

# Incidence of Secondary Malignancies Among Patients With Waldenström Macroglobulinemia: An Analysis of the SEER Database

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**BACKGROUND:** Waldenström macroglobulinemia (WM) is an indolent malignancy that predominantly affects older individuals who are at risk for secondary malignancies (SMs). The objective of this study was to characterize the incidence of SMs after a diagnosis of WM with the Surveillance, Epidemiology, and End Results (SEER) database. **METHODS:** With SEER-13 data (1992-2011), standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated for the rates of solid and hematologic SMs in WM patients versus the general population. The analysis was stratified by age, sex, race, year of diagnosis, and latency from the WM diagnosis. **RESULTS:** Among 4676 patients with WM, 681 SMs were recorded. The overall SIR was 1.49 (95% CI, 1.38-1.61), and the median time to an SM was 3.7 years. The cumulative incidence of SMs was 10% at 5 years and 16% at 10 years. The risk was significantly increased for cancers of the lungs, urinary tract, and thyroid; melanoma; aggressive lymphoma; and acute leukemia. The SIR for SMs in patients with WM was increased, regardless of age, sex, race, or year of diagnosis. **CONCLUSIONS:** Patients with WM had a 49% higher risk of SMs than the general population. The selectively increased risk for hematologic SMs and certain solid SMs may be associated with transformation, therapy, and immune dysregulation. *Cancer* 2015;000:000-000. © 2015 American Cancer Society.

**KEYWORDS:** epidemiology, incidence, lymphoplasmacytic lymphoma, secondary malignancies, Waldenström macroglobulinemia.

## INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent but incurable B-cell non-Hodgkin lymphoma characterized by the presence of a lymphoplasmacytic infiltrate in the bone marrow and immunoglobulin M monoclonal gammopathy.<sup>1</sup> Because the disease-specific mortality associated with WM includes approximately 25% of the cases, WM patients can experience prolonged survival times.<sup>2</sup> The prolonged survival, along with the immune dysregulation associated with WM, can affect the incidence of secondary malignancies (SMs) in patients with WM.

Some studies have suggested an increased risk of SMs in patients with WM.<sup>3-5</sup> However, these studies were smaller, single-center experiences or did not compare the incidence of SMs seen in patients with WM to that in the general population. The objectives of the current study were to analyze the incidence and patterns of occurrence of various SMs in survivors of WM in comparison with an appropriately matched general population of the United States.

## MATERIALS AND METHODS

### *Data Source and Cohort Selection*

We used data from the November 2013 submission of the Surveillance, Epidemiology, and End Results (SEER) program database (<http://www.seer.cancer.gov/>). The SEER program collects cancer incidence, stage, first course of treatment, and survival outcome data, and it has undergone several expansions since its inception in 1973. To include the long follow-up times necessary to assess the incidence of SMs, data from 13 US registries (SEER-13) continuously reporting cases between 1992 and 2011 were used for all incidence calculations.<sup>6</sup> The SEER-13 program covers approximately 13% of the US

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population, requires a case ascertainment rate of at least 98% to ensure the completeness of the incidence rates, and uses audits and case-finding studies for data quality assessment.

WM cases were defined according to the InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research, which is based on codes 9671/3 (lymphoplasmacytic lymphoma [LPL]) and 9761/3 (WM) from the 2008 World Health Organization (WHO) *International Classification of Diseases for Oncology, Version 3* (ICD-O-3).<sup>7</sup> Only the first record of LPL or WM was counted (ie, if a patient had a diagnosis of LPL and then WM, only the first record was included). Cases diagnosed by autopsy or death certificate were excluded. We considered all LPL cases as WM cases for the purposes of this study. SMs were classified according to WHO ICD-O-3 topography and morphology codes. We included acute myelogenous (n = 13), lymphoblastic (n = 1), and other acute leukemia (n = 1) in the category of acute leukemias. Neoplasms occurring within 3 months of the WM diagnosis (n = 71) were not counted to avoid bias related to incidental WM discovered during the evaluation of another cancer or vice versa. These included 47 solid SMs (lung, 11; genitourinary, 9; colorectal, 6; breast, 6; prostate, 5; upper gastrointestinal, 5; melanoma, 1; head and neck, 1; thyroid, 1; sarcoma, 1; and cancer of the penis, 1) and 24 hematologic SMs (lymphoma, 17; myeloma, 6; and acute leukemia, 1).

Incidence rates in the population, stratified by attained age, sex, race, and calendar year, were provided by SEER. We constructed stratified incidence rate tables for subtypes of lymphoma with the morphology code-based InterLymph classification. We additionally distinguished diffuse large B-cell lymphoma (DLBCL) and acute myelogenous leukemia (AML) as SMs of special interest because they are associated with histological transformation and chemotherapy, respectively. The multiple primary standardized incidence ratio (MP-SIR) was not calculated for SMs with fewer than 10 cases because estimates would have been imprecise.

### Statistical Methods

The association of WM with subsequent malignancies was expressed as MP-SIRs. MP-SIRs were calculated as the number of observed cases of a given cancer among WM patients divided by the number of cases expected from stratified incidence rate tables for the population under study. Confidence intervals (CIs) at the 95% level for MP-SIRs were calculated with the exact method.<sup>8</sup> We further calculated MP-SIRs for solid tumors and hematologic malignancies with respect to the latency from the

**TABLE 1.** Selected Characteristics of Patients With Waldenström Macroglobulinemia From the Surveillance, Epidemiology, and End Results 13 Database

Variable	No. of Cases (%)
Total	4676 (100.0)
Age, y	71 (61-79) <sup>a</sup>
Sex	
Female	1964 (42.0)
Male	2712 (58.0)
Race	
White	4071 (87.1)
Black	255 (5.5)
American Indian	12 (0.3)
Asian/Pacific Islander	261 (5.6)
Unrecorded	77 (1.6)
Decade	
1992-2000	1815 (38.8)
2001-2011	2861 (61.2)
Histology code	
Lymphoplasmacytic lymphoma	2069 (44.2)
Waldenström macroglobulinemia	2607 (55.8)
Vital status	
Alive	2254 (48.2)
Dead	2422 (51.8)
Secondary malignancy	
Did not occur	4068 (87.0)
Occurred	608 (13.0)

<sup>a</sup>Age is presented as the median (interquartile range).

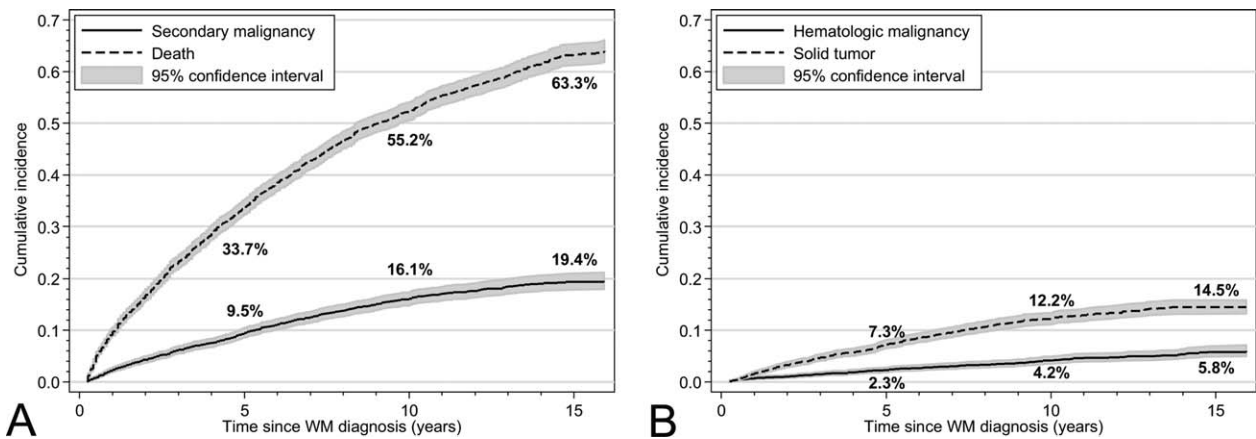
index WM diagnosis (<5, 5-10, or >10 years) and for subgroups defined by attained age (<65 or ≥65 years), sex, and calendar year (1992-2000 or 2001-2011). Nonoverlapping 95% CIs indicated statistical significance for differences between groups. The cumulative incidence of SMs from the initial WM diagnosis was calculated with a competing risk survival methodology, with death treated as a competing event.<sup>9</sup>

Incidence rates and CIs were calculated with SEER\* Stat software (version 8.1.5; Surveillance Research Program, National Cancer Institute, Bethesda, MD [http://www.seer.cancer.gov/seerstat/]). All other statistical analyses and figures were performed and obtained with Stata/SE 13.1 (StataCorp LP, College Station, TX).

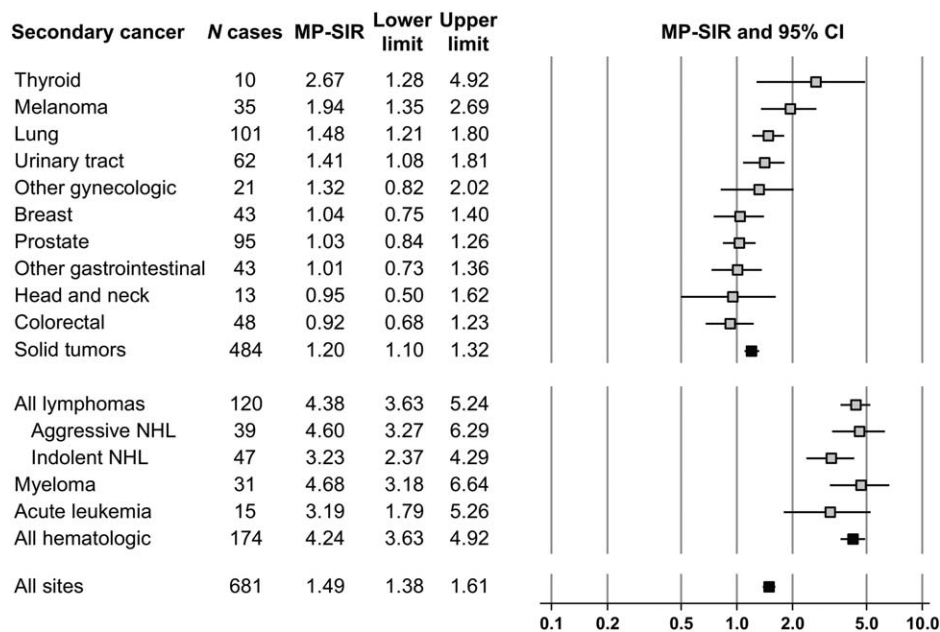
## RESULTS

### Risk of SMs Versus the General Population

We identified 4676 eligible WM patients reported by the SEER-13 registries between 1992 and 2011. Selected patient characteristics are shown in Table 1. The median time from WM diagnosis to first SM diagnosis was 3.7 years (95% CI 3.2-4.2 years). There were 681 SMs reported among 608 patients. The cumulative incidence function of SMs was 9.5% (95% CI, 8.6%-10.5%) at 5 years and 16.1% (95% CI, 14.8%-17.3%) at 10 years (Fig. 1A). The 5- and 10-year cumulative incidence functions were 7.3% (95% CI, 6.5%-8.1%) and 12.2%



**Figure 1.** Cumulative incidence of (A) secondary malignancies and competing events (death) among patients with WM from the Surveillance, Epidemiology, and End Results 13 database and (B) types of secondary malignancies. The occurrence of a solid tumor or a hematologic malignancy was not considered a mutually exclusive competing event. WM indicates Waldenström macroglobulinemia.

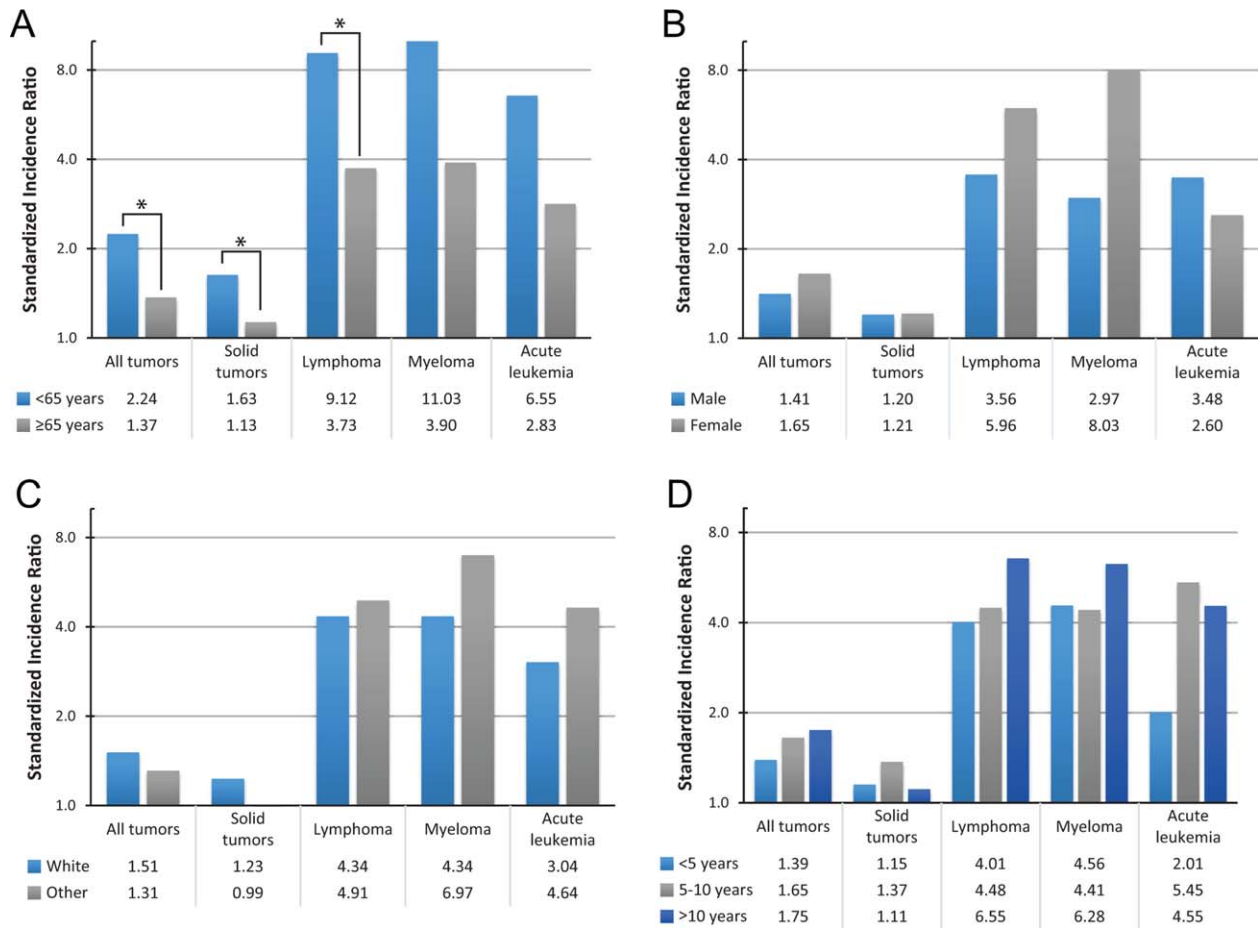


**Figure 2.** Forest plot of the standardized incidence ratios of secondary malignancies in patients with Waldenström macroglobulinemia from the Surveillance, Epidemiology, and End Results 13 database. CI indicates confidence interval; MP-SIR, multiple primary standardized incidence ratio; NHL, non-Hodgkin lymphoma.

(95% CI, 11.1%-13.3%), respectively, for solid tumors and 2.3% (95% CI, 1.9%-2.8%) and 4.2% (95% CI, 3.5%-4.9%), respectively, for hematologic malignancies (Fig. 1B).

The MP-SIR for all SMs among WM cases was 1.49, which corresponded to a 49% increase in risk over the general population. The risk for solid tumors was increased by 20%, whereas the risk for hematologic malignancies was

increased more than 4-fold. A forest plot of SM incidence in WM patients is shown in Figure 2. Among solid tumors, the risk was significantly increased for lung cancer, urinary tract cancer (including bladder/ureter cancer [45 cases] and kidney cancer [17 cases]), melanoma, and thyroid cancer. Among hematologic malignancies, the risk was significantly increased for all lymphomas, multiple myeloma, and acute leukemia. The risk of DLBCL (n = 31 cases) was 4.33



**Figure 3.** Multiple primary standardized incidence ratios for various types of secondary malignancies in patients with Waldenström macroglobulinemia from the Surveillance, Epidemiology, and End Results 13 database by (A) attained age, (B) sex, (C) race, and (D) latency (in years) from the initial Waldenström macroglobulinemia diagnosis.

(95% CI, 2.94-6.15), and for AML (n = 14), it was 3.21 (95% CI, 1.79-5.39).

The risk of SMs was significantly higher for patients younger than 65 years (MP-SIR, 2.24; 95% CI, 1.88-2.65) versus those who were older (MP-SIR, 1.37; 95% CI, 1.26-1.49; Fig. 3A). This difference was significant for solid tumors (MP-SIR for younger patients, 1.63 [95% CI, 1.31-2.00]; MP-SIR for older patients, 1.13 [95% CI, 1.03-1.25]) and hematologic malignancies (MP-SIR for younger patients, 9.04 [95% CI, 6.52-12.2]; MP-SIR for older patients, 3.62 [95% CI, 3.03-4.30]). The risk of solid tumors was the same for men and women, but women had a significantly higher risk of secondary hematologic malignancies (MP-SIR, 5.82; 95% CI, 4.62-7.23) than men (MP-SIR, 3.43; 95% CI, 2.77-4.20), specifically in the case of lymphoma and myeloma (Fig. 3B). The differences for white and nonwhite patients were not significant either for aggregate SMs or for the solid/hematologic categories (Fig. 3C).

The median latency from the WM diagnosis until the diagnosis of any SM (counting multiple occurrences in each patient as separate events) was 49 months (interquartile range [IQR], 19.5-82.5 months). The median latency from the diagnosis of WM to the diagnosis of any solid tumor was 48 months (IQR, 20-79 months), and the median latency to any hematologic malignancy was 51 months (IQR, 19-96 months). In a stratified analysis, the risk of solid tumors peaked 5 and 10 years after the diagnosis (Fig. 3D). In contrast, the risk of hematologic malignancies continued to increase with time (MP-SIRs of 3.79, 4.42, and 6.70 for latencies of <5, 5-10, and >10 years, respectively), although this was not statistically significant because of large CIs. The MP-SIRs for DLBCL were 3.80, 5.01, and 5.79 for latency periods of <5, 5 to 10, and >10 years, respectively.

When we compared the epochs of 1992-2000 and 2001-2011, the overall risk was not significantly different: MP-SIRs were 1.35 (95% CI, 1.13-1.60) and 1.53 (95%

CI, 1.40-1.66), respectively. There was also no difference between rates for patients with histology designated as LPL (MP-SIR, 1.47; 95% CI, 1.30-1.65) or WM (MP-SIR, 1.51; 95% CI, 1.37-1.66).

## DISCUSSION

To the best of our knowledge, this is the largest population-based analysis evaluating the incidence of SMs in patients with WM versus the general population. Our study shows that there is an increased incidence of lung cancer, urinary tract cancer (including bladder and kidney), thyroid cancer, melanoma, DLBCL, and acute leukemia in patients with WM versus the general US population.

Our study provides further insights into the risk of SMs in patients with WM. First, the risk of SMs, solid and hematologic, is higher for patients younger than 65 years versus patients who are 65 years old or older. Second, the risk of hematologic SMs (specifically lymphoma and myeloma) appears higher for women than men. Third, although the risk of hematologic SMs increases with a longer time from the WM diagnosis, the risk of solid tumors increases in the first 10 years and decreases afterwards.

Previous studies suggested an increased risk of SMs in patients with WM, although they lacked the power to analyze their occurrence with respect to a WM diagnosis and/or patient characteristics.<sup>3-5</sup> Varettoni et al<sup>5</sup> evaluated 230 patients with WM from 2 centers in Pavia and Milan, Italy, and they identified 32 patients who developed SMs for a cumulative incidence at 10 years of approximately 18% (12% for solid tumors and 6% for hematologic malignancies)<sup>5</sup>; this is comparable to our results. The risk of developing SMs in patients with WM was increased by 70% in comparison with the general Italian population. Notably, the risk for DLBCL, AML, and brain tumors was significantly increased. It is important to emphasize that the standardized incidence ratios for SMs were calculated on the basis of a small sample (6 cases of DLBCL, 3 cases of AML, and 2 cases of brain tumors), which might have not been powered to detect small to moderate increases in risk and/or to provide precise estimates.

A previous study from the Bing Center for Waldenström Macroglobulinemia in Boston analyzed a cohort of 924 patients with WM; 225 (24%) reported other malignancies.<sup>3</sup> The authors reported a number of cancers of the prostate and breast, nonmelanoma skin cancer, DLBCL, and AML. However, no comparison was made with the general US population, and more than 60% of the malignancies were identified before the diag-

nosis of WM. Because of these factors, it is likely that the incidence of prostate and breast cancer in this study may simply reflect their incidence in the general US population. On the other hand, all cases of DLBCL and AML were diagnosed after the diagnosis of WM, and this supports malignant transformation and the effect of chemotherapy, respectively.

Ojha and Thertulien<sup>4</sup> calculated the MP-SIR for SMs in WM patients from the SEER-9 database, but the period of their analysis (1973-2008) largely predated the introduction of consistent WHO coding of the cancer site and histology.<sup>4</sup> Moreover, their brief report did not include cases of LPL. In contrast, our study includes a comprehensive cohort of more than 4600 patients with a diagnosis of WM as well as LPL. WM constitutes approximately 95% of the cases of LPL,<sup>1</sup> and the therapy and survival outcomes of patients with WM and LPL do not differ.<sup>2</sup> Therefore, analyzing them as a single entity is appropriate and provides both less biased and more precise incidence estimates. Indeed, the risk of SMs between these 2 histology codes was not different. In addition, because of the larger sample size, we were able to perform stratified analyses to evaluate the incidence according to age, sex, race, year of diagnosis, and latency of WM.

An increased risk of SMs in patients with indolent lymphoproliferative disorders has been suggested by a number of studies.<sup>10-13</sup> This risk is thought to be mediated not only by increasing age but also by genetic predisposition, immunologic dysfunction, therapy, and other environmental factors. In the specific case of WM, age plays an important role in survival and hence affects the risk for SMs. For example, WM patients who are younger than 50 years of age at diagnosis have a median survival time that exceeds 20 years.<sup>14</sup> Our finding of an increased incidence of SMs in younger patients suggests that aging with WM rather than aging might be a driver of the risk of SMs. Aging with WM would suggest more likely exposure to therapy as well as more protracted antigenic stimulation and/or immune dysregulation. On the other hand, we have previously reported an approximately 20% increased risk of WM and other related hematologic malignancies in first-degree family members of patients with WM.<sup>15</sup> The risk of other cancers also appears increased in first-degree family members of WM patients,<sup>16</sup> and this suggests a genetic predisposition for the development of WM and other SMs. Additional research is ongoing to potentially identify the genetic mechanisms of cancer clustering in patients and families with WM.

According to our results, patients with WM have a higher risk of developing other hematologic malignancies

such as aggressive and indolent lymphomas, acute leukemia, and multiple myeloma. On the basis of our experience and data from the literature, WM can transform into more aggressive histologies, the most common being DLBCL,<sup>17,18</sup> but transformation into Burkitt lymphoma has also been reported.<sup>19</sup> The increased risk of AML can be explained by previous exposure to specific therapeutic agents. A previous study suggested that patients with WM who have been treated have a higher risk of developing acute leukemia than untreated patients.<sup>5</sup> In addition, data support an increased risk of AML in patients treated with nucleoside analogs and alkylating agents.<sup>20-22</sup> The potential factors leading to an increased risk of developing other indolent lymphoma subtypes and myeloma are rather unclear. This risk could be explained by a true common environmental factor or genetic predisposition, but it could also be due to misclassification. For example, bone marrow biopsies of patients with WM after treatment with anti-CD20 antibodies might mimic multiple myeloma because the CD20-positive B-cell component would have decreased but the clonal plasma cell population might remain. Similarly, patients with WM who relapse without a significant increase in immunoglobulin M levels might have been erroneously labeled with marginal zone lymphoma or atypical follicular lymphoma (FL).

We noted that the risk of solid SMs was particularly elevated for lung cancer, urinary tract cancer (including kidney cancer), and melanoma, and this is intriguing in the context of emerging data showing that evasion of immune surveillance plays a particularly important role in all those neoplasms and is mediated by overexpression of programmed death ligand 1.<sup>23</sup> Both humoral immunity and T cell-dependent immunity are known to be deregulated in WM, although the mechanisms and consequences of this deregulation remain poorly understood.<sup>24-26</sup> Whether cancers occurring in the setting of antecedent WM commonly engage immune evasion and how they might respond to treatment with immune checkpoint inhibitors highly active in melanoma, kidney cancer, and lung cancer remain to be evaluated.<sup>27-29</sup>

A previous study using SEER data reported an increased risk of SMs with other low-grade lymphoproliferative disorders such as FL and chronic lymphocytic leukemia (CLL).<sup>10</sup> It is interesting to note that, similarly to patients with WM, the risk of lung cancer, melanoma, aggressive lymphoma (DLBCL), and acute leukemia (AML) was increased in patients with FL and CLL. Also, the risk of thyroid cancer was increased in CLL patients but not in FL patients. This speaks in favor of similar bio-

logical behavior in these low-grade B-cell processes. However, whether these similarities are due to specific patterns of antigenic stimulation and/or genetic predisposition is unclear. Smaller studies evaluating the risk of SMs in patients with marginal zone lymphoma have rendered mixed results.<sup>30,31</sup>

Our study carries a series of limitations. First, some differences (eg, in the racially stratified analysis) were not significant because of large CIs, which reflected a lack of precision due to the small subgroup size. Second, the SEER database did not provide information on whether the patients received systemic chemotherapy or not and how this affected the MP-SIRs. Additional research using the SEER-Medicare database or large multi-institutional registry studies could potentially help in answering these areas of uncertainty. Third, our study includes patients who were diagnosed with the Revised European-American Lymphoma classification in 1990s and with the WHO classification in the 2000s. However, the diagnostic criteria for LPL and WM did not vary greatly between these classification systems. Furthermore, the risks for SMs between patients with WM diagnosed before and after 2000 were not statistically different. Fourth, the results of our study could have been affected by a detection bias because staging imaging for WM might have increased the rate of detection of SMs. We minimized this bias by excluding all SMs diagnosed within the first 3 months of the WM diagnosis.

In conclusion, patients with WM have a 49% higher risk of SMs than the general US population. Further research is needed to elucidate the increased incidence of AML and DLBCL (which possibly result from therapy and transformation, respectively) and melanoma and lung, urinary tract, and thyroid cancers (possibly associated with defective immune surveillance).

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#### CONFLICT OF INTEREST DISCLOSURES

Steven P. Treon has worked as a consultant to Pharmacyclics, Inc, Janssen Pharmaceuticals, Inc, and Onyx, Inc, outside the submitted work.

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