

Prior Autoimmune Disease and Risk of Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma: A Systematic Review

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Abstract

Background: Several observational studies have investigated autoimmune disease and subsequent risk of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma. Findings have been largely inconsistent and hindered by the rarity and heterogeneity of the autoimmune disorders investigated. A systematic review of the literature was undertaken to evaluate the strength of the evidence linking prior autoimmune disease and risk of MGUS/multiple myeloma.

Methods: A broad search strategy using key terms for MGUS, multiple myeloma, and 50 autoimmune diseases was used to search four electronic databases (PubMed, Medline, Embase, and Web of Science) from inception through November 2011.

Results: A total of 52 studies met the inclusion criteria, of which 32 were suitably comparable to perform a meta-analysis. "Any autoimmune disorder" was associated with an increased risk of both MGUS [$n = 760$ patients; pooled relative risk (RR) 1.42; 95% confidence interval (CI), 1.14–1.75] and multiple myeloma ($n > 2,530$ patients; RR 1.13, 95% CI, 1.04–1.22). This risk was disease dependent with only pernicious anemia showing an increased risk of both MGUS (RR 1.67; 95% CI, 1.21–2.31) and multiple myeloma (RR 1.50; 95% CI, 1.25–1.80).

Conclusions: Our findings, based on the largest number of autoimmune disorders and patients with MGUS/multiple myeloma reported to date, suggest that autoimmune diseases and/or their treatment may be important in the etiology of MGUS/multiple myeloma. The strong associations observed for pernicious anemia suggest that anemia seen in plasma cell dyscrasias may be of autoimmune origin.

Impact: Underlying mechanisms of autoimmune diseases, general immune dysfunction, and/or treatment of autoimmune diseases may be important in the pathogenesis of MGUS/multiple myeloma. *Cancer Epidemiol Biomarkers Prev*; 23(2); 332–42. ©2014 AACR.

Introduction

Multiple myeloma is a B-cell malignancy morphologically characterized by the monoclonal proliferation of plasma cells in the bone marrow, presence of monoclonal (M) protein in the serum and/or urine, and disease-related end organ damage (hypercalcemia, renal insufficiency, anemia and bone pain: CRAB criteria; ref. 1).

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Despite recent treatment advancements, 5-year survival remains poor at 42.6% (2). Multiple myeloma is consistently preceded by a premalignant condition monoclonal gammopathy of undetermined significance (MGUS; refs. 3, 4), which, on average, carries a 1% annual risk of progression to multiple myeloma or other lymphoproliferative disorders (5). The etiology of both MGUS and multiple myeloma remains largely unknown, but established risk factors include advancing age, male gender, family history, black race, and environmental factors such as radiation and pesticide exposure (6).

Although the role for immune dysregulation in lymphomagenesis is well established, little is known about immune-related diseases and risk of plasma cell disorders (6). Numerous clinical case reports have highlighted an increased frequency of MGUS and multiple myeloma in patients with autoimmune disease(s); refs. 7–10). Osserman and Takatsuki first proposed the theory of chronic antigenic stimulation as a trigger to the onset of plasmacytic dyscrasia (11). Theoretically, it is argued that chronic stimulation by activated immune cells may predispose individuals to malignancy via the

introduction of randomly occurring pro-oncogenic mutations in actively dividing plasma cells (12). Alternatively, the dysfunctional immune system found in autoimmune diseases may allow malignant clones to exist, escape, and persist (12). In addition, autoimmune disorders are associated with premature aging of the immune system thereby reducing the ability to decipher between "self" and "foreign" antigens (13).

Both autoimmune diseases and hematologic malignancies seem to be influenced by a genetic predisposition (14). Familial aggregation of autoimmune disorders in both patients with MGUS and multiple myeloma have been observed suggesting a common underlying genetic mechanism (15–17). In addition, medications used in the treatment of autoimmune disorders such as steroids, insulin, and immunomodulators have been associated with a heightened risk of malignancy (18).

Several observational studies have been conducted investigating the hypothesis of sustained or chronic antigenic stimulation and the development of multiple myeloma and most recently MGUS, but findings have been inconsistent and have largely been hindered by the rarity and heterogeneity of the autoimmune disorders investigated (15, 17, 19, 18, 20, 21). We therefore, sought to perform an extensive systematic review of the published literature to evaluate the strength of the evidence linking prior autoimmune disease and risk of MGUS and multiple myeloma.

Materials and Methods

Four electronic databases, namely PubMed (U.S. National Library of Medicine and the NIH, Bethesda, MD), Medline (U.S. National Library of Medicine, Bethesda, MD), Embase (Reed Elsevier PLC), and Web of Science (Thomson Reuters) were searched from inception through to November 8, 2011, restricted to human studies and with no English language restriction. Boolean operators "AND" and "OR" were used to combine key words and exploded terms. "Autoimmune disease," "autoimmunity," and "autoantibodies" together with a list of 50 autoimmune disease terms, which were gleaned from a literature search of association with multiple myeloma and MGUS, were combined using the "AND" operator with key terms for multiple myeloma and MGUS.

Duplicate records were removed and titles and abstracts were reviewed by the primary reviewer (C.M. McShane) together with a second reader (A.T. Kunzmann, L.A. Anderson, L.J. Murray, and M.R. Ismail) against the review topic and predetermined inclusion/exclusion criteria. Case reports, case series, and review articles were excluded. Where an abstract indicated autoimmune disease and risk of MGUS or multiple myeloma, the full text was reviewed. A snowball approach was used to search bibliographies of relevant articles for additional references not identified within the initial search. Papers were incorporated in the review if prior autoimmune disease and MGUS or

multiple myeloma were reported. Studies were excluded if only the abstract was available. Where serial publications from the same cohort of patients were reported, a decision was made to include the largest study. For studies thought to be of relevance, but where the required data were not reported, authors were contacted by email.

Using a standardized proforma designed separately for case-control and cohort studies, the principal reviewer extracted data from the results section of each study; data extraction was then checked for validity by a second reviewer (L.A. Anderson). Information extracted included study authors, publication year, study design, study period, exposure, sample size, incidence of multiple myeloma or MGUS, risk measurements, and confounders adjusted for.

Statistical analysis

Statistical analyses were conducted using the "metan" package in STATA version 12 (StataCorp). The association between autoimmune disease(s) and MGUS or multiple myeloma were investigated separately for (i) any autoimmune disease, (ii) specific autoimmune diseases and, (iii) in accordance with recent publications autoimmune diseases were categorized according to systemic or organ involvement and to those in whom autoantibodies are generally detectable and those that are not (15, 16, 19). The heading "any autoimmune disease" was defined to include all studies that reported an association between an autoimmune disease and subsequent risk of MGUS or multiple myeloma. Within this category, we included those studies that calculated risk for "all autoimmune diseases," in addition to studies that reported separate measurements for individual diseases. Adjusted relative risks (RR), odds ratios (OR), and standardized incidence ratios (SIR) with corresponding 95% confidence intervals (CI) were extracted from the included studies to take into account confounding variables such as gender and age. For those studies in which the risk measurement was not calculated but where sufficient data were presented, a fixed effects model was used to calculate the unadjusted RR (22–25). For those studies meeting the inclusion criteria but which reported unadjusted risk measurements, RR, OR, and SIRs were extracted (22–26).

To calculate pooled risk estimates, a random effects model was used to account for the expected heterogeneity between and within the included observational studies. Meta-analyses were conducted where there were two or more published articles.

Statistical heterogeneity was assessed using Cochran Q test, whereas the I^2 statistic was used to quantify the variation in the effect measure across the studies as a result of heterogeneity (27). An I^2 of 25% was considered to have low heterogeneity, whereas 50% indicated moderate heterogeneity and 75% and above, high heterogeneity (27). *Posthoc* sensitivity analysis was used to assess the degree of heterogeneity by eliminating studies in

turn and monitoring for changes in the overall estimate (I^2) and $P_{\text{heterogeneity}}$. Metaregression was undertaken to investigate potential sources of heterogeneity. We also performed subgroup analysis based on study design (cohort vs. case-control) for those autoimmune diseases that were significantly associated when analyzed together (cohort and case-control combined) and where the number of studies included was more than three. For this analysis, nested case-control studies were combined with cohort studies.

Publication bias was assessed using the Egger test. The "trim and fill" method was used to adjust for publication bias (28). This method, which is based on correcting funnel plot asymmetry resulting from publication bias, was used to estimate the number of missing studies and the adjusted risk measurement following imputation of the missing studies (28).

Results

Following removal of duplicates, a total of 11,329 studies remained, of which 110 were deemed to be of interest. In total, 52 studies (19 from search criteria, 33 from manual retrieval) were included. Of the 58 studies excluded, 14 were reviews, 20 were case reports/series/letters, 16 did not provide estimates for MGUS/multiple myeloma or include an appropriate control population, six focused on

mortality rather than incidence, and two did not include autoimmune diseases. Figure 1 displays the process of study selection.

In total, 32 studies were suitably comparable to perform a meta-analysis. Twenty studies were excluded on the basis of: insufficient data (29–33), analyzing multiple myeloma in combination with other hematologic malignancies (34–36), and use of same study cohort (12, 16, 24, 37–45). Asking and colleagues reported results for ulcerative colitis and Crohn disease based on both regional cohorts and the Swedish Inpatient Register; however, for the purpose of this meta-analysis, we only took into account findings relating to regional cohorts to avoid duplication (46).

Study characteristics

Of the 32 studies included in the meta-analyses, 11 were case-control ($n = 6$ population based; $n = 5$ hospital based) and 21 were cohort studies ($n = 19$ population based). The sample size in case-control studies was considerably smaller than in cohort studies. Twenty-one of the included studies were carried out in Europe, nine in the United States, one in Asia ($n = 1$ China), and one in New Zealand. Characteristics of the identified studies are available as an online supplement (see Supplementary Tables).

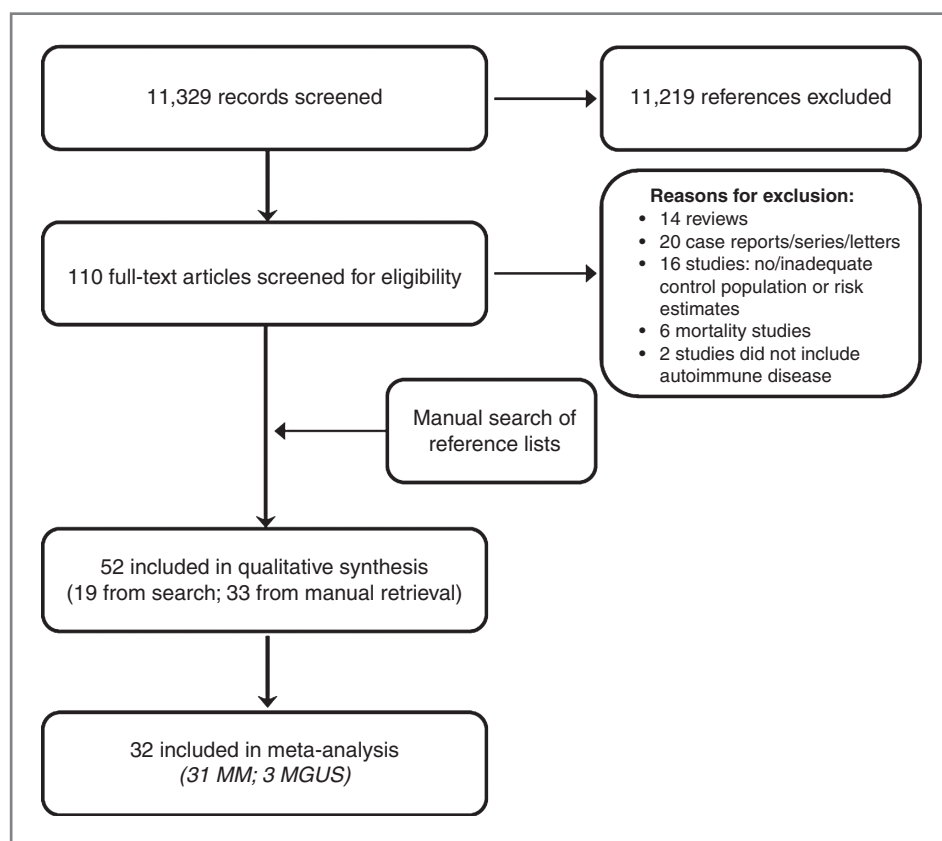


Figure 1. Flow chart of study selection.

Autoimmune disease and subsequent risk of multiple myeloma

A total of 31 studies (20 cohort; 11 case-control) investigated autoimmune disease(s) and subsequent risk of multiple myeloma (Table 1). For "any autoimmune disease," which included more than 2,530 patients, we observed a pooled RR of 1.13 (95% CI, 1.04–1.22). However, there was some evidence of moderate heterogeneity ($I^2 = 43\%$; $P \leq 0.001$). Using meta-regression to investigate the potential source of this heterogeneity, risk estimates were shown to differ by study location with stronger associations observed for European-based studies (data not shown). The Egger test revealed evidence of publication bias ($P = 0.02$). Using the trim and fill method, 11 to 12 studies were estimated as missing and following imputation, this resulted in a RR of 1.09 (95% CI, 1.00–1.19). Positive associations were also observed for autoimmune subcategories: autoantibodies detectable, systemic and organ involvement (Table 1).

Both autoimmune hemolytic anemia (AIHA) and pernicious anemia were associated with an elevated risk of multiple myeloma. For AIHA, a pooled RR of 2.80 (95% CI, 1.37–5.74) was detected on the basis of three studies. For pernicious anemia, a pooled RR of 1.50 (95% CI, 1.25–1.80) was observed, with low levels of heterogeneity detected with $I^2 = 27.8\%$, $P_{\text{heterogeneity}} = 0.23$ (Fig. 2A). In *posthoc* sensitivity analysis removing Brown and colleagues (19) obtained an attenuated RR of 1.44 (95% CI, 1.27–1.63), $I^2 = 0\%$, and $P_{\text{heterogeneity}} = 0.51$. Removal of the remaining studies did not significantly alter the heterogeneity score as assessed by I^2 or the P value (data not shown).

Eight studies investigated psoriasis and risk of multiple myeloma. A pooled RR of 0.89 (95% CI, 0.81–0.99) was observed with limited heterogeneity $I^2 = 0\%$ and $P_{\text{heterogeneity}} = 0.92$. A nonsignificant increased risk was observed for rheumatoid arthritis (RR 1.18; 95% CI, 0.96–1.44); however, a high level of heterogeneity (70.9%) was evident. In *posthoc* sensitivity analysis, removal of studies did not significantly alter the heterogeneity score as assessed by I^2 or the P value (data not shown).

In subgroup analysis by study design, a significant increased risk of multiple myeloma was observed with any autoimmune disease for cohort studies (RR 1.14; 95% CI, 1.05–1.23) but not case-control studies (RR 1.24; 95% CI, 0.91–1.69).

Autoimmune disease and subsequent risk of MGUS

Only three studies (2 cohort, 1 case-control) with a total of 760 patients investigating autoimmune conditions and risk of MGUS were identified (Table 2). Any autoimmune disease was associated with a 42% increased risk of MGUS (pooled RR 1.42; 95% CI, 1.14–1.75). High levels of heterogeneity were observed ($I^2 = 58.9\%$; $P = 0.003$). Similar to multiple myeloma findings, pooled risk measurements for autoimmune subcategories: autoantibodies detectable (RR 1.64; 95% CI, 1.36–1.97), systemic (RR 1.95; 95% CI, 1.57–2.42), and organ involvement (RR 1.55; 95% CI, 1.35–1.79) were positively associated with MGUS, whereas a

nonsignificant increased risk was observed for autoantibodies not detectable.

Three studies investigated pernicious anemia and risk of MGUS (Fig. 2B). Similar to multiple myeloma, pernicious anemia was associated with a significant increased risk of MGUS (RR 1.67; 95% CI, 1.21–2.31). Minimal heterogeneity was observed ($I^2 = 1.4\%$; $P = 0.36$) and publication bias was not evident (Egger $P = 0.24$). Ankylosing spondylitis and polymyositis/dermatomyositis were also positively associated with MGUS but analyses were based on less than 30 patients.

Discussion

In this, the first comprehensive systematic review of the literature to investigate autoimmune conditions and MGUS and multiple myeloma, we found an elevated risk of both MGUS and multiple myeloma in the presence of "any autoimmune disease." This risk was however disease dependent with only pernicious anemia showing an increased risk for both MGUS and multiple myeloma. Other autoimmune conditions (autoimmune hemolytic anemia, psoriasis, ankylosing spondylitis, and polymyositis/dermatomyositis) were associated with either MGUS or multiple myeloma but not with both disease groups. Our findings suggest that the underlying mechanisms of immune-related conditions, general immune dysfunction, and/or treatment of autoimmune diseases may be important in the pathogenesis of both MGUS and multiple myeloma.

As many autoimmune conditions are difficult to diagnose, broad categorizations such as "any autoimmune disease," which was significantly associated with an increased risk of MGUS and multiple myeloma within this review, may best capture the associations between autoimmune disease and risk of malignancy. Recent laboratory studies have identified specific antigenic targets associated with the development of MGUS and multiple myeloma. In a case-control study, Grass and colleagues proposed that hyperphosphorylation of partarg-7, a target of immunoglobulin A, M, and G (IgA, IgM, and IgG) paraproteins, may induce autoimmunity and thus be important in the pathogenesis of MGUS and/or multiple myeloma (47–49). Genetic analysis of eight families revealed that hyperphosphorylated paratarg-7 was inherited in a dominant manner, and carriers had an almost 8-fold increased risk of developing IgA or IgG MGUS and multiple myeloma (OR 7.9; 95% CI, 2.8–22.6; refs. 47–49). We also observed stronger associations for patients with MGUS compared with multiple myeloma (42% vs. 13%). Given the relationship of MGUS with multiple myeloma, one would expect associations between autoimmune diseases and these plasma cell disorders to be correlated; however, in this meta-analysis with the exception of pernicious anemia, this was not the case. Our findings may reflect the biologically heterogeneous nature of MGUS, which, unlike multiple myeloma, can progress to a number of lymphoproliferative disorders (15). This theory is consistent with a recent observational study,

Table 1. Autoimmune disease and subsequent risk of multiple myeloma

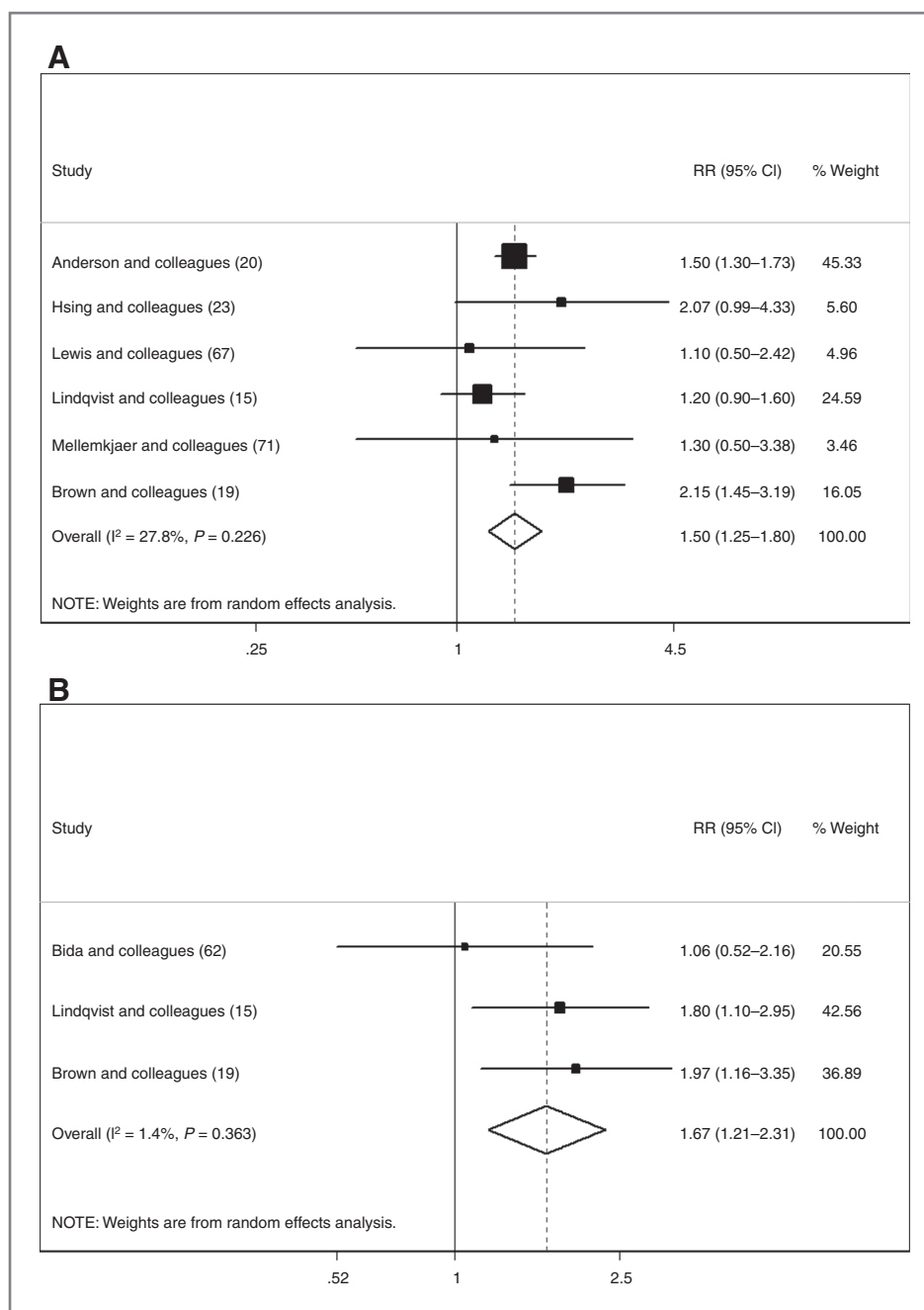
Autoimmune condition	Number of studies included	Study references	Pooled number of MM cases with AID ^a	Pooled estimate RR (95% CI)	Heterogeneity (I ² ; P)	Publication bias ^b (P)
Any autoimmune condition	31	(15, 19–20, 22, 23, 25, 26, 46, 66–87)	Unknown (but >2,530) ^a	1.13 (1.04–1.22)	43%, P ≤ 0.001	0.02
Autoantibodies detectable	22	(15, 19–20, 22–24, 26, 66–69, 71–79, 82, 85, 87)	Unknown (but >1,877) ^a	1.23 (1.09–1.38)	65.2%, P ≤ 0.001	0.02
Systemic involvement	16	(15, 19–20, 22, 26, 66–69, 72–75, 82, 85)	833	1.20 (1.01–1.43)	62.7%, P ≤ 0.001	0.01
Polymyositis/dermatomyositis	4	(15, 19, 20, 66)	20	1.41 (0.86–2.30)	7.8%, P = 0.36	0.83
Rheumatoid arthritis	13	(15, 19–20, 22, 26, 67, 68, 72–74, 82, 85)	713	1.18 (0.96–1.44)	70.9%, P ≤ 0.001	0.06
Sjögren syndrome	4	(15, 20, 72, 75)	30	2.37 (0.70–8.02)	73.9%, P = 0.009	0.27
Systemic lupus erythematosus	5	(15, 19, 20, 67, 69)	39	1.16 (0.75–1.79)	14.7%, P = 0.32	0.25
Systemic sclerosis	3	(15, 19, 20)	21	1.28 (0.66–2.48)	54.2%, P = 0.11	0.91
Organ involvement	11	(15, 19, 20, 23, 67, 71, 76–79, 87)	Unknown (but >1,105) ^a	1.18 (1.06–1.32)	29.9%, P = 0.07	0.39
Addison disease	2	(15, 20)	18	0.90 (0.54–1.51)	0%, P = 1.0	–
Amyotrophic lateral sclerosis	2	(15, 19)	9	1.10 (0.55–2.21)	0%, P = 0.62	–
Autoimmune hemolytic Anemia	3	(15, 19, 20)	22	2.80 (1.37–5.74)	40.8%, P = 0.18	0.32
Chronic rheumatic heart disease	3	(15, 19, 20)	450	0.98 (0.79–1.22)	68.8%, P = 0.04	0.39
Celiac disease	3	(15, 19, 20)	Unknown (but >11) ^a	1.59 (0.92–2.73)	0%, P = 0.47	0.88
Discoid lupus erythematosus	3	(15, 19, 20)	20	1.08 (0.67–1.74)	0%, P = 0.43	0.43
Grave disease	4	(15, 20, 67, 87)	43	1.06 (0.79–1.43)	0%, P = 0.59	0.69
Hashimoto thyroiditis	4	(15, 20, 67, 87)	44	1.69 (0.81–3.50)	48.8%, P = 0.12	0.17
Idiopathic thrombocytopenic purpura	3	(15, 19, 67)	17	1.34 (0.76–2.35)	0%, P = 0.46	0.09
Type I diabetes	2	(76, 77)	7	1.50 (0.5–4.47)	0%, P = 0.95	–
Scleroderma	2	(20, 78)	Unknown (but >9) ^a	0.78 (0.36–1.7)	0%, P = 0.52	–
Multiple sclerosis	2	(15, 20)	22	0.76 (0.49–1.19)	0%, P = 0.38	–
Myasthenia gravis	3	(15, 19, 20)	19	1.40 (0.84–2.33)	0%, P = 0.44	0.7
Pernicious anemia	6	(15, 19, 20, 23, 67, 71)	326	1.50 (1.25–1.80)	27.8%, P = 0.23	0.90
Polyarteritis nodosa	2	(15, 20)	Unknown (but >1) ^a	0.79 (0.26–2.43)	0%, P = 0.67	–
Primary biliary cirrhosis	3	(15, 19, 79)	13	1.83 (0.55–6.11)	25.4%, P = 0.26	0.71
Autoantibodies not detectable	11	(15, 19–20, 25, 46, 67, 70, 78, 80, 84)	Unknown (but >673) ^a	1.07 (0.95–1.20)	31.2%, P = 0.09	0.81
Ankylosing spondylitis	3	(15, 19, 20)	47	1.49 (0.86–2.60)	63.3%, P = 0.07	0.1
Crohn disease	4	(15, 20, 46, 70)	47	1.09 (0.77–1.54)	0%, P = 0.95	0.96
Polymyalgia rheumatica	2	(15, 20)	155	1.37 (0.73–2.56)	91.0%, P = 0.001	–
Psoriasis	8	(15, 19–20, 25, 67, 78, 84)	Unknown (but >194) ^a	0.89 (0.81–0.99)	0%, P = 0.92	0.07
Sarcoidosis	4	(15, 19, 20, 80)	33	1.06 (0.72–1.56)	0%, P = 0.65	0.36
Ulcerative colitis	5	(15, 19, 20, 46, 78)	Unknown (but >93) ^a	1.15 (0.94–1.42)	0%, P = 0.66	0.09
Giant cell arteritis	2	(15, 20)	53	2.94 (0.47–18.37)	93.3%, P ≤ 0.001	–
Aplastic anemia	2	(15, 20)	18	1.67 (0.96–2.92)	0%, P = 0.36	–

Abbreviations: MM, multiple myeloma; AID, autoimmune disease.

^aPooled numbers are listed as unknown as the studies included failed to report approximate numbers. Accompanying numbers in parentheses are based on pooled numbers from remaining studies.

^bWe were unable to assess publication bias using the Egger test for individual autoimmune diseases where only two studies were identified (–).

Figure 2 A, forest plot of pernicious anemia and subsequent risk of multiple myeloma. B, forest plot of pernicious anemia and subsequent risk of MGUS.



which reported differing levels of adverse biology amongst patients with MGUS and smoldering multiple myeloma both with and without a preceding autoimmune condition (50). Furthermore, MGUS can afflict a broad spectrum of individuals ranging from those who are otherwise healthy to those who are gravely ill.

Our findings of an elevated risk for both MGUS and multiple myeloma in patients with pernicious anemia suggest that anemia, or more precisely the underlying biologic mechanism, may be related to the onset of MGUS/multiple myeloma. This association is supported by numerous case reports that have highlighted an

increased frequency of multiple myeloma within a pernicious anemia setting (7). Pernicious anemia results from the autoimmune destruction of the gastric parietal cells, which secrete intrinsic factor needed to absorb cobalamin (vitamin B12). As a result, patients are cobalamin deficient. Prevalence of vitamin B12 deficiency in patients with plasma cell disorders, including MGUS and multiple myeloma, was previously shown to be 13.6% (51). Non-immune-mediated mechanisms of systemic vitamin B12 deficiency have been proposed, including the concept of sequestering and over usage of vitamin B12 in hyperproliferating multiple myeloma cells. Increased uptake and

Table 2. Autoimmune disease and subsequent risk of MGUS

Autoimmune condition	Number of studies included	Study references	Pooled number of MGUS cases with AID	Pooled estimate relative risk (95% CI)	Heterogeneity (I^2 , P)	Publication bias ^a (P)
Any autoimmune condition	3	(15, 19, 62)	760	1.42 (1.14–1.75)	58.9%, $P = 0.003$	0.01
Autoantibodies detectable	3	(15, 19, 62)	529	1.64 (1.36–1.97)	32.8%, $P = 0.14$	0.02
Systemic involvement	3	(15, 19, 62)	290	1.95 (1.57–2.42)	36.6%, $P = 0.16$	0.19
Polymyositis/dermatomyositis	3	(15, 19, 62)	9	2.34 (1.11–4.92)	0%, $P = 1.00$	0.1
Rheumatoid arthritis	2	(15, 62)	146	1.83 (1.20–2.78)	67.2%, $P = 0.08$	—
Sjögren syndrome	2	(15, 62)	18	2.72 (0.85–8.66)	65.6%, $P = 0.09$	—
SLE	2	(15, 62)	8	1.61 (0.52–5.00)	27.6%, $P = 0.24$	—
Systemic sclerosis	2	(15, 19)	13	4.87 (2.49–9.54)	0%, $P = 0.51$	—
Organ involvement	3	(15, 19, 62)	257	1.55 (1.35–1.79)	0%, $P = 0.45$	0.07
Hashimoto thyroiditis	2	(15, 62)	13	1.88 (0.30–11.7)	74.3%, $P = 0.05$	—
Myasthenia gravis	2	(15, 62)	2	0.86 (0.23–3.25)	0%, $P = 0.56$	—
Pernicious anemia	3	(15, 19, 62)	41	1.67 (1.21–2.31)	1.4%, $P = 0.36$	0.24
Autoantibodies not detectable	3	(15, 19, 62)	283	1.40 (0.89–2.18)	84.2%, $P \leq 0.001$	0.49
Ankylosing spondylitis	3	(15, 19, 62)	29	2.18 (1.43–3.33)	0.0%, $P = 0.50$	0.46
Psoriasis	2	(15, 62)	44	1.16 (0.70–1.91)	59.9%, $P = 0.11$	—
Sarcoidosis	2	(15, 62)	19	1.66 (0.99–2.80)	0%, $P = 0.87$	—

Abbreviations: AID, autoimmune disease; SLE, systemic lupus erythematosus.

^aWe were unable to assess publication bias using the Egger test for individual autoimmune diseases where only two studies were identified (—).

accumulation of vitamin B12 in bone marrow-derived multiple myeloma cells grown in culture have been observed (52); however, Baz and colleagues failed to find a higher prevalence of vitamin B12 deficiency in patients with multiple myeloma compared with patients with MGUS (17% vs. 9%, $P = 0.19$; ref. 51).

Given the observed associations between pernicious anemia and MGUS/multiple myeloma and the temporal preceding relationship MGUS has with multiple myeloma, we speculate that pernicious anemia could be a direct manifestation of the underlying plasma cell dyscrasia (3, 4). Compelling and supportive evidence for this biologic argument is the observation that specifically IgA plasma cell disorders seem to have an increased prevalence of vitamin B12 deficiency (51). This suggests a mechanistic link between pernicious anemia and secretory immunoglobulin released by IgA plasma cell dyscrasias. One plausible explanation is that secreted monoclonal protein from plasma cell dyscrasias has anti-intrinsic factor-like activity (51), resulting in an autoimmune paraneoplastic process. Such autoimmune processes involving the monoclonal protein have been described before, and a range of other immune-related conditions have been linked with plasma cell dyscrasias, including TEMPI syndrome (53), POEMS syndrome (54), bleeding dyscrasias (55), and necrobiotic xanthogranulomatous disease (56).

Anemia is a common symptom in multiple myeloma and often cited as end organ damage necessary to make the clinical diagnosis. On the basis of these facts, it

seems reasonable to propose that a functional relationship between altered plasma cell and erythroid precursor may exist. Classically, theories explaining the anemia of multiple myeloma include high interleukin 6 levels present in patients with multiple myeloma that may cause hepcidin increases and iron dysregulation (57), erythroid inhibition by the IgG monoclonal protein (58), or direct effects from the neoplastic plasma cell microenvironment (59). The association between pernicious anemia and plasma cell dyscrasias evident in this meta-analysis may suggest another cause for the anemia witnessed in patients with multiple myeloma. Vitamin B12 has long been recognized as an important coenzyme involved in maintaining normal hematopoiesis. Vitamin B12 deficiency has been associated with a number of malignancies, including breast, colon, and lung cancers (60), and also been shown to disrupt normal homeostasis of methyl group metabolism as a result of abnormal DNA methylation and synthesis, causing hallmark features of megaloblastic anemia, which is common in patients with multiple myeloma. Indeed such aberrant DNA methylation patterns have been noted in both MGUS and multiple myeloma (61) and may therefore account for the increased risk observed (20).

However, the diagnosis of pernicious anemia is challenging and accurate diagnosis relies on the presence of autoantibodies. As antibody-based confirmation of pernicious anemia was not undertaken in any of the studies included within this meta-analysis, there is the potential for diagnostic misclassification bias relating to pernicious

anemia diagnosis potentially explaining the observed association in some studies (19, 20). The only study to characterize individuals as MGUS/non-MGUS based on laboratory confirmation of the monoclonal protein observed no association with pernicious anemia (RR 1.06; 95% CI, 0.52–2.16; ref. 62). Despite these limitations, the excess risk of both MGUS and multiple myeloma observed with pernicious anemia within this meta-analysis warrants further investigation.

AIHA was also associated with an excess risk of multiple myeloma; however, findings were based on a small number of studies. An excess risk of similar magnitude has previously been reported in patients with MGUS (15, 19). Sallah and colleagues found serum monoclonal gammopathy and more specifically IgM gammopathy to be a significant predictor for the appearance of lymphoproliferative disorders in patients with AIHA (63). However, more than one third of this study population had underlying autoimmune diseases and intermittent or continuous immunosuppression.

Clinically, anemia may be an important biomarker of MGUS/multiple myeloma disease onset. Although the associated absolute risk may be small, future studies utilizing molecular profiling techniques are needed to biologically differentiate those who are at an increased risk of developing MGUS and/or progressing to multiple myeloma, or other lymphoproliferative disorders.

Psoriasis was found to be negatively associated with multiple myeloma; however, as the risk measurements of all studies investigating psoriasis and multiple myeloma crossed one, caution must be taken when interpreting this finding, which may have resulted from chance or be explained by medication usage. Pooled estimates for rheumatoid arthritis, one of the more widely reported associations with multiple myeloma demonstrated a nonsignificant increased risk with high levels of heterogeneity evident, whereas significant excess risk was observed for MGUS, but findings were based on just two studies.

Our review has a number of strengths. Our findings are based on the largest number of patients with autoimmune disease and MGUS/multiple myeloma reported to date, thus allowing for a more precise measurement of the associated risk. A broad search strategy was used in four electronic databases and subsequently a large number of studies meeting the eligibility criteria were included. However, many of the findings, in particular for MGUS, are based on small numbers of studies. Our findings for multiple myeloma, for "any autoimmune disease," showed publication bias; however, we adjusted for this using the "trim and fill" plot, and even with the addition of 11 to 12 missing studies, the positive association remained. High heterogeneity was observed for several autoimmune disorders, except psoriasis and *posthoc* sensitivity analysis was undertaken to determine which studies were most heterogeneous and results presented excluding these studies. In subgroup analysis, only cohort studies iden-

tified a significant association between "any autoimmune condition" and MGUS/multiple myeloma. The case-control studies included had limited sample sizes and may have been underpowered to detect small increases in risk. In addition, these studies were largely interview based and may have resulted in misclassification of disease. However, in meta-regression analyses, risk of multiple myeloma did not differ significantly by exposure ascertainment.

Like all meta-analyses, the findings are only as strong as the studies included. A large number of the studies reported on hospital data using inpatient records or hospital discharge records, and as such our findings are most likely applicable to those patients with moderate to severe disease. Owing to the population-based nature of record linkage studies, medical record validation was not possible in most studies and therefore there is the potential for diagnostic misclassification. A large number of studies failed to report information on potential confounders, for example, lifestyle factors, medications, and additional environmental exposures. Few studies reported isotype status, and hence it is difficult to determine whether findings are isotype specific or applicable to the MGUS and multiple myeloma population as a whole.

Surveillance bias may also account for the excess risk of MGUS/multiple myeloma amongst patients. With the exception of one study by Bida and colleagues (62), studies included within this meta-analysis did not involve screening of normal populations for the presence of monoclonal protein. Per diagnostic criteria, MGUS is an asymptomatic condition. To study the temporality of the association between autoimmune conditions and a subsequent diagnosis of MGUS has inherent limitation when it comes to the risk for reverse causality. For example, it is possible that an individual with unclear symptoms was seen by a doctor and work-up led to the diagnosis of an autoimmune disorder, and subsequent additional work-up led to the diagnosis of MGUS. Because 3% of the population above the age of 50 years has been reported to have MGUS, the risk for this phenomenon is not trivial (64). On the other hand, prior studies have stratified for latency and found associations between autoimmune conditions and subsequent MGUS to be significant even when latency intervals have been restricted to 5+ years. Also, the fact that this meta-analysis found autoimmune conditions as a broad category and specifically pernicious anemia to be associated with both MGUS and multiple myeloma, strengthens the underlying biologic role for antigenic stimulation in the development of these plasma cell dyscrasias. Given the prevalence of undetected MGUS within the general population, it is possible that the control populations recorded in the studies included within this meta-analysis also included some undiagnosed MGUS individuals (65) but this would only serve to push the findings toward the null.

In summary, the strong associations observed for pernicious anemia with both MGUS and multiple myeloma, suggest that anemia seen in plasma cell dyscrasias may be of autoimmune origin, and that immune-based biomarkers may be useful in predicting disease onset and progression from MGUS to multiple myeloma in individual patients. Overall our findings suggest that autoimmune conditions and/or their treatments have important etiologic consequences for both MGUS and multiple myeloma and that further research is warranted within this area.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.M. McShane, L.J. Murray, O. Landgren, L.A. Anderson

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. McShane, L.A. Anderson

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