Second primary malignancy in multiple myeloma: does a prior malignancy matter?

Patients with multiple myeloma (MM) are living substantially longer due to advances in therapy, creating a growing survivor population at risk of second primary malignancies (SPM). The cumulative risk of a SPM increases with age and exposure to potentially mutagenic treatments and is especially relevant as patients with MM are heavily treated wth multiple lines of therapy. In the era of novel agents, the estimated incidence of invasive solid malignancies after autologous stem cell transplantation (ASCT) ranges from 3.3% to 10% by 3-10 years after the diagnosis of MM.[1-3] While prior studies have characterized SPM risk over time in MM, few have examined whether a previous history of malignancy before the MM diagnosis confers additional risk, particularly in the contemporary era. A prior invasive malignancy may reflect underlying genetic or immunological susceptibility, cumulative mutagenic exposures, or persistent immune dysregulation which predispose to further malignant transformation. This question is especially relevant among MM patients as MM is a cancer of older adults who may already have a history of a previous malignancy and current standards of care for MM treatment increasingly incorporate agents with known or potential carcinogenic effects, such as lenalidomide maintenance, alkylating agents, and T-cell-redirecting immunotherapies, earlier in the treatment course.[4-6] Understanding how a history of prior malignancy influences SPM risk could inform personalized treatment decisions, survivorship surveillance, and long-term toxicity counseling. Therefore, the aim of this study was to evaluate whether a history of a prior malignancy is associated with an increased risk of SPM in patients diagnosed with MM and treated in a contemporary treatment era.

The Ontario ICES repository of administrative healthcare data was used to identify a population-based cohort of adults with incident MM diagnosed between 2007-2023 and treated with anti-myeloma therapy. The Ontario Cancer Registry was used to identify patients with a prior malignancy, defined as any invasive cancer diagnosed before a diagnosis of MM. SPM was any new cancer first identified *after* the MM diagnosis. Non-melanoma skin cancers were excluded in the prior malignancy and SPM definitions. Malignancy types were summarized using ICD-O-3 topography-based groupings. Treatment data were accessed through the Ontario Drug Benefit database and the Cancer Activity Level Reporting database. A competing risk analysis using the Fine-Gray subdistribution hazards model was conducted to assess the time to first SPM after the diagnosis of MM, accounting for death as a competing risk, and stratifying by prior malignancy status. Given that exposure to lenalidomide occurs after MM diagnosis, a time-dependent analysis was conducted. Supportive analyses were performed using landmark times of 12, 18, 24, and

Table 1. Characteristics of patients with multiple myeloma stratified by prior malignancy status.

Characteristics	No prior malignancy N=10,670	Prior malignancy N=2,083
Age at MM diagnosis, years, median (IQR)	69 (60-76)	75 (68-81)
Male sex, N (%)	5,940 (56)	1,278 (61)
Time period of MM diagnosis, N (%)		
2007-2010	1,903 (18)	288 (14)
2011-2014	2,389 (22)	474 (23)
2015-2018	2,815 (26)	576 (28)
2019-2022	3,563 (33)	745 (36)
First-line treatment within 12 months of MM diagnosis, N (%)		
Cyclophosphamide	5,544 (52)	709 (34)
ASCT	4,096 (38)	366 (18)
Novel agents (PI/IMID/anti-CD38 mAb)	8,687 (81)	1,549 (74)
Lenalidomide	4,062 (38)	725 (35)
Bortezomib	7,579 (71)	1,229 (59)
Daratumumab	658 (6)	151 (7)
Treatment at any time following MM diagnosis, N (%)		
Cyclophosphamide	6,355 (60)	871 (42)
ASCT	4,336 (41)	395 (19)
Novel agents (PI/IMID/anti-CD38 mAb)	9,587 (90)	1,677 (81)
Ixazomib	671 (6)	100 (5)
Bortezomib	8,386 (79)	1,359 (65)
Carfilzomib	968 (9)	125 (6)
Lenalidomide	7,363 (69)	1,235 (59)
Thalidomide	83 (1)	13 (1)
Pomalidomide	1,380 (13)	227 (11)
Daratumumab or isatuximab	2,560 (24)	423 (20)
Number of ASCT after MM diagnosis, N (%)		
0	6,334 (59)	1,688 (81)
1	3,078 (29)	285 (14)
2	1,108 (10)	96 (5)
≥3	150 (1)	14 (1)
Never received lenalidomide or ASCT after MM diagnosis, N (%)	2,527 (24)	770 (37)
Treated with lenalidomide after MM diagnosis (never ASCT), N (%)	3,807 (36)	918 (44)
Received ASCT at any time (never exposed to lenalidomide), N (%)	780 (7)	78 (4)
Received ASCT and lenalidomide after MM diagnosis, N (%)	3,556 (33)	317 (15)

MM: multiple myeloma; IQR: interquartile range; ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory drug; mAb: monoclonal antibody.

30 months after diagnosis. The study was approved by the ethics committee of McMaster University and followed data confidentiality and privacy guidelines of the ICES.

Overall, 12,753 patients with MM diagnosed between January 2007 and August 2023 were included in this study, of whom 2,083 (16.3%) had a prior history of invasive malignancy. Overall, 11,264 (88%) patients received a novel agent (proteasome inhibitor, immunomodulatory drug, or anti-CD38 monoclonal antibody) during their treatment course, and 4,731 (37%) received an ASCT. The baseline and treatment characteristics of patients, stratified by prior malignancy status, are summarized in Table 1. Patients with a prior malignancy tended to be older (median age at MM diagnosis 75 *vs*. 69 years), and had lower rates of exposure to an ASCT (N=395 [19%] *vs*. N=4,556 [41%]) or lenalidomide (N=1,235 [59%] *vs*. N=7,363 [69%]) after the MM diagnosis, compared to those without a prior malignancy. The median time to first lenalidomide exposure after the MM diagnosis was 11.1 (interquartile range [IQR], 4.7-23.8) months *versus* 9.73 (IQR, 1.6-21.0) months in patients with or without a history of a prior malignancy, respectively. The most common prior malignancies were male reproductive (28%), female reproductive (19%), and gastrointestinal (13%) malignancies, as shown in Figure 1A.

Of those with *versus* without a prior malignancy history, 220 (10.6%) *versus* 931 (8.7%), respectively, were diagnosed with a SPM. The median time to first SPM diagnosis was 2.4 (IQR, 0.7-4.9) years *versus* 3.2 (IQR, 1.2-5.7) years among patients with *versus* without a prior malignancy history, respectively, and only 0.9% (N=19 and 100 respectively) had ≥2 SPM. The most common SPM developed were a combination of acute myeloid or lymphoid leukemia or myelodysplastic syndrome (N=267, 23%), followed by gastrointestinal malignancies (N=221, 19%), and female reproductive malignancies (N=114, 10%) (Figure 1A). Of the 245 patients with a prior hematologic malignancy requiring chemotherapy (acute leukemia, myelodysplastic syndrome, or lymphoma), 12 (4.9%) had a subsequent different hematologic SPM.

Among patients with a prior history of malignancy, the cumulative incidence of SPM was 4.5% (95% confidence interval [95% CI]: 3.7-5.4) at 2 years, 8.9% (95% CI: 7.6-10.2) at 5 years, and 12.9% (95% CI: 11.3-14.7) at 10 years after the MM diagnosis, as shown in Figure 1B. In patients without a prior malignancy history, the cumulative incidence of SPM, accounting for death as a competing risk, was 3.1% (95% CI: 2.8-3.4) at 2 years, 6.7% (95% CI: 6.3-7.3) at 5 years, and 10.6% (95% CI: 10.0-11.4) at 10 years after the MM diagnosis. The hazard ratio was 1.38 (95% CI: 1.10-1.73, *P*=0.005 (Table 2) after adjusting for age at MM diagnosis, sex, diagnosis time-period, ASCT exposure in the previous 36 months, and duration of lenalidomide exposure (categorized as no prior lenalidomide, <6 months, or ≥6 months of lenalidomide exposure at 36 months after the MM diagnosis). This indicates that the risk of a SPM among patients with a prior malignancy was increased by 38%, and results were similar in landmark analyses at 12-, 18-, 24-, and 30-month timepoints (*Online Supplementary Table S1*).

In this large, population-based study of more than 12,000 patients with MM treated with contemporary treatments, we found that a history of prior invasive malignancy was independently associated with a 38% higher risk of developing a SPM following the MM diagnosis, after adjusting for age, sex, treatment exposure, and duration of lenalidomide treatment and accounting for death as a competing risk. Although the absolute cumulative incidence of SPM was modest – approximately 9% at 5 years – this absolute excess risk of approximately 1.7% by 5 years among patients with prior malignancy identifies a clinically relevant subgroup that may

Table 2. Univariable and multivariable landmark Fine-Gray model at 36 months after the diagnosis of multiple myeloma to identify factors associated with second primary malignancies, accounting for death as a competing risk (N=7,740 patients).

Potential risk factors	Univariate results, sHR, 95% CI				Multivariate results, sHR, 95% CI			
	sHR	Lower	Upper	*P*	sHR	Lower	Upper	*P*
Prior malignancy (pre-MM diagnosis)	1.28	1.03	1.59	0.026	1.38	1.10	1.73	0.005
Age	0.99	0.99	1.00	0.020	1.01	1.00	1.02	0.244
Male sex	1.26	1.07	1.49	0.006	1.24	1.05	1.47	0.011
Diagnosis year 2011-2014	1.07	0.86	1.32	0.555	1.07	0.86	1.32	0.570
Diagnosis year 2015-2018	1.24	1.00	1.53	0.046	1.21	0.96	1.53	0.113
Diagnosis year 2019-2022	1.54	1.09	2.18	0.014	1.49	1.03	2.15	0.033
<6 months of lenalidomide within 36 months after diagnosis	0.67	0.47	0.95	0.024	0.64	0.45	0.92	0.014
6+ months of lenalidomide within 36 months after diagnosis	1.12	0.95	1.32	0.161	1.01	0.84	1.20	0.953
ASCT within 36 months after diagnosis	1.50	1.27	1.77	<.001	1.69	1.34	2.13	<0.001

sHR: subdistribution hazard ratio; 95% CI: 95% confidence interval; MM: multiple myeloma; ASCT: autologous stem cell transplant.

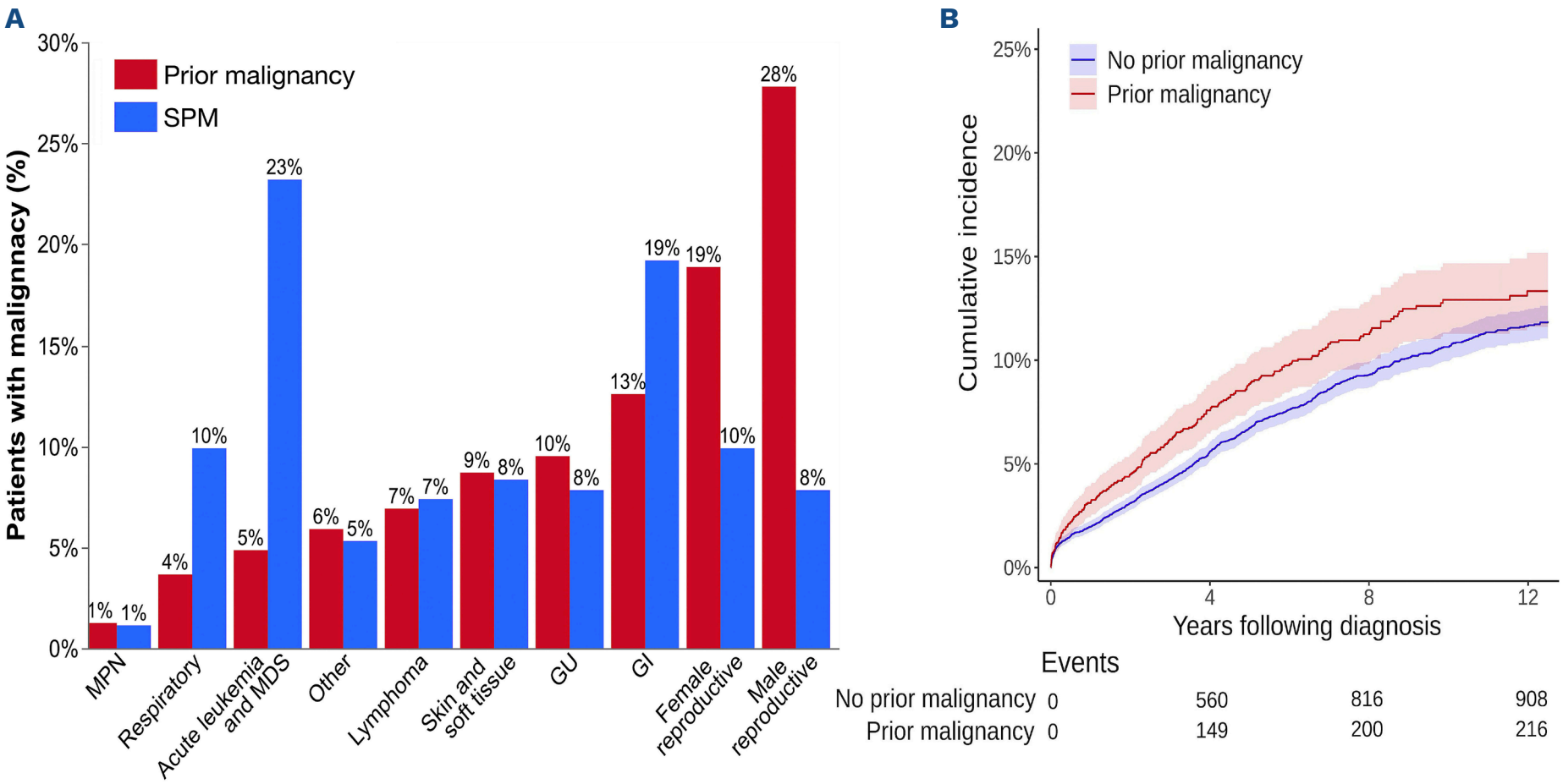

Figure 1. Characterization of malignancy risk in patients with multiple myeloma. (A) Distribution of second primary malignancies and prior malignancies among patients with multiple myeloma. (B) Cumulative incidence of second primary malignancies, stratified by patients with *versus* without a prior malignancy history. SPM: second primary malignancy; MPN: myeloproliferative neoplasm; MDS: myelodysplastic syndrome; GU: genitourinary; GI: gastrointestinal.

warrant tailored long-term surveillance. These findings suggest that host-related factors, beyond MM treatment exposure, contribute meaningfully to SPM risk. Potential mechanisms include underlying genomic instability, germline mutations in DNA repair or tumor suppressor genes, and chronic immune dysregulation, which predispose to malignant transformation.[7,8] In addition, prior exposure to cytotoxic chemotherapy or radiotherapy may cause latent mutagenic effects that synergize with subsequent myeloma-directed therapies, compounding the risk of secondary neoplasia. Given the increasing use of immunomodulatory drugs and novel immunotherapies, it is possible that the SPM risk may increase with time, beyond what was observed in this report.

Our results add an important dimension to existing literature, which has largely focused on treatment-related SPM risk, with few studies systematically evaluating the impact of pre-existing malignancy history. A prior prospective study of 744 MM patients treated between 1997 and 2011 reported that 11% had a prior non-MM malignancy, including non-invasive skin cancers, at MM diagnosis, while a large Swedish population-based study found that 12.5% of MM patients diagnosed between 1973 and 2010 had a history of prior malignancy.[9,10] The latter study also demonstrated that prior malignancy was associated with an increased risk of SPM (hazard ratio=1.42, 95% CI: 1.23-1.65, *P*<0.001); however, it did not provide information on the MM treatment regimens used. Given the older diagnostic eras (median year of diagnosis 1999 *vs*. 1992 for those with and without prior malignancy, respectively), most patients would not have been exposed to novel therapeutic agents, further limiting the applicability of those findings to contemporary treatment contexts.

The strengths of our study include its large, population-based design, comprehensive ascertainment of malignancy diagnoses, and adjustment for competing mortality. Limitations include the absence of cytogenetic, germline, and cumulative dose data, and the potential under-ascertainment of SPM diagnosed outside hospital settings. Additionally, treatment details for the prior malignancy were unavailable, leaving uncertainty as to whether the increased SPM risk reflects inherent patient biology or the mutagenic effects of prior therapy.

In conclusion, our study provides real-world evidence that prior malignancy independently increases SPM risk in MM survivors. This information should be incorporated into shared decision-making, risk stratification, and long-term survivorship follow-up care discussions.

Authors

Alissa Visram,[1] Hsien Seow,[1] Rajeshkar Chakraborty,[2] Gregory Pond,[1] Ana Gayowsky,[3] Ghulam Rehman Mohyuddin,[4] Samer Al Hadidi,[5-7] Doris K. Hansen,[8] Surbhi Sidana,[9] Rohan Gouda,[1] Alejandro Garcia-Horton,[1] Rafael Fonseca[8] and Hira Mian[1]

[1]Department of Oncology, McMaster University, Hamilton, Canada; [2]Herbert Irving Comprehensive Cancer Center, Columbia University

Irving Medical Center, New York, NY, USA; [3]Institute for Clinical Evaluative Sciences, McMaster University, Hamilton, Canada; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]Department of Hematology and Oncology, Simmons Comprehensive Cancer Center, Dallas, TX, USA; [6]Southwestern Medical Center, Dallas, TX, USA; [7]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Scottsdale, AZ, USA; [8]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA and [9]Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, Stanford, CA, USA

Correspondence:
ALISSA VISRAM - visrama@hhsc.ca

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Disclosures

No conflicts of interest to disclose.

Contributions

AV, GP and HM conceived and designed the study. AG-H collected data. All authors (AV, HS, RC, GP, AG, GRM, SAH, DKH, SS, RG, AG-H, RF and HM) analyzed and interpreted the data, contributed to drafting the manuscript, and approved the final version.

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Data-sharing statement

The dataset from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at *www.ices.on.ca/DAS* (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, with the understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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