ORIGINAL ARTICLE

Variable risk of second primary malignancy in multiple myeloma patients of different ethnic subgroups

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Second primary malignancies (SPMs) among multiple myeloma (MM) patients have been reported with an estimated incidence varying from 1 to 15%. We have previously reported that significant disparity exists in MM survival across patients of different ethnicities. We undertook a Surveillance Epidemiology and End Results-based analysis to describe the incidence of SPMs among MM patients of different ethnicities, to explore the variable impact that SPMs might have on MM outcomes of patients across racial subgroups. We found that the risk of developing SPMs among MM patients is variable depending on the patient's ethnic background. This warrants further exploration of the impact of SPMs on outcomes of MM patients across different racial subgroups, especially in the form of prospective data collection and analyses.

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INTRODUCTION

Second primary malignancies (SPMs) among multiple myeloma (MM) patients have been reported with an estimated incidence that varies from 1 to 15%.^{1–6} The incidence of cancer per year of life in the general population is calculated to be 1.7% in those aged 65–69 years, and it increases with advancing age.⁷ Cancer survivors have a 14% increased risk of developing another malignancy compared to the general population.⁸ With major advancements in the treatment of MM, there has been an increase in the overall survival. This has led to an increased life expectancy of those diagnosed with MM as a primary malignancy. This has, however, led to the renewed concern about long-term comorbidities including the risk of SPM in surviving MM patients. Recently, an increase in the incidence of SPM in MM patients treated with certain novel anti-myeloma treatments, particularly the immuno-modulatory drugs, has been reported in large randomized clinical trials.^{9–11} Although the specific causative role of these agents is still not established, several factors including the duration and timing of treatment, the use of various combination regimens and certain patient-related factors such as age and tumor micro-environment have been postulated. We have previously reported a comprehensive analysis of SPM in MM patients utilizing the Surveillance Epidemiology and End Results (SEER) registry database.¹² Furthermore, we also noted in a separate analysis that significant disparity exists in MM survival across patients of different ethnicities.¹³ Considering the rapidly changing US population demographics and the fact that the Hispanic and Asian populations are the two fastest growing racial subgroups in the US, we undertook a SEER-based analysis to describe the incidence of SPM among MM patients of different ethnicities.

MATERIALS AND METHODS

Patients

We utilized data from the National Cancer Institute's SEER program's original nine registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico,

San Francisco-Oakland, Seattle and Utah) with incidence data from over a 35-year interval (1973–2008). Our analysis was restricted to patients with MM as the first primary malignancy and with a microscopic confirmation of diagnosis. We excluded cases whose reporting sources were coded as autopsy or death-certificate-only, cases where MM was not the first primary cancer diagnosis and cases with SPM diagnosed within the first 2 months of MM diagnosis. Mutually exclusive race/ethnicity categories were: African Americans (AA), Asians/Pacific Islanders (API), Hispanic whites (HW), non-Hispanic whites (NHW) and others. The risk of SPM among MM patients was explored by ethnicity, type of SPM and latency period.

Statistical analysis

To estimate SPM risk, we defined a cohort of MM patients with no history of malignancy. Person-years for age strata (5-year age-groups), sex, race (AA, API, HW, NHW and others) and the year of diagnosis were calculated from 2 months after diagnosis of MM to the date of death, date of diagnosis of SPM, date of loss to follow-up, the end of study (31 December 2008) or whichever came first. General population incidence rates for each stratum were multiplied by their respective accumulated person-years-at-risk to estimate the overall expected cancer cases in that cohort of MM patients.

Observed-to-expected ratio (O/E) of SPM was calculated using incidence rates of cancers for the general population. The 95% confidence interval (CI) were constructed using Fisher's exact test. We used likelihood ratio tests based on Poisson regression models that included SEER registry general population rates to evaluate linear trends and heterogeneity across different SPM sites. We included at least five observed occurrences in each stratum. We further performed multivariate Poisson regression analysis adjusted for age, sex and latency to compare the standardized incidence ratios across different year categories. All analyses were completed using SEER*Stat version 7.0.5 statistical software (Surveillance Research Program, National Cancer Institute, <http://www.seer.cancer.gov/seerstat>) and Stata version 11.2 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 3090 cases of MM with SPM were diagnosed between 1973 and 2008, of which, 2021 patients met our inclusion criteria.

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Stratification of SPM by ethnicity revealed: 387 AA (19%), 72 API (4%), 51 HW (3%), 1500 NHW (74%) and 11 other (< 1%) cases. There was an average 4.7 year latency period between diagnosis of MM and SPM (mean age 68.2 and 72.9 years, respectively). The latency period was not significantly different by type of SPM (solid organ versus hematological) or ethnicity. AA had the youngest age at diagnosis for both MM and SPM (65.6 and 70.1 years, respectively; Figure 1). Detailed results of the SPM in MM analysis other than that related to patient race/ethnicity have been previously reported.¹² The overall risk of observed SPM was not different from expected rates by ethnicity, with the exception of HW who had a significantly decreased overall SPM risk (O/E 0.67; 95% CI 0.50–0.88; Figure 2). Table 1 summarizes the SPM sites that had a significant difference (marked by ^a) in observed and expected risks by race. HW were also less likely to develop all solid-organ SPM (0.66; 95% CI 0.48–0.89). Within solid-organ sites, HW had a significantly decreased O/E risk of developing lung/bronchus (O/E 0.34; 95% CI 0.08–0.88) and prostate SPM (O/E 0.48; 95% CI 0.19–0.99). NHW were the only ethnic subgroup with an increased O/E risk of developing melanoma of the skin (O/E 1.38; 95% CI 1.06–1.78) and non-Hodgkin lymphoma (O/E 1.28; 95% CI 1.01–1.61), while the O/E risk of developing SPM of the kidney/renal pelvis was increased only among AA (O/E 2.17; 95% CI 1.31–3.39). The O/E risk of acute non-lymphocytic leukemia as SPM was significantly increased among AA (O/E 6.24; 95% CI 3.41–10.47), API (O/E 6.32; 95% CI 1.72–16.19) and among NHW (O/E 6.85; 95% CI 5.55–8.38).

DISCUSSION

Major advancements in the treatment options for MM have led to a significant increase in overall survival. This may have translated into an increase in the observed incidence of SPM in MM patients. Mailankody *et al.*¹⁴ demonstrated a twofold increase in risk of SPM in the Swedish population of MM patients compared to their age and sex-matched general population, irrespective of the year of diagnosis and the treatment received. They also duplicated the 11-fold increased risk of developing acute myeloid leukemia/myelodysplastic syndrome in MM patients as compared to the general population, as has been demonstrated in prior studies here in the United States.^{2,4,15,16} They further established an eight-fold increased risk of developing acute myeloid leukemia/myelodysplastic syndrome in patients with monoclonal gammopathy of undetermined significance (MGUS). Similarly a 2.4-fold increased risk of myelodysplastic syndrome in MGUS patients was reported by Roeker *et al.*¹⁷ at the Mayo clinic. However, they observed no increase in the incidence of acute myeloid leukemia in their screened population, which was comprised of individuals

Figure 1. Mean age at diagnosis of MM and SPM, respectively by race.

from Olmsted County in Minnesota, and is noticeably different from the Scandinavian population in the Swedish study.

Racial disparity has been proven in multiple studies to be an independent risk factor in the incidence of MGUS and MM.^{18–27} Although, exploring SPMs in MGUS, MM and in patients who develop MM from previously reported MGUS would be very insightful, such an analysis is not feasible from the SEER database due to the lack of uniform reporting of MGUS in SEER as well as a much less than universal reporting of sequential diagnoses of MGUS and MM. Hence, we performed one of the largest population-based analyses for the risk of SPM developing in patients with an established diagnosis of MM, stratified by race/ethnicity. We found that the risk of developing SPM among MM patients is variable depending on the patient's ethnic background. For all SPM sites analyzed together, there was no significant difference between the observed and expected incidence. However, O/E risk was significantly decreased for solid-organ SPM and increased for hematological malignancies, with the highest risk being for acute non-lymphocytic leukemia. This was consistent with the observation by Chakraborty *et al.*²⁸ We also had similar findings in terms of the increased incidence of

Figure 2. Observed-to-expected (O/E) incidence of overall, all solid-organ and acute non-lymphocytic leukemia (ANLL) SPM in MM patients by race.

Table 1. Sites with significant difference in observed and expected risk of SPM for various race/ethnic subgroups

Race	SPM type	Risk	O/E risk HR	95% CI
HW	Overall	Decreased	0.67 ^a	0.50–0.88
	All solid organ	Decreased	0.66 ^a	0.48–0.89
	Lung/bronchus	Decreased	0.34 ^a	0.08–0.88
	Prostate	Decreased	0.48 ^a	0.19–0.99
	ANLL	Increased	1.54	0.04–8.58
NHW	All solid organ	Decreased	0.90 ^a	0.85–0.95
	Melanoma of the skin	Increased	1.38 ^a	1.06–1.78
	ANLL	Increased	6.85 ^a	5.55–8.38
	NHL	Increased	1.28 ^a	1.01–1.61
AA	Overall	Increased	0.97	0.92–1.02
	Kidney/renal pelvis	Increased	2.17 ^a	1.31–3.39
	ANLL	Increased	6.24 ^a	3.41–10.47
API	All solid organ	Increased	1.05	0.94–1.17
	Overall	Increased	1.07	0.97–1.18
	ANLL	Increased	6.32 ^a	1.72–16.19
	All solid organ	Increased	1.03	0.79–1.33
	Overall	Increased	1.11	0.87–1.40

Abbreviations: AA, African American; ANLL, acute non-lymphocytic leukemia; API, Asians/Pacific Islanders; CI, confidence interval; HW, Hispanic Whites; NHL, non-Hodgkin lymphoma; NHW, non-Hispanic Whites. ^aSites with significant difference in observed and expected risk of SPM for different race/ethnic subgroups.

melanoma in NHW and kidney cancer in the AA population. Our analysis had two additional subgroups of HW and API, and revealed further differences among the incidence of SPM (Table 1).

Recently, Tzeng *et al.* reported several differences in the characteristics of SPM in the Asian population of Taiwan. They reported a 13-fold increased risk in the overall incidence of SPM, which increased 24-fold for myeloid leukemia.²⁹ These incidence rates were significantly different than what was reported for our API population, but our API population was not strictly Asian and not regionally constrained. They were also quite different from the incidence established in the Swedish population study (twofold and 11-fold increase in overall SPM and myelodysplastic syndrome/acute myeloid leukemia, respectively).¹⁴ The latency period for occurrence of these SPMs was also shorter (1.9 years) compared to our API population (6.7 years) and the Western population (~4 years).¹⁴ Interestingly, Tzeng *et al.*²⁹ and colleagues also demonstrated a decreased risk of developing SPM with increasing age in this Asian population. This has not been observed in any other patient population so far and likely highlights the importance of disparity not only in race but also possibly in environmental, behavioral and host genetic factors as proposed by others in studies of SPM after MM.^{30,31} These have looked at the effect of various treatment modalities and the molecular disease heterogeneity as possible explanations for the causality of SPM.

Palumbo *et al.*³² recently published results of meta-analyses of seven trials for the cumulative incidence of all SPM in newly diagnosed MM patients who had received lenalidomide therapy. They demonstrated an increased incidence of SPM in this patient population, but no subset data were presented for ethnic miscellany. Autologous stem cell transplant remains one of the primary modalities in the treatment of MM. The post-autologous stem cell transplant incidence of SPM was reportedly increased in a single German institution analysis of MM patients.³³ Recently, Krishnan *et al.* also identified a possible causal association between autologous stem cell transplant and the development of SPM. Their study population included patients from a single institution with a relatively larger HW population mix, which maybe because it is based out of Los Angeles, California. Their patient population had an augmented exposure to sunlight, which had the authors also include non-melanoma skin cancers in their analysis. They identified race/ethnicity as an independent risk factor and reported an increase in the incidence of SPM (particularly non-melanoma skin cancers) only among NHW population, after adjustment for sex and year of autologous stem cell transplant.³⁴ Our analysis also identifies that NHW have an increased incidence of both melanoma and non-melanoma skin cancers, but we did not have individual treatment data, and therefore no patient-level comparison can be made (Table 1).

Merrill *et al.*³⁵ have reported an overall increased incidence of cancer in NHW as compared to HW, which was adjusted for sex. Our analysis revealed that among all ethnicities, HW had the lowest overall O/E ratio for development of SPM, both hematological and solid-organ type. They also had the lowest overall O/E incidence of prostate cancer. Socioeconomic status and access to healthcare has been ascertained as one of the primary reasons for different outcomes in prostate cancer among various racial groups. Tyson and Castle³⁶ recently published that Hispanics with equal access to treatment for prostate cancer have similar overall survival compared to the white population. They also showed that the Asian population did better after adjustment for the receipt of treatment, while the AA population did worse. Socioeconomic status has been associated with survival in cancer patients.^{37,38} A patient's address/postal code could be used as a surrogate for their socioeconomic status, but unfortunately this information is not included in the SEER database and hence precludes this analysis in our study. In our analyses, AA patients had a higher incidence of kidney/renal pelvis SPM compared to other

ethnicities. Historically, the incidence of primary renal cell cancer has been higher among AA patients.³⁹ Chow *et al.*⁴⁰ verified that AA patients with renal cell cancer had a worse outcome in terms of survival compared to the white population, and this was irrespective of age, sex, tumor stage or size, histological subtype or surgical treatment. Most studies so far have evaluated the disparities among the two most prevalent races in the United States, NHW and AA. With the diversification of patient population in the United States and worldwide, it has become imperative to further define prognostic factors and treatment modalities on the basis of racial dissimilarity.

The strength of our study lies in the large number of population-based MM and SPM cases identified in the time period analyzed. We were also able to eliminate selection bias, which is generally introduced when data from hospital-based populations are utilized. The SEER ascertainment also helped expand the generalizability of the findings to patients who are not enrolled in clinical trials. MM is a relatively rare cancer and the survival time is shorter compared with other hematological malignancies, making SPM case ascertainment a challenge. Therefore, we chose to exclude cases diagnosed with a second cancer within the first 2 months of MM diagnosis. To address the issue of surveillance bias within the first year of a primary cancer diagnosis, we performed a sensitivity analysis excluding SPM cases diagnosed within the first year, and the results were similar.¹² The SEER database does not provide us with individual-level treatment information; thus we were unable to test the effect/association of treatment modalities on the variance in incidence of SPM among the different ethnic groups.

CONCLUSION

Exploring potential causes of outcome disparities is important for evaluating disease characteristics and optimal triaging of health-care resources for specific patient populations. The demonstration of an increased risk of developing specific SPMs in MM patients of certain ethnicity may be utilized in clinical practice to target the defined population for appropriate screening. We have performed the largest population-based analysis for the risk of SPM in MM patients stratified by race/ethnicity. We found that the risk of developing SPM among MM patients is variable depending on the patient's ethnic background. This warrants further exploration of the impact of SPM on outcomes of MM patients across different racial subgroups, especially in the form of prospective data collection and analyses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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