 1553, 1520, 1955
Lung	C34, C33, C384, C45	34, 33, 1620, 163, 1622, 1623, 1624, 1625, 1629, 1628, 384, 45	1621, 1620, 163, 1622
Male reproductive	C60, C61, C62, C63	60, 187, 61, 185, 62, 63, 186	177, 178, 1797, 1791
Melanoma	C43	43, 172	190
Other	C47, C37	47, 37	
Thyroid and endocrine	C73, C74, C75, D35	73, 193, 74, 1940, 75, 35, 1941, 1942, 1943, 1944, 1945, 1946, 1948, 1949	194, 1950
Urinary tract	C67, C66, C65, C64, C68	67, 66, 65, 188, 1891, 1892, 1897, 1898, 1899, 64, 1890, 1896, 68	1801, 181, 1800, 1809

Supplementary table 2: Odds ratios for MGUS and MGUS subtypes for the different solid cancer subtypes included in the study. 1: Adjusted for sex and age; 2: Modelling not performed due to low number of events (<10) in the MGUS group.

	w/t MGUS	with MGUS	OR (95% CI)[1]
n	73,316	3,846	
Gastrointestinal	850 (1.2%)	71 (1.8%)	1.00 (0.78 - 1.29)
Head and Neck	174 (0.2%)	17 (0.4%)	1.32 (0.80 - 2.20)
Hepatic, biliary, and pancreatic	72 (0.1%)	12 (0.3%)	**2.59 (1.39 - 4.84)**
Lung	284 (0.4%)	25 (0.7%)	1.21 (0.80 - 1.83)
Breast	1,869 (2.5%)	117 (3.0%)	1.09 (0.90 - 1.33)
Female reproductive organs	681 (0.9%)	36 (0.9%)	0.93 (0.66 - 1.31)
Male reproductive organs	1,504 (2.1%)	150 (3.9%)	1.00 (0.84 - 1.19)
Urinary tract	750 (1.0%)	79 (2.1%)	**1.27 (1.00 - 1.61)**
Thyroid and endocrine	323 (0.4%)	19 (0.5%)	1.07 (0.67 - 1.71)
Central nervous system	274 (0.4%)	12 (0.3%)	0.77 (0.43 - 1.37)
Bone and soft tissues[2]	76 (0.1%)	3 (0.1%)	
Melanoma	428 (0.6%)	27 (0.7%)	1.09 (0.73 - 1.62)

Supplementary table 3: Subdistribution hazard ratios (sHRs) for MGUS progression overall and to specific disorders for those with MGUS and a prior history of cancer compared to those without a prior history of cancer. Statistically significant results are shown in bold.

	n with prior cancer	n with progression		sHR (95% CI)
		prior cancer	*no prior cancer*	
Any progression				
Any prior cancer	1,834	170	1,488	1.13 (0.97-1.32)
Solid cancer	1,508	144	1,514	0.99 (0.84-1.17)
Non-melanoma skin cancer	240	26	1,634	1.20 (0.82-1.77)
Myeloid cancer	115	5	1,653	**0.41 (0.17-0.97)**
Multiple myeloma				
Any prior cancer	1,834	92	867	0.95 (0.77-1.18)
Solid cancer	1,508	75	884	0.91 (0.72-1.15)
Non-melanoma skin cancer	240	17	943	1.43 (0.87-2.35)
Myeloid cancer	115	3	956	0.44 (0.14-1.36)
Waldenströms macroglobulinemia				
Any prior cancer	1,834	34	295	0.96 (0.67-1.37)
Solid cancer	1,508	30	299	1.00 (0.68-1.47)
Non-melanoma skin cancer	240	5	324	1.04 (0.43-2.51)
Myeloid cancer	115	0	329	-
Amyloidosis				
Any prior cancer	1,834	11	112	0.85 (0.46-1.60)
Solid cancer	1,508	10	113	0.88 (0.46-1.69)
Non-melanoma skin cancer	240	1	122	0.62 (0.09-4.51)
Myeloid cancer	115	0	123	-
Other LP				
Any prior cancer	1,834	33	214	1.31 (0.91-1.91)
Solid cancer	1,508	28	219	1.37 (0.92-2.85)
Non-melanoma skin cancer	240	3	244	0.91 (0.29-2.85)
Myeloid cancer	115	2	245	1.16 (0.29-4.67)

HR: Hazard ratio; CI: Confidence interval