Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders

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In a retrospective cohort of more than 4 million white and black male United States (US) veterans, we explored the role of specific prior autoimmune, infectious, inflammatory, and allergic disorders in the etiology of multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS). Patients were selected from computerized inpatient discharge records at US Veterans Affairs hospitals. The analysis included 4641 patients (3040 white, 1601 black) and 2046 patients (1312 white; 734 black) with a discharge diagnosis of MM and MGUS, respectively. Using Poisson regression, we calculated age-adjusted relative risks (RRs) and 95% confidence intervals (CIs) for the relationship between MM, MGUS, and specific prior medical conditions. Significantly elevated risks of MM were associated with broad categories of autoimmune (RR, 1.15; 95% CI, 1.02-1.28), infectious (RR, 1.29; 95% CI, 1.20-1.38), and inflammatory disorders (RR, 1.18; 95% CI, 1.10-1.27) and specific prior autoimmune (polymyositis/dermatomyositis, systemic sclerosis, autoimmune hemolytic anemia, pernicious anemia, and ankylosing spondylitis), infectious (pneumonia, hepatitis, meningitis, septicemia, herpes zoster, and poliomyelitis), and inflammatory (glomerulonephritis, nephrotic syndrome, and osteoarthritis) disorders. Risks for MGUS were generally of similar magnitude. Our results indicate that various types of immune-mediated conditions might act as triggers for MM/MGUS development. (Blood. 2008;111: 3388-3394)

Introduction

Multiple myeloma (MM) is a B-cell malignancy morphologically characterized by a monoclonal proliferation of plasma cells in the bone marrow. Diagnostic criteria also require evidence of hypercalcemia, renal insufficiency, anemia, or bone lesions.[1] MM is an incurable disease reflected in an average survival of 3 to 4 years with standard treatment; however, survival can range from only a few months to more than 10 years.[2,3] According to estimates provided by the American Cancer Society, almost 19 900 new MM diagnoses and 10 800 MM deaths were expected in the United States (US) during 2007.[4] Incidence rates among men are 1.5 times higher than among women and 2 times higher among African Americans than among whites; however, the etiology of MM is elusive. A typically clinically asymptomatic precursor condition, monoclonal gammopathy of undetermined significance (MGUS), is thought to be the first pathogenetic step in the development of most, if not all MM[5]; however, the specific trigger that initiates the progression from MGUS to MM is unknown.[5]

Several studies have investigated the hypothesis that repeated or chronic stimulation of the immune system may lead to MM.[6-9] Some studies have observed elevated risks for categories of immune-stimulating medical conditions (eg, autoimmune conditions, infections, and allergies) or for specific immune-stimulating medical conditions (eg, rheumatoid arthritis and eczema); however, results have generally been inconsistent.[7,8,10-17] Although the incidence rate of MM for 2000-2004[18] is more than twice as high in black (14.0/100 000) compared with white men (6.6/100 000), most of these studies were conducted in primarily white American or European populations and thus lacked sufficient racial diversity to assess risks separately for whites and blacks. In this paper, we use hospital discharge diagnoses from 3 669 244 white and 832 334 black US male veterans to evaluate the possible role of specific prior autoimmune, infectious, inflammatory, and allergic disorders in the etiology of MM.

Methods

Patients

Patients were selected from computerized discharge records for inpatient visits captured by the Patient Treatment File[19] from July 1, 1969, to September 30, 1996, at US Veterans Affairs (VA) hospitals. The eighth and ninth revisions of the International Classification of Diseases (ICD8-A,[20] ICD9-CM[21]) were used to code diagnoses for MM (code = 203) as well as for specific medical conditions (Table S1, available on the *Blood* website; see the Supplemental Table link at the top of the online article), which were recorded throughout the long-term follow-up of the cohort. The initial study population consisted of 26 million hospital discharge records from 5 790 493 veterans with at least one hospital visit. Due to small percentages, veterans with an age less than 18 years or older 100 (n = 2969; 0.05%), with a race other than black or white (n = 135 651; 2.3%), or of female sex (n = 112 527; 1.9%) were excluded from analysis. In addition, in order to study etiologic risk factors for incident cancers, patients who had cancer at admission or who died the day of admission (666 650; 11.5%) or developed cancer or died within the first year (371 129; 6.4%) were also excluded. Thus, the current analyses included a total of 4 501 578 veterans.

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The same methodology was used to create a data file with MGUS as the outcome variable with the exception that a specific ICD code (273.1) was only available in ICD9-CM. For more details, see Landgren et al.[22] An exemption from institutional review board (IRB) review was obtained from the National Institutes of Health (NIH) Office of Human Subjects Research because these data were analyzed without personal identifiers. In addition, there was no contact with the study patients and thus no need for informed consent.

Statistical methods

Follow-up began 1 year after the date of the first hospital discharge and continued until the end of the observation period, the diagnosis of a first cancer, or death, whichever occurred first. Dates of death were obtained from VA hospital records and by linkage to Social Security Administration mortality files. Poisson regression using the Epicure procedure AMFIT (version 1.4 [2002]; HiroSoft International Corp, Seattle, WA)[23] was used to calculate age-adjusted relative risks (RRs) and 95% confidence intervals (CIs) comparing the risk of MM/MGUS among white and black men with specific prior medical conditions with men without such conditions. RRs were adjusted for attained age (< 40 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and > 79 years), attained calendar year (1969-1974, 1975-1979, 1980-1984, 1985-1989, and 1990-1996), latency between study entry and study exit (2-3 years, 4-5 years, 6-9 years, 10-14 years, and > 14 years), number of hospital visits (< 3 visits, 3-4 visits, and 5 or more visits), and race (white or black) to control for differences in these variables between patients with and without MM/MGUS. All variables with the exception of race and number of hospital visits were treated as time-dependent variables, with person-years allocated to disease and nondisease categories as appropriate. RRs were not calculated when the number of patients with MM/MGUS was less than 5 because the RRs were likely to be unreliable. Analysis of the frequency of prior infectious disorders was carried out; however, the results were uninformative (data not shown).

Results

Included in the analysis were 4 501 578 male veterans (3 669 244 white; 832 334 black), of whom 4641 (3040 white, 1601 black) had a discharge diagnosis of MM (Table 1). Patients were followed for 1 to 27 years; average number of years of follow-up was greater for patients without MM than for patients with MM. Median age at study entry was substantially older for MM (59.9 years for white patients, 57.6 years for black patients) than for non-MM (53.5 years for white patients, 47.7 years for black patients), reflecting the older age at MM diagnosis. Median number of hospital visits was slightly higher for patients with MM (4 visits) compared with patients without MM (3 visits). A total of 2046 patients (1312 white; 734 black) had a diagnosis of MGUS. For a detailed presentation of data, see Landgren et al.[22] Of the 2046 patients with MGUS, 179 (8.7%) progressed to MM.

Risks for white and black patients combined were significantly elevated for prior autoimmune diseases, particularly those with detectable autoantibodies regardless of whether they were classified as systemic involvement or organ involvement (Table 2). Statistically elevated risks were also observed for the following specific autoimmune diseases: polymyositis/dermatomyositis, systemic sclerosis, autoimmune hemolytic anemia, pernicious anemia, and ankylosing spondylitis. Where numbers allowed comparison, risks were generally similar for white and black men.

Risks were also significantly elevated for both races combined for prior infectious disorders, specifically pneumonia, hepatitis, meningitis, septicemia, herpes zoster, and poliomyelitis (Table 3). Risk of influenza was significantly elevated for white men, but not for both races combined.

Risks associated with inflammatory disorders and allergies are presented in Table 4. There was a statistically increased risk of 18% associated with inflammatory disorders, largely due to significantly elevated risks for osteoarthritis (the most commonly reported disorder in our dataset) glomerulonephritis, and nephrotic syndrome. There were no significant elevations in risk for allergies overall or for any specific allergies for both races combined, although the risk for allergic rhinitis was elevated and of borderline significance among white men.

Shown in Table 5 are risks for autoimmune, infectious, inflammatory, and allergic disorders with significantly elevated risks from Tables 2 through 4 stratified by latency. Significantly elevated risks of MM were observed for patients with pernicious anemia, ankylosing spondylitis, pneumonia, septicemia, herpes zoster, poliomyelitis, and osteoarthritis who were followed for 10 or more years. Poliomyelitis was the only disease with an increased risk observed only for 10 or more years of follow-up. In general, risks for these specific diseases were elevated for men regardless of age at first visit (younger than 50 years vs 50 years and older), with the exception of herpes zoster, which occurred predominately in men whose first visit was at age 50 years and older (RR, 2.17; 95% CI, 1.56-3.02; n = 40; data not shown).

Risks for MGUS following selected autoimmune, infectious, inflammatory, and allergic disorders for both races combined are presented in Table 6. For most conditions, risks for MM and MGUS were of similar magnitude. Only glomerulonephritis appeared to be more strongly associated with MGUS than MM (χ^2 test of homogeneity $P < .001$). Analysis of the association between MGUS and history of prior pneumonia revealed a significantly higher risk in the latency interval of 2 to 4 years compared with latency periods of 5 to 9 years and 10 or more years (χ^2 test of homogeneity $P < .001$). Similar latency effects were observed for osteoarthritis (χ^2 test of homogeneity $P = .005$).

Table 1. Characteristics of the MM study cohort of white and black US male veterans

	Whites		Blacks	
Characteristics	**Non-MM**	**MM**	**Non-MM**	**MM**
No. of patients	3 666 204	3 040	830 733	1 601
Median age at study entry, y*	53.5	59.9	47.7	57.6
Mean y of follow-up†	11.7	7.6	11.9	8.5
Person-y at risk†	42 741 577	23 112	9 875 835	13 658
Median no. of hospital visits	3	4	3	4
Median age at MM diagnosis, y	NA	67.6	NA	66.3

NA indicates not applicable.

*Age at first discharge record for inpatient hospitalization at Veterans Affairs hospitals between July 1, 1969, and September 30, 1996.

†The first year of follow-up was censored.

Table 2. Autoimmune disease and risk of MM in white and black US male veterans

	Whites			Blacks			Combined		
	N	RR*	95% CI	N	RR*	95% CI	N	RR*	95% CI
Total autoimmune disease	256	1.14	1.00-1.31	106	1.15	0.94-1.42	362	1.15	1.02-1.28
Autoantibodies detectable	199	1.25	1.08-1.46	85	1.19	0.94-1.50	284	1.23	1.09-1.40
Systemic involvement	75	1.21	0.95-1.55	37	1.40	0.99-2.00	112	1.26	1.04-1.55
Polymyositis/dermatomyositis	3	—	—	3	—	—	6	2.29	1.03-5.09
Rheumatoid arthritis	63	1.10	0.85-1.43	31	1.34	0.91-1.98	94	1.17	0.94-1.45
Systemic lupus erythematosus	5	1.45	0.47-4.51	2	—	—	7	1.64	0.68-3.93
Systemic sclerosis	4	—	—	2	—	—	6	2.41	1.08-5.36
Organ involvement	132	1.30	1.09-1.56	51	1.07	0.80-1.43	183	1.23	1.05-1.43
Amyotrophic lateral sclerosis	6	1.25	0.52-2.99.	2	—	—	8	1.18	0.56-2.47
Autoimmune hemolytic anemia	8	3.52	1.58-7.85	3	—	—	11	2.82	1.41-5.64
Celiac disease	3	—	—	2	—	—	5	2.07	0.86-4.98
Chronic rheumatic heart disease	51	1.06	0.80-1.40	27	1.11	0.74-1.65	78	1.07	0.85-1.35
Discoid lupus erythematosus	5	1.31	0.49-3.49	3	—	—	8	1.28	0.61-2.69
Immune thrombocytopenic purpura	8	1.00	0.41-2.40	3	—	—	11	1.08	0.54-2.16
Myasthenia gravis	4	—	—	2	—	—	6	2.09	0.94-4.66
Pernicious anemia	22	2.30	1.50-3.54	5	1.68	0.70-4.05	27	2.15	1.45-3.16
Primary biliary cirrhosis	8	1.52	0.76-3.04	2	—	—	10	1.18	0.61-2.28
Autoantibodies not detectable	75	0.95	0.75-1.20	32	1.25	0.87-1.81	107	1.02	0.84-1.25
Ankylosing spondylitis	16	1.82	1.12-2.98	9	4.23	2.20-8.16	25	2.29	1.55-3.40
Hemorrhagic proctitis	18	1.21	0.73-2.01	6	0.70	0.26-1.88	24	1.05	0.67-1.65
Psoriasis	29	0.85	0.59-1.23	5	0.92	0.38-2.22	34	0.86	0.61-1.21
Sarcoidosis	0	—	—	6	1.20	0.54-2.69	6	0.92	0.42-2.07
Ulcerative colitis	7	0.81	0.39-1.71	1	—	—	8	0.78	0.39-1.56

— indicates RR and CI not calculated due to small numbers.
*RR adjusted for visits, attained age, calendar time, and latency (combined also adjusted for race).

Discussion

This study is unique in that it includes both a large black population and the comparison with the white population. We found significantly elevated risks of MM and its precursor condition MGUS associated with broad categories of autoimmune, infectious, and inflammatory disorders, but not allergies. We also found significantly elevated risks associated with a number of specific autoimmune diseases (polymyositis/dermatomyositis, systemic sclerosis,

Table 3. Infectious disorders and risk of MM in white and black US male veterans

	Whites			Blacks			Combined		
	N	RR*	95% CI	N	RR*	95% CI	N	RR*	95% CI
Total infectious disorders	764	1.37	1.25-1.50	461	1.16	1.03-1.30	1225	1.29	1.20-1.38
Respiratory system									
Sinusitis	65	1.22	0.95-1.59	23	1.02	0.66-1.59	88	1.17	0.94-1.46
Influenza	27	1.49	1.01-2.21	3	—	—	30	1.18	0.81-1.71
Nasopharyngitis/laryngitis	12	1.27	0.71-2.23	4	—	—	16	1.22	0.75-2.00
Otitis media/mastoiditis	14	1.06	0.63-1.79	4	—	—	18	1.12	0.71-1.78
Pneumonia	382	1.60	1.42-1.80	214	1.45	1.24-1.69	596	1.54	1.40-1.69
Tuberculosis	53	0.98	0.73-1.30	56	0.92	0.70-1.21	109	0.95	0.78-1.16
Digestive system									
Gastroenteritis	30	1.07	0.80-1.42	6	0.61	0.35-1.05	36	0.92	0.71-1.18
Hepatitis	19	2.22	1.39-3.54	10	1.37	0.73-2.57	29	1.82	1.25-2.65
Genitourinary system									
Cystitis	4	—	—	4	—	—	8	1.72	0.82-3.62
Gonorrhea	3	—	—	5	0.94	0.39-2.61	8	1.04	0.52-2.09
Pyelonephritis	7	0.97	0.46-2.04	7	1.13	0.53-2.37	14	1.04	0.62-1.76
Syphilis	27	1.20	0.80-1.80	62	0.98	0.75-1.27	89	1.03	0.83-1.29
Systemic									
Meningitis	9	1.89	0.90-3.96	8	2.50	1.19-5.27	17	2.15	1.27-3.64
Septicemia	70	1.63	1.25-2.12	37	1.14	0.78-1.66	107	1.43	1.15-1.77
Other									
Herpes simplex	13	1.64	0.88-3.05	3	—	—	16	1.36	0.77-2.39
Herpes zoster	35	2.12	1.48-3.02	8	1.59	0.76-3.35	43	2.00	1.45-2.75
Mycoses	95	1.05	0.85-1.31	60	1.13	0.86-1.48	155	1.08	0.91-1.28
Rickettsioses	11	1.16	0.62-2.15	15	1.27	0.72-1.24	26	1.21	0.80-1.85
Poliomyelitis	6	2.27	0.94-5.45	3	—	—	9	2.28	1.14-4.56

— indicates RR and CI not calculated due to small numbers.
*RR adjusted for visits, attained age, calendar time, and latency (combined also adjusted for race).

Table 4. Inflammatory disorders and allergies and risk of MM in white and black US male veterans

	Whites			Blacks			Combined		
	N	RR*	95% CI	N	RR*	95% CI	N	RR*	95% CI
Total inflammatory disorders	807	1.17	1.07-1.27	362	1.22	1.07-1.38	1169	1.18	1.10-1.27
Atrophic gastritis	10	1.16	0.55-2.43	5	1.54	0.64-3.72	15	1.29	0.73-2.28
Chronic bronchitis	190	0.95	0.81-1.12	67	1.06	0.82-1.38	257	0.98	0.86-1.12
Dacryadenitis	6	1.21	0.54-2.70	4	—	—	10	1.44	0.77-2.68
Dermatitis	25	0.69	0.46-1.05	6	0.91	0.41-2.02	31	0.73	0.51-1.06
Glomerulonephritis	45	1.90	1.33-2.73	35	1.02	0.68-1.51	80	1.37	1.05-1.79
Nephrotic syndrome	29	2.53	1.43-4.46	15	1.79	0.93-3.44	44	2.15	1.40-3.30
Osteoarthritis	510	1.23	1.11-1.36	232	1.36	1.17-1.57	742	1.27	1.17-1.38
Pericarditis, nonrheumatic	16	1.32	0.76-2.27	8	1.18	0.56-2.47	24	1.26	0.81-1.96
Prostatitis	17	1.01	0.60-1.67	4	—	—	21	0.87	0.55-1.40
Valvular disease, nonrheumatic	80	1.09	0.85-1.39	32	0.83	0.56-1.24	112	1.00	0.81-1.23
Total allergies	169	1.04	0.89-1.23	88	1.20	0.96-1.51	257	1.09	0.96-1.25
Allergic rhinitis	16	1.56	0.95-2.55	4	—	—	20	1.45	0.93-2.25
Asthma	51	0.87	0.65-1.17	40	1.18	0.84-1.64	91	0.98	0.79-1.22
Eczema and dermatitis	75	1.08	0.85-1.37	34	1.20	0.84-1.70	109	1.11	0.91-1.35
Erythema	24	1.05	0.69-1.60	8	0.98	0.47-1.96	32	1.03	0.72-1.48
Urticaria	8	0.79	0.35-1.76	6	1.99	0.89-4.44	14	1.13	0.64-1.99

— indicates RR and CI not calculated due to small numbers.
*RR adjusted for visits, attained age, calendar time, and latency (combined also adjusted for race).

autoimmune hemolytic anemia, pernicious anemia, and ankylosing spondylitis; however, with the exception of pernicious anemia and ankylosing spondylitis, findings were based on 8 or fewer patients), specific prior infectious disorders caused by bacteria or viruses (pneumonia, hepatitis, meningitis, septicemia, herpes zoster, and poliomyelitis), and for several inflammatory disorders (glomerulonephritis, nephrotic syndrome, and osteoarthritis).

MM typically presents with symptoms (eg, fatigue, bone pain, and recurrent infections[1]) that can be confused with other health problems. However, given that the median length of survival after diagnosis is only 3 to 4 years,[2] and we observed elevated risks of MM 5 or more years following a diagnosis of a medical condition of interest, it is unlikely that most of the associations we found were due to reverse causality (ie, undetected MM manifesting with symptoms that mimic other diseases).

Our finding of an excess risk of MM/MGUS for prior pernicious anemia is consistent with several previous epidemiologic studies[10,24,25] and case reports (for a review, see Baz et al[26]), and may result from the presence of immune alterations or chromosome abnormalities in the bone marrow of patients with pernicious anemia.[25] Alternatively, pernicious anemia may be related to the development/presence of MGUS since an increased prevalence of

Table 5. Risk of MM for selected conditions by latency in white and black US male veterans

	Follow-up 2 to 4 y			Follow-up 5 to 9 y			Follow-up 10 or more y		
	N	RR*	95% CI	N	RR*	95% CI	N	RR*	95% CI
Total autoimmune	111	1.31	1.06-1.61	99	1.14	0.91-1.41	152	1.07	0.90-1.26
Autoantibodies detectable	84	1.32	1.04-1.68	77	1.21	0.95-1.55	123	1.20	1.00-1.44
Systemic involvement	27	1.20	0.80-1.80	34	1.43	1.00-2.06	51	1.20	0.90-1.61
Polymyositis/dermatomyositis	3	—	—	2	—	—	1	—	—
Systemic sclerosis	1	—	—	4	—	—	1	—	—
Organ involvement	58	1.38	1.03-1.85	46	1.03	0.75-1.43	79	1.26	1.01-1.57
Autoimmune hemolytic anemia	4	—	—	4	—	—	3	—	—
Pernicious anemia	9	2.00	0.95-4.21	6	2.14	1.02-4.51	12	2.25	1.28-3.98
Autoantibodies not detectable	33	1.31	0.90-1.91	30	1.02	0.69-1.52	44	0.90	0.67-1.21
Ankylosing spondylitis	5	2.04	0.85-4.92	8	2.17	0.97-4.84	12	2.46	1.46-4.17
Total infections	386	1.40	1.22-1.60	311	1.26	1.10-1.45	528	1.24	1.11-1.37
Influenza	8	1.68	0.79-3.51	4	—	—	18	1.32	0.83-2.10
Pneumonia	206	1.82	1.53-2.16	148	1.50	1.25-1.80	242	1.42	1.23-1.63
Hepatitis	4	—	—	10	2.61	1.35-5.05	15	1.66	0.99-2.76
Meningitis	6	3.45	1.29-9.22	3	—	—	8	1.84	0.87-3.86
Septicemia	30	1.45	0.93-2.26	19	1.12	0.69-1.81	58	1.57	1.17-2.09
Herpes zoster	8	1.30	0.58-2.90	15	2.54	1.47-4.40	20	2.04	1.30-3.21
Poliomyelitis	2	—	—	1	—	—	6	3.69	1.75-7.75
Total inflammatory disorders	358	1.18	0.99-1.40	317	1.21	1.02-1.44	494	1.01	0.89-1.16
Glomerulonephritis	28	1.89	1.17-3.06	28	2.22	1.46-3.37	24	0.72	0.43-1.19
Nephrotic syndrome	15	3.91	2.03-7.55	18	3.15	1.57-6.33	11	0.81	0.30-2.16
Osteoarthritis	216	1.21	1.03-1.43	201	1.32	1.1.13-1.55	325	1.27	1.12-1.44
Total allergies	69	1.22	0.93-1.60	68	1.18	0.91-1.52	120	1.00	0.83-1.21
Allergic rhinitis	5	1.63	0.61-4.34	2	—	—	13	1.59	0.92-2.74

— indicates RR and CI not calculated due to small numbers.
*RR adjusted for number of visits, race, latency, attained age, and calendar time.

Table 6. Risk of MGUS for selected conditions in white and black US male veterans

	N	RR*	95% CI
Total autoimmune	303	1.67	1.47-1.90
Autoantibodies detectable	233	1.78	1.54-2.06
Systemic involvement	99	1.95	1.57-2.42
Polymyositis/dermatomyositis	5	2.39	0.89-6.36
Systemic sclerosis	6	4.21	1.89-9.38
Organ involvement	143	1.62	1.35-1.94
Autoimmune hemolytic anemia	6	2.58	1.07-6.20
Pernicious anemia	14	1.97	1.16-3.34
Autoantibodies not detectable	88	1.34	1.07-1.67
Ankylosing spondylitis	13	2.02	1.14-3.56
Total infections	779	1.40	1.27-1.53
Influenza	23	1.53	1.00-2.33
Pneumonia	415	1.72	1.53-1.93
2 to 4 y prior	179	2.48	2.05-3.00
5 to 9 y prior	121	1.46	1.18-1.80
10 or more y prior	115	1.41	1.15-1.73
Hepatitis	28	2.10	1.36-3.25
Meningitis	6	1.19	0.62-2.28
Septicemia	78	1.32	1.02-1.71
Herpes zoster	25	1.70	1.11-2.58
Poliomyelitis	3	—	—
Total inflammatory disorders	766	1.43	1.30-1.57
Glomerulonephritis	78	2.62	2.06-3.34
Nephrotic syndrome	38	2.68	1.68-4.27
Osteoarthritis	448	1.37	1.23-1.53
2 to 4 y prior	187	1.72	1.43-2.08
5 to 9 y prior	125	1.29	1.06-1.54
10 or more y prior	136	1.20	0.99-1.45

— indicates RR and CI not calculated due to small numbers.
*RR adjusted for number of visits, race, latency, attained age, and calendar time.

vitamin B12 deficiency, most commonly caused by pernicious anemia, has been reported among patients with MGUS (9%) as well as MM (17%).[26]

Ours is the first retrospective cohort study to report significantly elevated risks of MM/MGUS subsequent to the musculoskeletal disease ankylosing spondylitis. However, an association of MM or MGUS in patients with a prior history of ankylosing spondylitis was previously described in several case studies/series,[27-29] and long-term follow-up of more than 14 000 patients who received X-ray treatment for ankylosing spondylitis (mean total body dose = 2.64 Gy) revealed significantly elevated risks for MM.[30] In addition, an excess risk of MM 10, 15, and 20 years following "musculoskeletal disease not otherwise specified (NOS)" was reported in a hospital-based study.[15] Although the specific mechanism for this apparent association is not known, the early age at diagnosis of ankylosing spondylitis (primarily during adolescence or early adulthood[31]) and the long time interval between diagnosis of ankylosing spondylitis and diagnosis of MM (10 or more years) in our data, rule against ankylosing spondylitis as an early manifestation of MM. Some investigators have suggested that malignant changes resulting from prolonged plasma cell stimulation and proliferation due to elevated levels of IgA associated with ankylosing spondylitis[27] or radiation treatment for ankylosing spondylitis[30] may be related to the pathogenesis of MM; however, we were unable to investigate these factors in our study.

There is also the possibility that treatment for certain conditions rather than the condition itself may increase susceptibility to MM. For example, we previously reported an increased risk of MM among Connecticut women following use of steroids.[12] Thus, the observed association between certain prior autoimmune diseases (eg, autoimmune hemolytic anemia) and MM/MGUS in the present study may be due to treatment with high doses of steroids such as prednisone.

Our observation of an association between MM/MGUS and specific prior bacterial or viral infections suggest that these infectious conditions may be a potential trigger for MM/MGUS development[2] or a manifestation of underlying immune disturbances due to undetected MM or late-stage MGUS.[11,32] Recurrent infections largely of bacterial origin (septicemia, meningitis, and pneumonia) are often part of the natural history of MM.[32] Although there have been only a few case reports of pneumonia or meningitis as the initial manifestation of MM,[32] recent epidemiologic studies, including our study in Denmark,[11] have noted an excess risk of MM following pneumonia or meningitis.[33] Similar to the findings from the MM Denmark study, we found that prior history of pneumonia was a predictor of MGUS risk, particularly among patients with a diagnosis of pneumonia in the 5 years preceding MGUS, suggesting that pneumonia could be a precipitating event for the development of MGUS.[11]

Although the specific pathologic mechanism is not known, several viruses (eg, hepatitis and herpes virus) have been implicated in the triggering of myeloma because they can interact with plasma cells and interfere with plasma cell growth, differentiation, and cell survival. However, reports linking MM with a prior diagnosis of infection with herpes zoster[12,16,34] or hepatitis C virus (HCV)[35-37] have been inconsistent. Conversely, a high prevalence of MGUS was noted in a series of patients with chronic active hepatitis,[38] and a 30% increased risk of MGUS was noted among a cohort of patients with HCV infection.[35]

The significantly elevated risk of greater than 3.5 for patients diagnosed with poliomyelitis 10 or more years prior to MM is intriguing and unlikely due to delayed diagnosis of neurologic findings. Although poliomyelitis has not previously been associated with MM, it has been associated with other hematologic diseases.[39]

Renal failure is seen in more than 25% of patients with MM at presentation.[40] In addition, an association of nephrotic syndrome and glomerulonephritis with monoclonal gammopathy has been noted in several case reports and case series.[41,42] Although the pathogenesis is not known, the overproduction of monoclonal antibodies may lead to hyperviscosity, hypercalcemia, and renal failure. Thus, some of the associations with glomerulonephritis and nephrotic syndrome could be due to reverse causality (ie, MM causing glomerulonephritis and nephrotic syndrome) or to a sequela of late-stage MGUS. Also, the increased risk of MM and MGUS for nephrotic syndrome could be related to the presence of AL amyloidosis, which occasionally occurs in these patients.[43]

Our lack of an elevated risk for allergic conditions is consistent with some[6,12] but not all studies[15,17] of MM that looked at this factor. Allergic conditions are generally less stringently defined than other medical conditions, making them more difficult to study.

We also did not find a significant excess of rheumatoid arthritis (RA). An excess risk of RA has previously been noted in patients with MM in some studies,[14,44,45] but not in others.[16,34,46] This discrepancy may be due to reverse causality, as there are clinical reports of RA or RA-like polyarthritis being the first manifestation of MM[47] or MGUS.[48]

We observed a long-term (10 or more years of latency) elevated risk of MM for patients with prior osteoarthritis of approximately 27%. Osteoarthritis is characterized by degeneration of articular cartilage, limited intraarticular inflammation with synovitis, and changes in periarticular and subchondral bone. Because MM is known to cause bone lesions, the observed association should be interpreted with caution because MM may have been present, but undetected, when the

diagnosis of osteoarthritis was made.[3] However, we also found osteoarthritis to be associated with an increased risk of MGUS, and in many patients the latency interval was 10 or more years. In a related study, we found a 2-fold increased risk of MM among Danish men and women with prior osteoporosis.[49] This is of interest since there is emerging evidence that bone pathophysiology and clonal myeloma cell growth is a consequence of a complex interaction between myeloma cells and the bone marrow microenvironment.[50] Several cell types in the bone marrow (eg, stromal cells, osteoblasts, bone marrow leukocytes, endothelial cells, and osteoclasts) have been found to interplay bidirectionally with myeloma cells through certain major biological pathways.[51] Also, there is growing evidence that these same pathways are critical for the development and modulation of osteoporosis.[50,51] This commonality of pathways suggests that a preexisting inflammatory bone process might be a risk factor for the development of MM. Future work is needed to confirm these findings, which may provide novel insights into the etiology and pathogenesis of MM.

The strengths of our study include its large sample size with sufficient numbers of patients with MM to assess associations separately for white and black men with medical diagnoses obtained from discharge diagnoses, which eliminates the possibility of recall bias, and a sufficient follow-up period to look at disorders 10 or more years prior to diagnosis of MM. In addition, to account for the higher incidence of MM and comorbidities among male veterans in the VA system compared with the general population,[52,53] we used an internal comparison of men in the VA without a discharge diagnosis of MM. Although there were differences in the average number of years of follow-up and mean age at study entry between patients with MM and patients without MM, tight control for attained age, attained calendar year, and latency between study entry and study exit in the analysis allowed us to include contributing data from almost 4.5 million veterans. We were also able to examine the relationship between MGUS and selected autoimmune, infectious, inflammatory, and allergic disorders.

Limitations include the lack of clinical and laboratory data to verify diagnoses, our inability to distinguish HCV from other types of hepatitis or specific agents causing pneumonia based on ICD-8 codes, the possibility of coding errors due to mistakes in the coding of millions of pieces of data (especially those with similar names or similar symptoms from more than 140 hospitals in the VA system by hundreds of coders), and our inability to review medical records for patients with MM/MGUS. Also, the use of a hospitalized cohort might have resulted in underascertainment of patients with cancer and milder immune-mediated and inflammatory conditions such as those diagnosed in outpatient settings. However, because personal history of immune-mediated and inflammatory disorders were assessed similarly among the patients with MM/MGUS and patients without MM/MGUS, any underdiagnosis of immune-mediated and inflammatory disease should be nondifferential, and any bias should be toward the null. The exclusion of women might limit the generalizability of our results. Further limitations are the lack of systematic follow-up in the VA system, since veterans can be treated at either VA or civilian facilities, and the overrepresentation of lower social class patients who lack other forms of health insurance and thus may not be representative of patients seen at other US hospitals or clinics.[53] An additional consideration is the large number of conditions evaluated and the potential for chance associations due to multiple comparisons.

In summary, we found significantly elevated risks of MM/MGUS associated with broad categories of autoimmune, infectious, and inflammatory disorders, but not with allergic conditions or RA. We also observed significantly elevated risks for a number of specific autoimmune disorders. Some of these disorders may be a potential trigger for MM/MGUS development, while others may represent underlying conditions due to undetected MM or late-stage MGUS. These results highlight the need to explore the pathologic mechanisms underlying the association of these diseases with MM/MGUS and to consider the diagnosis of MM/MGUS in patients presenting with these conditions.

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Authorship

Contribution: L.M.B., G.G., and O.L. designed the study, obtained, analyzed, and interpreted data, and contributed to the final version of this report. D.C. analyzed and interpreted data and contributed to the final version of this report. L.M.B. drafted the manuscript. All authors read, gave comments, and approved the final version of the manuscript.

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