

# Chronic Immune Stimulation and Subsequent Waldenström Macroglobulinemia

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**Background:** Certain autoimmune and infectious conditions are associated with increased risks of subtypes of non-Hodgkin lymphoma. A few previous studies suggest that chronic inflammation may particularly elevate risk of the distinct non-Hodgkin lymphoma subtype Waldenström macroglobulinemia (WM).

**Methods:** We assessed WM risk in relation to a variety of chronic immune stimulatory conditions in 4 million US veterans. We identified 361 patients with WM with up to 27 years of follow-up. Using time-dependent Poisson regression, we estimated rate ratios (RRs) and 95% confidence intervals (CIs) for WM risk in relation to history of autoimmune diseases that typically have autoantibodies (with systemic or organ involvement) or do not have autoantibodies, infections, and allergies. All the models were adjusted for attained age, calendar year, race, number of hospital visits, and latency between study entry and exit.

**Results:** The age-standardized incidence of WM was 0.34 per 100 000 person-years. Risk of WM was elevated in individuals with any previous autoimmune condition (RR, 2.23; 95% CI, 1.68-2.97), autoantibodies with systemic involvement (2.50; 1.55-4.02), or autoantibodies with organ involvement (2.30; 1.57-3.37). Risks of WM were also increased with hepatitis (RR, 3.39; 95% CI, 1.38-8.30), human immunodeficiency virus (12.05; 2.83-51.46), and rickettsiosis (3.35; 1.38-8.14).

**Conclusions:** In the largest investigation of WM risk factors to date, we found a 2- to 3-fold elevated risk of WM in persons with a personal history of autoimmune diseases with autoantibodies and notably elevated risks associated with hepatitis, human immunodeficiency virus, and rickettsiosis. These findings provide novel insights into the still unknown etiology of WM.

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**W**ALDENSTRÖM MACROGLOBULINEMIA (WM) is a distinct B-cell subtype of non-Hodgkin lymphoma (NHL) characterized by lymphoplasmacytic infiltration of the bone marrow and a monoclonal IgM protein.<sup>1,2</sup> Patients often present initially with nonspecific symptoms. The most common symptoms are fatigue and malaise attributable to anemia. Other findings may include hepatomegaly (20% of patients), splenomegaly (15%), lymphadenopathy (15%-20%), hyperviscosity (15%), and peripheral neuropathy (20%).<sup>3</sup> Typically, clinical symptoms are attributable to the extent of tumor infiltration and to elevated monoclonal IgM levels.<sup>4</sup>

Based on data from the Surveillance, Epidemiology, and End Results (SEER) Program, WM is a rare malignancy, affecting 3 to 4 of every 1 million people in the United States annually.<sup>5,6</sup> In the SEER Program, white individuals seem to have a higher incidence rate than black individuals, and risk increases with age.<sup>5,6</sup> Indi-

viduals with a history of the precursor condition monoclonal gammopathy of undetermined significance (MGUS) of IgM class have an elevated risk of WM, other types of lymphomas, or related disorders.<sup>7</sup> Based on data from the Mayo Clinic, risk of progression from MGUS to WM is associated with the initial monoclonal protein concentration.<sup>8</sup> Reports of multiply affected families from case series and smaller single-center studies suggest that genetic factors may contribute.<sup>9-16</sup> Although the first genomewide linkage analysis<sup>17</sup> based on 11 high-risk WM families was recently conducted, the genetic determinants of WM susceptibility remain to be defined.

Small case studies<sup>18,19</sup> of patients with WM have found immunoglobulin gene mutations that suggest a role for repeated antigenic stimulation in the etiology of WM. Indeed, a recent study<sup>20</sup> on hepatitis C virus (HCV) infection in US military veterans found an almost 3-fold increased risk of WM in HCV-infected compared with uninfected individuals. The study also found a slight increase in MGUS

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incidence, which may suggest that HCV infection drives progression from MGUS to WM through chronic immune stimulation.<sup>20</sup> In addition, the incidence of lymphoma increases notably with age for most subtypes.<sup>6</sup> This pattern suggests that chronic inflammation, which is associated with older age and cancer,<sup>21,22</sup> may be a potential risk factor.<sup>6</sup> Thus, it may be important to evaluate a broad range of infectious diseases that could increase the risk of WM through chronic inflammation and immune stimulation. Finally, autoimmune disease is another important source of chronic immune stimulation. Although autoimmune disease is associated with lymphomas overall,<sup>23-25</sup> the association between autoimmune disease and WM has not been well examined. To our knowledge, only 1 previous small case-control study<sup>26</sup> of 65 cases has evaluated WM risk in relation to autoimmunity. Analysis of all conditions combined found no association with WM risk. However, because of the restricted sample size, autoimmune conditions could not be analyzed individually.

To address these gaps and further explore underlying pathologic mechanisms, we conducted a study of WM risk in a cohort of 4 million adult male military veterans admitted to US Veterans Affairs (VA) hospitals. This study is the largest to date to evaluate a wide range of chronic immune stimulatory conditions in relation to WM risk.

## METHODS

### PATIENTS, OUTCOMES, AND EXPOSURES

The study population came from a pool of approximately 30 million US veterans entitled to VA hospital admission during the study period.<sup>27</sup> The cohort was identified from the VA database of inpatient records from 142 US VA hospitals between July 1, 1969, and September 30, 1996. Eligible patients included male white or black US veterans 18 years or older with at least 1 hospitalization during the study period. They also had to be cancer free during the first year of follow-up and had to survive at least 1 year after the initial visit. Other ethnic/racial groups and females were excluded given their limited representation. The National Institutes of Health Office of Human Subjects Research granted exemption from institutional review board review and waived informed consent because the study was restricted to existing data that were stripped of personal identifiers.

The eighth and ninth revisions of the *International Classification of Diseases (ICD-8-A and ICD-9-CM)* were used to code diagnoses for WM (coded 275.5 and 273.3, respectively) and for specific autoimmune, infectious, and allergic conditions. In accord with previous studies,<sup>23</sup> autoimmune conditions were categorized as those that generally have detectable autoantibodies and those that do not. Bacterial, viral, parasitic, and total infections were analyzed as combined categories. Results for individual immune stimulatory conditions are presented only if 3 or more people with the condition developed WM.

### STATISTICAL ANALYSIS

For all the patients, person-time began 1 year after the index hospital discharge and continued until diagnosis of the first malignancy (WM), death, or the end of the observation period (September 30, 1996), whichever came first. Dates of death were ascertained from record linkage to Social Security Administra-

tion mortality files. The length of time from diagnosis of a chronic immune stimulatory condition (autoimmunity, infections, and allergies) to the development of WM was calculated by subtracting the date of the first hospital discharge diagnosis for an immune stimulatory condition from the date of the first hospital discharge diagnosis of WM.

Incidence rates for WM were age standardized to the 2000 US population distribution (<http://factfinder.census.gov/>). Rate ratios (RRs) and 95% confidence intervals (CIs) for the association between chronic immune stimulatory conditions and risk of WM were calculated using time-dependent Poisson regression<sup>28</sup> (AMFIT module in Epicure version 1.4) adjusting for attained age (<40, 40-49, 50-59, 60-69, 70-79, ≥80 years), calendar year (1969-1974, 1975-1979, 1980-1984, 1985-1989, and 1990-1996), race (black vs white), number of hospital visits (1-2, 3-4, ≥5 times), and latency between study entry and exit (2-3, 4-5, 6-9, 10-14, ≥15 years). All *P* values and CIs were 2-sided.

To evaluate the potential for reverse causality (ie, undetected WM causing the immune-related conditions), models were stratified by latency (time in the cohort) of 5 years or less and more than 5 years for conditions with more than 10 exposed cases and at least 3 in each stratum (≤5 and >5 years). Modification of the RRs for these conditions and WM by latency was formally evaluated using the likelihood ratio test (LRT) for multiplicative interaction. For conditions of particular interest with fewer than 10 exposed cases, we described the time between exposure and WM for the exposed cases. We evaluated models stratified by median calendar time (before 1985 and 1985 and later) using the strategy described previously herein (>10 exposed cases, >2 in each stratum) to assess whether the estimates were stable across time, and the results were very similar before and after 1985. Because the incidence of WM varies by race,<sup>5,6</sup> we also stratified the models by race.

## RESULTS

There were 361 patients with WM in this cohort of hospitalized veterans with mean follow-up of 12 years (**Table 1**). The age-standardized incidence rate for WM was 0.34 per 100 000 person-years. There was some evidence that the rate was lower in black patients (0.26 per 100 000 person-years) than in white patients (0.37 per 100 000 person-years), corresponding to an RR of 0.74 (95% CI, 0.54-1.01).

Autoimmune disease was associated with a 2- to 3-fold increase in risk of subsequent WM (**Table 2**). The RR for autoimmune disease overall was 2.23 (95% CI, 1.68-2.97). Much of this increase seemed to be due to autoimmune diseases that generally have detectable autoantibodies (RR, 2.50; 95% CI, 1.55-4.02 for systemic involvement and 2.30; 1.57-3.37 for organ involvement). However, Crohn disease, which does not have detectable autoantibodies, seemed to be very strongly associated with WM (RR, 6.68; 95% CI, 2.76-16.20), although the estimate was imprecise because there were only 5 exposed cases. The relation between WM and immune thrombocytopenic purpura (ITP) was also strong (RR, 6.88; 95% CI, 2.84-16.64), and Sjögren syndrome produced the most prominent association with WM (13.59; 4.36-42.41), although it was based on small numbers.

The RRs for WM associated with autoimmune conditions tended to be higher for latency of 5 years or less compared with more than 5 years (Table 2). For ex-

**Table 1. Characteristics of the Study Cohort (US Veterans Affairs): White and Black Male Veterans With at Least 1 Hospital Admission Between July 1, 1969, and September 30, 1996, and Followed Up for More Than 1 Year**

Characteristic	White Patients		Black Patients	
	Non-WM (n=3 668 667)	WM (n=316)	Non-WM (n=832 250)	WM (n=45)
Age at study entry, mean, y <sup>a</sup>	51.1	61.0	47.7	53.2
Follow-up, mean, y <sup>b</sup>	11.7	7.4	11.9	7.5
Person-years at risk <sup>b</sup>	42 759 826	2352	9 888 663	338
Hospital visits, median, No.	3	4 <sup>c</sup>	3	4 <sup>c</sup>

Abbreviation: WM, Waldenström macroglobulinemia.

<sup>a</sup>Age at first discharge record for inpatient hospitalization at Veterans Affairs hospitals between July 1, 1969, and September 30, 1996.

<sup>b</sup>Follow-up started 1 year after the first hospital visit.

<sup>c</sup>Includes visits up to the exit date.

ample, the RR for total autoimmune disease was 4.01 (95% CI, 2.06-6.18) for 5 years or less vs 1.61 (1.11-2.34) for more than 5 years (LRT  $P=.002$ ). Numbers were too small to evaluate Sjögren syndrome, ITP, and Crohn disease in stratified latency models, but the mean time between exposure and WM was fairly short for Sjögren syndrome and ITP: 2.2 years (median, 0.9 years; range, 0.3-5.4 years) and 2.6 years (median, 2.1 years; range, 0.8-4.2 years), respectively. However, the mean time between exposure and WM was 9.2 years for Crohn disease (median, 9.9 years; range, 0.7-18.1 years).

The RR for autoimmune disease and WM in black patients was lower than that in white patients, but there was no indication of multiplicative interaction between race and autoimmune disease (LRT  $P=.41$ ) (**Figure**). Only 4 black patients had both autoimmune disease and WM.

Infectious diseases generally did not seem to be associated with increased risk of WM, with a few exceptions: hepatitis (RR, 3.39; 95% CI, 1.38-8.30), human immunodeficiency virus (HIV) (12.05; 2.83-51.46), and rickettsiosis (3.35; 1.38-8.14) (**Table 3**). There was also some evidence of a positive association between herpes zoster and WM (RR, 2.30; 95% CI, 0.95-5.58). There were no apparent associations with grouped bacterial (RR, 1.13; 95% CI, 0.87-1.51), viral (1.39; 0.87-2.22), or parasitic (1.24; 0.77-2.02) infections or with infections overall (0.92; CI, 0.74-1.15).

In contrast to the latency pattern for autoimmune conditions, the RRs for infectious conditions were fairly similar for latency of 5 years or less compared with more than 5 years (Table 3). The RRs seemed to be somewhat elevated in the 5 years or less group for chronic sinusitis and tuberculosis, although there was little evidence of multiplicative interaction (LRT  $P=.47$  and  $.20$ , respectively). The mean time between exposure and WM was 3.4 years for hepatitis (median, 2.9 years; range, 0.1-7.9 years), 9.8 years for gingivitis and periodontitis (median, 6.8 years; range, 0.1-24.1 years), 1.6 years for HIV (median, 1.1 years; range, 1.1-2.7 years), 4.2 years for rickettsiosis (median, 1.4 years; range, 0.7-15.4 years), and 4.7 years for herpes zoster (median, 4.7 years; range, 1.5-7.4 years).

For infectious diseases, the RRs from models restricted to black individuals were higher than those from models restricted to white individuals (Figure). There was some evidence of multiplicative interaction between race

**Table 2. Risk of Waldenström Macroglobulinemia (WM) in Relation to Previous Personal History of Selected Autoimmune Diseases<sup>a</sup>**

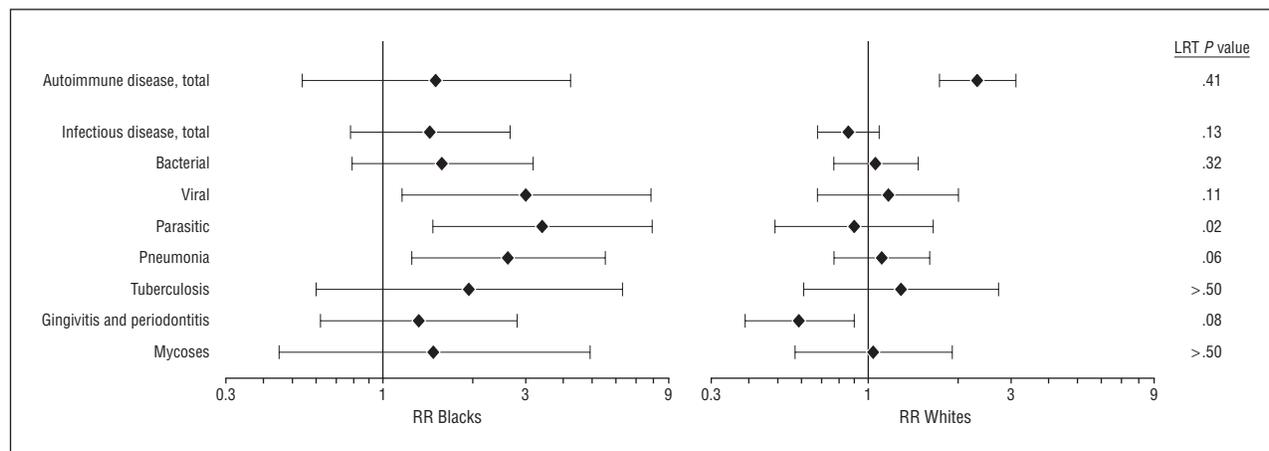
Category/Group	Patients Exposed, No.		RR (95% CI)
	Non-WM	WM	
Autoantibodies detectable			
Systemic involvement, total <sup>b</sup>	66 290	18	2.50 (1.55-4.02)
Systemic involvement, by latency <sup>c</sup>			
≤5 y	15 459	8	3.60 (1.68-7.74)
>5 y	50 831	10	2.08 (1.14-3.82)
Rheumatoid arthritis, total	59 463	14	2.09 (1.22-3.57)
Rheumatoid arthritis, by latency <sup>c</sup>			
≤5 y	13 642	7	3.32 (1.46-7.55)
>5 y	45 821	7	1.63 (0.80-3.30)
Sjögren syndrome	1 887	3	13.59 (4.36-42.41)
Organ involvement, total <sup>b</sup>	137 376	30	2.30 (1.57-3.37)
Organ involvement, by latency <sup>c</sup>			
≤5 y	37 326	14	3.89 (2.19-6.91)
>5 y	100 050	16	1.66 (1.00-2.77)
Chronic rheumatic heart disease, total <sup>b</sup>	64 969	13	1.94 (1.12-3.39)
Chronic rheumatic heart disease, by latency <sup>c</sup>			
≤5 y	18 710	4	2.18 (0.80-5.91)
>5 y	46 259	9	1.86 (0.95-3.62)
Immune thrombocytopenic purpura	9 187	5	6.88 (2.84-16.64)
Multiple sclerosis	19 365	3	1.92 (0.61-5.99)
Pernicious anemia	9 241	4	2.32 (0.74-7.20)
Autoantibodies not detectable, total <sup>b</sup>	106 627	15	1.38 (0.80-2.35)
Autoantibodies not detectable, by latency <sup>c</sup>			
≤5 y	20 389	5	2.02 (0.82-4.95)
>5 y	86 238	10	1.17 (0.60-2.27)
Crohn disease	9 339	5	6.68 (2.76-16.20)
Psoriasis	40 664	4	0.97 (0.36-2.31)

Abbreviations: CI, confidence interval; RR, rate ratio.

<sup>a</sup>All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.

<sup>b</sup>Includes individual conditions for which fewer than 3 people with the exposure developed WM.

<sup>c</sup>Time between the first inpatient discharge listing the defined condition and subsequent WM. Likelihood ratio test  $P$  values for interaction with latency were  $.28$  for systemic involvement,  $.21$  for rheumatoid arthritis,  $.04$  for organ involvement,  $>.50$  for chronic rheumatic heart disease, and  $.35$  for autoantibodies not detectable.



**Figure.** Forest plots of the rate ratios (RRs) for specific conditions and subsequent Waldenström macroglobulinemia in black and white patients. The likelihood ratio test (LRT) provides a formal evaluation of the difference in RRs by race. Error bars indicate confidence intervals. All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.

and parasitic infections (LRT  $P = .02$ ), pneumonia (LRT  $P = .06$ ), and gingivitis and periodontitis (LRT  $P = .08$ ), although the estimates were imprecise. Of the infections included in the Figure, black patients had a higher percentage of the infectious conditions than did white patients (**Table 4**). However, the percentage of infections was generally only 1% to 2% higher in black vs white non-WM patients but approximately 3% to 14% higher in black vs white patients with WM (Table 4).

Twenty-two patients with WM had allergies, including 10 with asthma, 5 with dermatitis, and 2 with urticaria. Overall, allergy was not associated with WM (RR, 1.03; 95% CI, 0.67-1.60). The RRs were 0.53 (95% CI, 0.22-1.29) for dermatitis and 1.28 (0.68-2.40) for asthma. The RRs for allergy by latency were the same (LRT  $P > .50$ ). The data were too sparse to evaluate allergies by race.

In a subanalysis, we found that 19 of the 361 patients with WM (5%) had a previously reported MGUS diagnosis. There is likely a very high degree of underascertainment of MGUS in the database because MGUS is generally an asymptomatic condition. Also, this patient population was never systematically screened for MGUS.

#### COMMENT

In the first large, systematic assessment of immune-related risk factors in relation to risk of WM, we found that autoimmune conditions, such as rheumatoid arthritis, Sjögren syndrome, and Crohn disease, were positively associated with WM, consistent with previous studies of NHL overall.<sup>24,25</sup> Infections generally did not seem to be associated with WM risk, with a few exceptions, and allergies were not associated, although power was limited.

To our knowledge, the only previous study of chronic immune stimulatory conditions and WM is a case-control study<sup>26</sup> of 65 patients with WM and 213 hospital controls that could not evaluate specific individual immune-related conditions owing to the small number of cases. We found that the risk of WM was elevated 2- to 3-fold for autoimmune disorders with detectable autoantibodies but not for those without detectable autoantibodies. Thus, associations with WM may vary by cat-

egory of autoimmune disease. We also found that specific autoimmune diseases—Sjögren syndrome, ITP, and Crohn disease—were the most strongly associated with WM risk, although these estimates were imprecise.

Based on small numbers, we found a prominent 14-fold risk of WM in persons with Sjögren syndrome. Previous studies<sup>25</sup> have consistently shown an increased risk of B-cell NHL in patients with Sjögren syndrome. Anatomically, these lymphomas are typically of indolent NHL subtypes, often of the mucosa-associated lymphoid tissue type.<sup>25</sup> Recently, there has been some evidence that patients with Sjögren syndrome might also have an elevated risk of other lymphomas, such as diffuse large B-cell and anaplastic large T-cell lymphomas.<sup>29</sup> To our knowledge, this study is the first to report an association between Sjögren syndrome and WM.

The present study and the previous study by Linet et al<sup>26</sup> found no association between infectious diseases overall and WM. However, in the present study, we evaluated specific individual infections and found that some (eg, hepatitis, HIV, and rickettsiosis) were associated with an increased risk of WM. This study expands on the previous analysis of HCV and risk of WM by demonstrating that hepatitis B was also associated with WM, supporting the hypothesis that infection with hepatitis viruses may cause chronic immune stimulation, leading to the development of WM.<sup>20</sup> To our knowledge, we are the first to find that HIV was associated with increased WM risk. This observation is consistent with the large body of literature that shows that HIV is associated with highly elevated risks of B-cell NHLs.<sup>30</sup> The association with rickettsiosis is unexpected, especially because rickettsiosis is rare. Patients with rickettsial pathogens can show symptoms of lymphadenopathy,<sup>31</sup> which may indicate activation of the immune system, leading to chronic immune stimulation. Alternatively, hospitalization due to rickettsiosis may suggest the presence of an underlying immune deficit, leading to the diagnosis of WM.

This study is also the first to evaluate the effect of race on the association between chronic immune stimulatory conditions and WM. The risk of WM associated with infections was consistently higher in black patients than

**Table 3. Risk of Waldenström Macroglobulinemia (WM) in Relation to Previous Personal History of Selected Infectious Diseases<sup>a</sup>**

Category/Group	Patients Exposed, No.		RR (95% CI)
	Non-WM	WM	
<b>Upper airway</b>			
Acute bronchitis/bronchiolitis	89 592	10	0.86 (0.43-1.74)
Chronic sinusitis, total	74 924	11	1.49 (0.79-2.80)
Chronic sinusitis, by latency <sup>b</sup>			
≤5 y	13 497	4	2.22 (0.70-7.00)
>5 y	61 427	7	1.30 (0.61-2.77)
Nasopharyngitis/pharyngitis	54 541	7	1.23 (0.50-2.98)
<b>Lower airway</b>			
Pneumonia, total	362 543	47	1.27 (0.92-1.77)
Pneumonia, by latency <sup>b</sup>			
≤5 y	268 002	17	1.35 (0.74-2.46)
>5 y	82 357	30	1.24 (0.84-1.85)
Tuberculosis, total	82 357	11	1.43 (0.78-2.69)
Tuberculosis, by latency <sup>b</sup>			
≤5 y	19 333	4	2.61 (0.96-7.11)
>5 y	63 024	7	1.09 (0.49-2.47)
<b>Gastrohepatic</b>			
Cholangitis/cholecystitis	32 922	4	0.98 (0.37-2.64)
Hepatitis virus, total	45 967	6	3.39 (1.38-8.30)
Hepatitis B virus	14 727	3	5.56 (1.76-17.54)
Intestinal	70 599	7	0.90 (0.40-2.02)
<b>Genital</b>			
Syphilis	49 309	5	1.15 (0.47-2.81)
<b>Reproductive</b>			
Orchitis and epididymitis	48 968	5	0.91 (0.37-2.19)
<b>Urinary</b>			
Cystitis	39 289	6	1.21 (0.54-2.73)
Pyelonephritis	31 808	3	0.91 (0.29-2.83)
<b>Cardiovascular</b>			
Endocarditis, total	104 732	14	1.08 (0.59-1.98)
Endocarditis, by latency <sup>b</sup>			
≤5 y	25 707	5	1.29 (0.47-3.52)
>5 y	79 025	9	0.99 (0.46-2.11)
<b>Systemic</b>			
HIV	14 736	3	12.05 (2.83-51.46)
Septicemia	72 798	8	1.19 (0.56-2.51)
<b>Other</b>			
Gingivitis and periodontitis, total	479 190	37	0.69 (0.48-0.99)
Gingivitis and periodontitis, by latency <sup>b</sup>			
≤5 y	72 949	8	0.77 (0.36-1.65)
>5 y	406 241	29	0.67 (0.45-1.01)
Herpes zoster	18 992	5	2.30 (0.95-5.58)
Mycoses	175 519	16	1.10 (0.65-1.90)
Rickettsiosis	22 068	5	3.35 (1.38-8.14)
Osteomyelitis	57 757	7	1.13 (0.50-2.55)
Skin and soft-tissue infections, total	297 226	27	0.97 (0.64-1.46)
Skin and soft-tissue infections, by latency <sup>b</sup>			
≤5 y	53 122	10	1.43 (0.69-2.93)
>5 y	244 104	17	1.84 (0.51-1.38)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; RR, rate ratio.

<sup>a</sup>All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.

<sup>b</sup>Time between the first inpatient discharge listing the defined condition and subsequent WM. Likelihood ratio test *P* values for interaction with latency were .47 for chronic sinusitis, >.50 for pneumonia, .20 for tuberculosis, >.50 for endocarditis, >.50 for gingivitis and periodontitis, and .25 for skin and soft-tissue infections.

in white patients, which is surprising given that the incidence of WM is lower in black patients than in white patients. If true, some other risk factor must be driving the risk in whites. It is possible that the pattern of elevated RRs for infections in black patients might reflect

**Table 4. Selected Infectious Conditions in Black and White Patients With and Without Waldenström Macroglobulinemia (WM)**

Infectious Condition	Patients, No. (%)			
	WM		Non-WM	
	Black (n=45)	White (n=316)	Black (n=832 250)	White (n=3 668 667)
Bacterial	11 (24)	53 (17)	142 023 (17)	438 156 (12)
Viral	6 (13)	16 (5)	40 825 (5)	143 894 (4)
Parasitic	7 (16)	13 (4)	52 930 (6)	150 971 (4)
<b>Lower airways</b>				
Pneumonia	10 (22)	37 (12)	72 617 (9)	289 926 (8)
Tuberculosis	3 (7)	8 (3)	26 760 (3)	55 597 (2)
<b>Other</b>				
Gingivitis and periodontitis	10 (22)	27 (9)	103 739 (12)	375 451 (10)
Mycoses	3 (7)	13 (4)	46 643 (6)	128 876 (4)

racial differences in immune responses to infectious agents.<sup>32-34</sup> However, given the number of exposures evaluated, these findings have to be interpreted with caution because they could be due to chance.

To evaluate the possibility that WM may have been present before diagnosis of the chronic immune stimulatory conditions and may have actually caused these conditions (ie, reverse causality), we stratified by latency of 5 years or less and more than 5 years. For autoimmune disease, the increase in the risk of WM was evident mainly in the 5 years before WM, and some conditions were diagnosed less than 1 year before WM diagnosis. These patterns suggest that in some patients, the autoimmune disease could be a manifestation of underlying undetected WM, especially considering that WM often has a long latency period.<sup>35</sup> In particular, ITP is a recognized complication of WM.<sup>36,37</sup> However, because the risk of WM in patients with autoimmune diseases remained elevated after 5 years, similar to the results of a population-based study<sup>24</sup> of NHL in Denmark and Sweden, we believe that these findings are not entirely due to undetected WM. Clinical workup for the suspicion of an autoimmune disease typically includes a complete blood cell count and may include protein electrophoresis, which should lead to WM diagnosis at or shortly after onset of the autoimmune disease. Although some autoimmune diseases did have a relatively short median time to WM diagnosis (eg, ITP and Sjögren syndrome), others did not (eg, Crohn disease). We do not have access to individual detailed clinical data that would allow us to evaluate the role of previous diagnosis of MGUS or undetected early-stage WM directly. Thus, future epidemiologic studies must verify these findings through medical record validation of clinical, diagnostic, prognostic, and treatment data.

For infections, the similarity in RRs for latency of 5 years or less and more than 5 years argues against reverse causality for this group of chronic immune stimulatory conditions. Although the data for many individual infectious conditions were too sparse to stratify by latency, the relatively short medians for some conditions suggest that interpretation requires caution. For example, the median time to WM diagnosis was approxi-

mately 1 year for rickettsiosis and HIV, which could reflect detection bias (ie, rickettsiosis or HIV detected owing to workup for WM). On the other hand, the short time to WM diagnosis for HIV may reflect the fact that a separate ICD code for HIV was not added until 1987, resulting in a shorter amount of time available for the diagnosis of HIV and WM.

Chronic immune stimulatory conditions may contribute to lymphomagenesis through persistent activation of lymphocytes, leading to a reduced antigen response, increased mutation rates, and a downregulated T-cell response, potentially disrupting the immune response to pathogens and malignant cells.<sup>38,39</sup> Although further studies are needed, the present findings support the hypothesis that chronic immune stimulation may contribute to the development of WM.

This study has some limitations. First, these results may not be generalizable to the US population. It is, however, encouraging that the age-adjusted rates of WM in this cohort are similar to those found for males in the SEER Program overall (0.35 per 100 000 person-years in the present study vs 0.35 per 100 000 person-years in the SEER Program),<sup>5</sup> in white patients (0.37 per 100 000 person-years in the present study vs 0.36-0.56 per 100 000 person-years in the SEER Program),<sup>5,6</sup> and in black patients (0.26 per 100 000 person-years in the present study vs 0.17-0.25 per 100 000 in the SEER Program).<sup>5,6</sup> Because the data are based on hospital claims, it is possible that some conditions might have developed before the patient entered the VA system. The definition of WM is limited by the fact that the ICD-8-A code for WM was not entirely specific but also included macroglobulinemia (ie, MGUS type IgM); by the lack of review for WM cases and immune-mediated conditions because demographic, clinical, treatment, laboratory, and biomarker information were unavailable; and by revisions in the definition of WM with time (eg, it was not reportable as a malignancy in the United States until 1988<sup>40</sup>). However, as mentioned previously herein, the risk estimates were similar when stratified by calendar period, suggesting that these limitations have not introduced any major bias. Because we did not have treatment data, we could not evaluate potential confounding by immunosuppressive therapy, which is used to treat severe autoimmune disease and is also associated with the development of lymphoma.<sup>41</sup> Because the clinical workup of immune-related diseases might include protein electrophoresis, it is possible that some of the present results for autoimmune conditions are overestimated owing to surveillance bias: patients with autoimmune disease may be more likely to have WM diagnosed than patients without autoimmune disease. Also, one has to keep in mind that all patients (with and without WM) in this cohort were hospitalized, which presumably led to more clinical workup than in the general population. For this reason, we did not use external controls but instead applied a cohort study design, allowing us to use internal controls. Although this cohort included more than 4 million patients, the rarity of WM and of some of the chronic immune stimulatory conditions evaluated limited analyses and led to imprecision in some estimates. Mul-

iple comparisons may result in chance findings. Furthermore, exposures that have been discovered recently (eg, HCV in 1989 and HIV in 1983) and less severe autoimmune and infectious conditions that do not lead to hospitalization may not be well represented.

The strengths of this study include its extensive follow-up in a patient population with access to standardized medical care that does not depend on socioeconomic status. Furthermore, there is no recall bias because the exposure information is obtained from medical records. Because of the size of this population, we could evaluate the incidence of WM in black patients and provide the first analysis of risk factors for WM in black patients.

In summary, we found that WM is associated with autoimmune diseases, especially those with detectable autoantibodies, in the largest study of chronic immune stimulatory conditions and WM to date. Patients with specific infectious diseases, such as hepatitis, HIV, and rickettsiosis, also seemed to be at increased risk for WM. These results suggest that chronic immune stimulation plays an important role in the etiology and pathogenesis of WM. Better characterization of the mechanisms that mediate clonal proliferation and survival will ultimately enhance our understanding of the pathogenesis of WM, provide clues to etiology, and allow identification of novel molecular targets.

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**Author Contributions:** Dr Koshiol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Landgren. *Acquisition of data:* Gridley. *Analysis and interpretation of data:* Koshiol, Gridley, Engels, McMaster, and Landgren. *Drafting of the manuscript:* Koshiol and Landgren. *Critical revision of the manuscript for important intellectual content:* Koshiol, Gridley, Engels, McMaster, and Landgren. *Statistical analysis:* Koshiol, Gridley, and Engels. *Obtained funding:* Gridley. *Administrative, technical, and material support:* Koshiol, McMaster, and Landgren. *Study supervision:* Landgren.

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