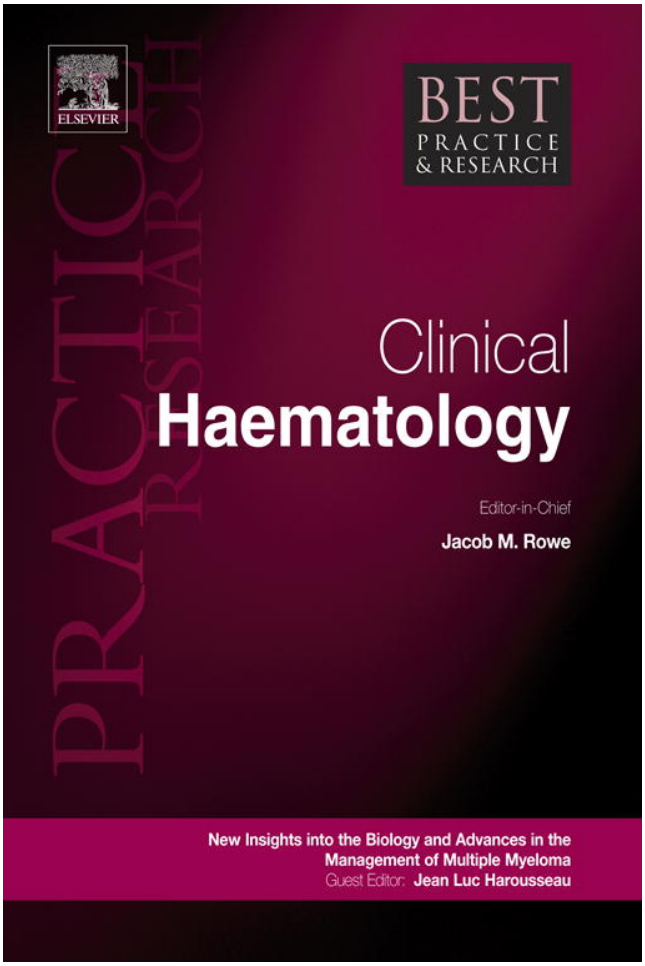

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Epidemiology of the plasma-cell disorders

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This review of the plasma-cell disorders begins with the definition of monoclonal gammopathy of undetermined significance (MGUS). The prevalence of MGUS in white and black populations is described. MGUS is a common finding in the medical practice of all physicians, and thus it is important to both the patient and the physician to determine whether the monoclonal protein remains stable or progresses to multiple myeloma (MM), Waldenström's macroglobulinemia (WM), primary systemic amyloidosis (AL), or a related disorder. The long-term (almost 40 years) follow-up data of 241 patients in the Mayo Clinic population is provided. In a large study of 1384 patients with MGUS from southeastern Minnesota, the risk of progression to MM, WM, AL, or other disorders was approximately 1% per year. Risk factors for progression are provided. The incidence of MM in Olmsted County, Minnesota, remained stable for the 56-year span 1945–2001. The apparent increase in incidence and mortality rates among patients with MM in many studies is due to improved case ascertainment, especially among the elderly. The incidence and mortality rates of MM in the United States and other countries are presented. The major emphasis is on the cause of MM, which is unclear. Exposure to radiation from atomic bombs, therapeutic and diagnostic radiation, and in workers in the nuclear industry field are addressed. Many studies involving agricultural occupations, exposure to benzene, petroleum products, and engine exhaust and other industrial exposures are discussed. Tobacco use, obesity, diet, and alcohol ingestion are all possible causes of MM. Clusters of MM have been noted. Multiple cases of MM have been found in first-degree relatives.

Key words: agricultural workers; atomic bombs; benzene and solvent exposure; familial aspects; incidence; monoclonal gammopathy of undetermined significance; multiple myeloma; therapeutic and diagnostic radiation.

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The plasma-cell disorders are characterized by the proliferation of a single clone of plasma cells that produces a homogeneous monoclonal (M) protein (Table 1); these disorders have been defined by the International Myeloma Working Group.[1] In 2006, a total of 1684 cases of plasma-cell disorders were identified at Mayo Clinic: monoclonal gammopathy of undetermined significance (MGUS), 921 (55%); multiple myeloma (MM), 276 (16.5%); primary amyloidosis (AL), 194 (11.5%); lymphoproliferative disorders, 62 (4%); smoldering multiple myeloma (SMM), 57 (3%); Waldenström's macroglobulinemia (WM), 36 (2%); solitary or extramedullary plasmacytoma, 35 (2%); and other, 103 (6%) (Figure 1).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

MGUS is characterized by a serum M-protein concentration of <30 g/L, fewer than 10% plasma cells in the bone marrow, and no related organ or tissue impairment (no end-organ damage such as hypercalcemia, renal insufficiency, anemia, or lytic bone lesions related to the plasma-cell disorder).[1] There must be no evidence of MM, WM, AL, or related plasma-cell proliferative disorders.

Table 1. Classification of plasma-cell proliferative disorders.

I. Monoclonal gammopathies of undetermined significance (MGUS)
- A. Benign (IgG, IgA, IgD, IgM, and, rarely, free light chains)
- B. Associated neoplasms or other diseases not known to produce monoclonal proteins
- C. Biclonal and triclonal gammopathies
- D. Idiopathic Bence Jones proteinuria

II. Malignant monoclonal gammopathies
- A. Multiple myeloma (IgG, IgA, IgD, IgE, and free light chains)
  1. Symptomatic multiple myeloma
  2. Smoldering multiple myeloma
  3. Plasma-cell leukemia
  4. Non-secretory myeloma
  5. IgD myeloma
  6. POEMS syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (osteosclerotic myeloma)
  7. Solitary plasmacytoma of bone
  8. Extramedullary plasmacytoma
- B. Malignant lymphoproliferative disorders
  1. Waldenström's macroglobulinemia
  2. Malignant lymphoma
  3. Chronic lymphocytic leukemia

III. Heavy-chain diseases (HCDs)
- A. γHCD
- B. αHCD
- C. μHCD

IV. Cryoglobulinemia

V. Primary amyloidosis (AL)

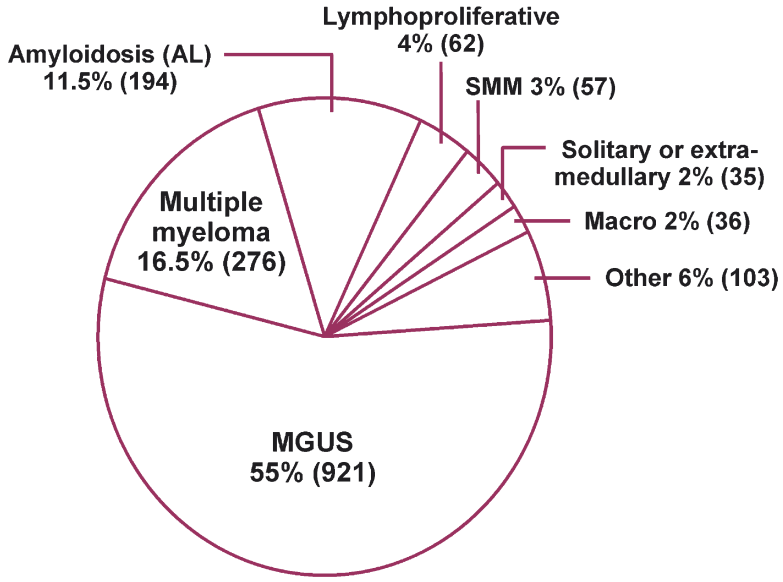

Figure 1. Types of monoclonal gammopathies diagnosed in 1684 cases at Mayo Clinic during 2006. Macro, macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.

M proteins without MM, AL, or WM have been reported in approximately 3% of people older than 70 years in Sweden[2], the United States[3], and France.[4]

MGUS is more common in blacks than in whites.[5] An M protein was found in 8.4% of 916 blacks and in 3.6% of whites in North Carolina.[6] In a study of 4 million African American and white males admitted to Veterans Affairs hospitals in the United States, the prevalence of MGUS was 0.98% in African Americans and 0.4% in whites.[7] The age-adjusted prevalency ratio of MGUS in African Americans was three-fold greater than in whites (95% confidence interval, 2.7–3.3).

The first population-based study using modern laboratory techniques to detect M proteins was recently reported.[8] Serum samples were obtained from 21,463 of the 28,038 (77%) enumerated residents of Olmsted County during the course of their routine clinical care. The overall prevalence of MGUS was 3.2% of people 50 years or older. Of the 20,072 Olmsted County residents whose race or ethnic group was known, 97.3% were white and 1.4% were Asian. Of the 605 patients with MGUS whose race or ethnic group was known, 99.3% were white. MGUS was found in 3.7% of men and in 2.9% of women ($P < 0.001$) (Table 2). Interestingly, the rate among men was similar to that among women a decade older. In both sexes, the prevalence increased with advancing age and was almost four times as high among people 80 years or older compared with those 50–59 years of age. The prevalence leveled off after 85 years of age in men and after 90 years of age in women (Figure 2). In people older than 85 years, the prevalence of MGUS was 8.9% in men and 7.0% in women. There was no significant difference in the M-protein value among age groups.

The isotype of the M protein was immunoglobulin G (IgG) in 68.9%, IgM in 17.2%, IgA in 10.8%, and biclonal in 3.0%. The serum light-chain type was κ in 62% and λ in 38% of the 694 patients. The M-protein concentration was <10 g/L in 63.5%, 10–14.9 g/L in 16.6%, 15–19.9 g/L in 15.4%, and ≥ 20.0 g/L in 4.5%. In 91 patients (13.1%), the M-protein concentration was too small to measure. The median value was 5 g/L (7 g/L if the unmeasurable proteins were excluded). One or more uninvolved immunoglobulins were reduced in 27.7%, and a monoclonal light chain was found in the urine in 21.5%. Thus, MGUS is a common finding in the medical practice

Table 2. Prevalence of monoclonal gammopathy of undetermined significance (MGUS) according to age group and sex among residents of Olmsted County, Minnesota, USA.

Age (years)	No./total no. (%)[a]					
	Men		Women		Total	
50–59	82/4038	(2.0)	59/4335	(1.4)	141/8373	(1.7)
60–69	105/2864	(3.7)	73/3155	(2.3)	178/6019	(3.0)
70–79	104/1858	(5.6)	101/2650	(3.8)	205/4508	(4.6)
≥80	59/709	(8.3)	111/1854	(6.0)	170/2563	(6.6)
Total	350/9469	(3.7)[b]	344/11,994	(2.9)[b]	694/21,463	(3.2)[b,c]

From Kyle et al (2006, *New England Journal of Medicine* **354:** 1362–1369) with permission.

[a] The percentage was calculated as the number of patients with monoclonal gammopathy of undetermined significance divided by the number who were tested.

[b] Prevalence was age-adjusted to the 2000 US total population as follows: men, 4.0% (95% confidence interval, 3.5–4.4); women, 2.7% (95% confidence interval, 2.4–3.0); and total, 3.2 (95% confidence interval, 3.0–3.5).

[c] Prevalence was age- and sex-adjusted to the 2000 US total population.

of all physicians. It is important to both the patient and the physician to determine whether the M protein remains stable or progresses to MM or a related disorder.

Mayo Clinic referral population of 241 patients

We reviewed the medical records of all patients with monoclonal gammopathy who were seen at Mayo Clinic from 1956 through 1970.[9] Patients with MM, WM, AL, or related plasma-cell disorders were excluded, and 241 patients were eligible for long-term follow-up. After 3579 patient-years of follow-up (median, 13.7 years; range, 0–39 years), the number of patients who were still living, whose M protein had remained stable, and who could be classified as having benign monoclonal gammopathy had decreased to 14 (6%). During follow-up, 25 patients had a serum M protein value of ≥30 g/L but did not require chemotherapy for MM, WM, or AL; 138 patients (57%) died without evidence of MM, WM, or AL.

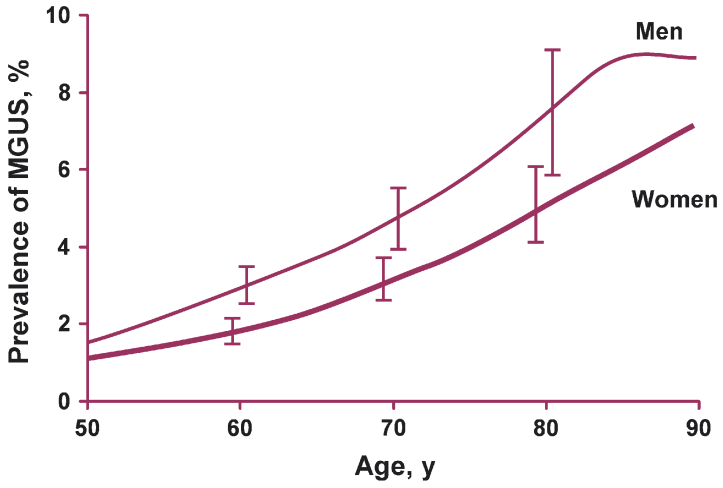

Figure 2. Prevalence of monoclonal gammopathy of undetermined significance (MGUS) according to age. The I bars represent 95% confidence intervals. Years of age >90 were collapsed to 90 years of age. From Kyle et al (2006, *New England Journal of Medicine* **354:** 1362–1369) with permission.

Table 3. Development of multiple myeloma or related disorder in 64 patients with monoclonal gammopathy of undetermined significance.

Type of progression	No. (%) of patients	Interval to disease (years)	
		Median	Range
Multiple myeloma	44 (69)	10.6	1–32
Macroglobulinemia	7 (11)	10.3	4–16
Amyloidosis	8 (12)	9.0	6–19
Lymphoproliferative disease	5 (8)	8.0	4–19
Total	64 (100)	10.4	1–32

From Kyle et al (2004, *Mayo Clinic Proceedings* **79:** 859–866) with permission.

MM, AL, WM, or a malignant lymphoproliferative disorder developed in 64 patients (27%) (Table 3). The actuarial rate of progression was 17% at 10 years, 34% at 20 years, and 39% at 25 years, a rate of approximately 1.5% per year (Figure 3). Of the 64 patients who progressed, 44 (69%) had MM. The interval from diagnosis of MGUS to diagnosis of MM ranged from 1 to 32 years (median, 10.6 years).

AL was found in eight patients 6–19 years (median, 9 years) after MGUS was recognized, and WM developed in seven patients 4–16 years (median, 10.3 years) after the M protein was detected. A malignant lymphoproliferative process developed in five patients (malignant lymphoma in three, chronic lymphocytic leukemia in one, and a malignant lymphoproliferative process in one) 4–19 years (median, 8 years) after the M protein was detected.

Long-term follow-up in 1384 patients with MGUS from southeastern Minnesota

A population-based study was done to confirm the findings of the original Mayo Clinic study, which consisted mainly of patients referred to a tertiary care center. A total of 1384 patients who resided in the 11 counties of southeastern Minnesota were identified

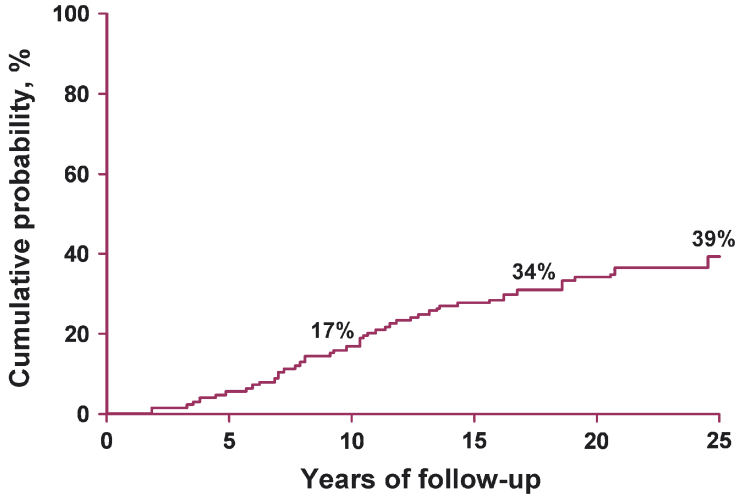

Figure 3. Rate of development of multiple myeloma or related disorders in 241 patients with monoclonal gammopathy of undetermined significance. From Kyle et al (2004, *Mayo Clinic Proceedings* **79:** 859–866) with permission.

as having MGUS between 1960 and 1994.[10] Of the 1384 patients, 54% were men and 46% were women. The median age at diagnosis of MGUS was 72 years, which was 8 years older than in the cohort of 241 patients. This difference suggests that older patients are less likely to visit tertiary referral centers. Only 2% were younger than 40 years at diagnosis, whereas 59% were 70 years or older. The median value of the serum M protein at diagnosis ranged from unmeasurable (visible as a small band on electrophoresis but not quantifiable by densitometry) to 30 g/L; 70% were IgG, 12% IgA, 15% IgM, and 3% biclonal. The light chain was κ in 61% and λ in 39%. The uninvolved immunoglobulin level was reduced in 38% of 840 patients whose immunoglobulin concentrations were determined quantitatively. Of the 418 patients whose urine was examined, 31% had a monoclonal light chain. Only 17% with a urinary M protein had a value >150 mg/24 h. The median percentage of bone marrow plasma cells was 3% (range, 0–10%) in the 160 patients who were examined at the time of diagnosis.

The 1384 patients were followed for a total of 11,009 person-years (median, 15.4 years; range, 0–35 years). Of these, 963 patients (70%) died. During follow-up, MM, AL, lymphoma with an IgM serum M protein, WM, plasmacytoma, or chronic lymphocytic leukemia developed in 115 patients (8%) (Table 4). The cumulative probability of progression to one of these disorders was 10% at 10 years, 21% at 20 years, and 26% at 25 years (Figure 4). The overall risk of progression was approximately 1% per year, and patients were at risk for progression even after 25 years or more of stable MGUS. In addition, 32 patients were identified in whom the M-protein value increased to more than 30 g/L or the percentage of bone-marrow plasma cells increased to more than 10% but symptomatic MM or WM did not develop. These findings confirmed the result of the initial Mayo Clinic study.

The rates of death due to other diseases, which included cardiovascular and cerebrovascular disease and non plasma-cell cancers, were 53% at 10 years, 72% at 20

Table 4. Risk of progression among 1384 residents of Southeastern Minnesota, USA, in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed from 1960 through 1994.

Type of progression	Observed no. of patients	Expected no. of patients[a]	Relative risk (95% CI)
Multiple myeloma	75	3.0	25.0 (20–32)
Lymphoma	19[b]	7.8	2.4 (2–4)
Primary amyloidosis	10	1.2	8.4 (4–16)
Macroglobulinemia	7	0.2	46.0 (19–95)
Chronic lymphocytic leukemia	3[c]	3.5	0.9 (0.2–3)
Plasmacytoma	1	0.1	8.5 (0.2–47)
Total	115	15.8	7.3 (6–9)

CI, confidence interval.

From Kyle et al (2002, *New England Journal of Medicine* **346:** 564–569) with permission.

[a] Expected numbers of cases were derived from the age- and sex-matched white population of the Surveillance, Epidemiology, and End Results program in Iowa[11], except for primary amyloidosis, for which data are from Kyle et al.[12]

[b] All 19 patients had serum IgG monoclonal protein. If the 30 patients with IgM, IgA, or IgG monoclonal protein and lymphoma were included, the relative risk would be 3.9 (95% CI, 2.6–5.5).

[c] All three patients had serum IgM monoclonal protein. If all six patients with IgM, IgA, or IgG monoclonal protein and chronic lymphocytic leukemia were included, the relative risk would be 1.7 (95% CI, 0.6–3.7).

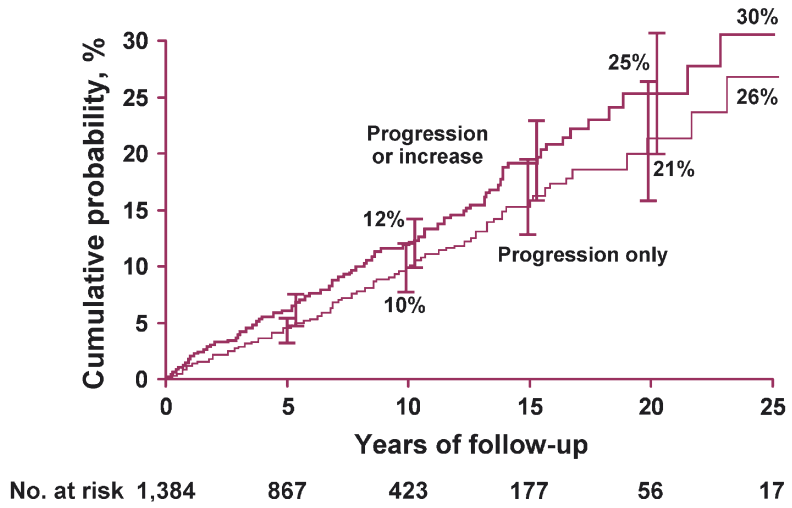

Figure 4. Probability of progression among 1384 residents of southeastern Minnesota, USA, in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed from 1960 through 1994. The top curve shows the probability of progression to a plasma-cell cancer (115 patients) or of an increase in the monoclonal protein concentration to >30 g/L or the proportion of plasma cells in bone marrow to >10% (32 patients). The bottom curve shows only the probability of progression of MGUS to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma (115 patients). The bars show 95% confidence intervals. From Kyle et al (2002, *New England Journal of Medicine* **346:** 564–569) with permission.

years, and 76% at 25 years, and the rates of progression due to plasma-cell disorders were 6% at 10 years, 10% at 20 years, and 11% at 25 years (Figure 5).

The number of patients with progression to a plasma-cell neoplasm or related disorder (115 patients) was more than seven times that expected on the basis of incidence rates for those conditions in the general population (Table 4). The risk of disease was increased by a factor of 25.0 for MM, 46.0 for WM, and 8.4 for AL. The risk of lymphoma was only moderately increased with a relative risk of 2.4, but this value is an underestimate because only lymphomas associated with an IgM protein were counted in the observed number, whereas the incidence rates for all lymphomas were used to calculate the expected number. The risk of chronic lymphocytic leukemia was only slightly increased when all cases were included.

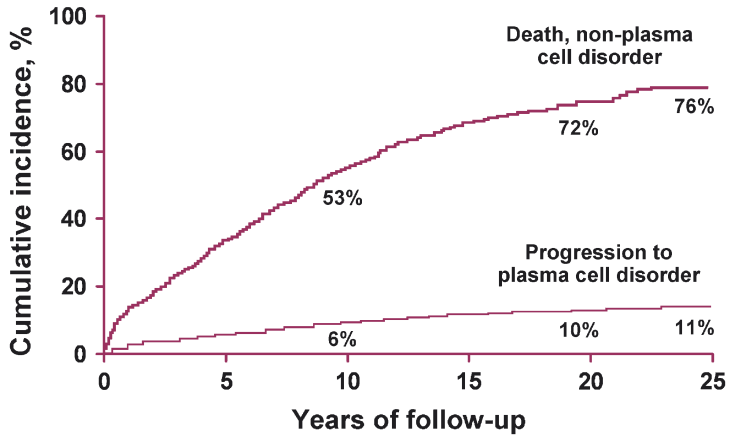

Figure 5. Rate of death from non plasma-cell disorders compared with progression to plasma-cell disorders in 1384 patients with monoclonal gammopathy of undetermined significance from southeastern Minnesota, USA. From Kyle and Rajkumar (2003, *Immunological Reviews* **194:** 112–139) with permission.

The 75 patients in whom MM developed accounted for 65% of the 115 patients who had progression to a plasma-cell disorder. The characteristics of these 75 patients were comparable to those of the 1027 patients with newly diagnosed MM referred to Mayo Clinic from 1985 to 1998, except that the southeastern Minnesota patients were older (median, 72 versus 66 years) and less likely to be male (46% versus 60%).[13]

The M protein disappeared with no apparent cause in 27 patients (2%). Only six of these 27 patients (0.4% of all patients) had a discrete spike on the densitometer tracing of the initial electrophoresis (median, 12 g/L). Thus, spontaneous disappearance of a measurable M protein after the diagnosis of MGUS was rare.

The cause of malignant transformation of MGUS is poorly understood. Genetic changes, bone-marrow angiogenesis, cytokines related to myeloma bone disease, and infections may play a role but are not discussed further in this review.[14]

Predictors of progression in MGUS

No findings at diagnosis of MGUS can determine which patients will remain stable and which will have malignant progression.

Size and class of M protein

The size of the M protein at recognition of MGUS was the most important predictor of progression in a series of 1384 patients with MGUS. Rates for progression at 20 years were 14% for patients with an initial M-protein level of $\leq$5 g/L, 16% for 10 g/L, 25% for 15 g/L, 41% for 20 g/L, 49% for 25 g/L, and 64% for 30 g/L (Figure 6). Patients with IgM or IgA M protein had an increased risk compared to those with IgG M protein in the southeastern Minnesota cohort ($P = 0.001$).

Abnormal serum free light-chain ratio

One-third of 1148 patients with MGUS from southeastern Minnesota had an abnormal free light-chain ratio. The risk of progression in patients with an abnormal ratio was significantly higher than that in patients with a normal ratio (hazard ratio, 3.5; $P < 0.001$). This was independent of the size and type of the serum M protein.[15]

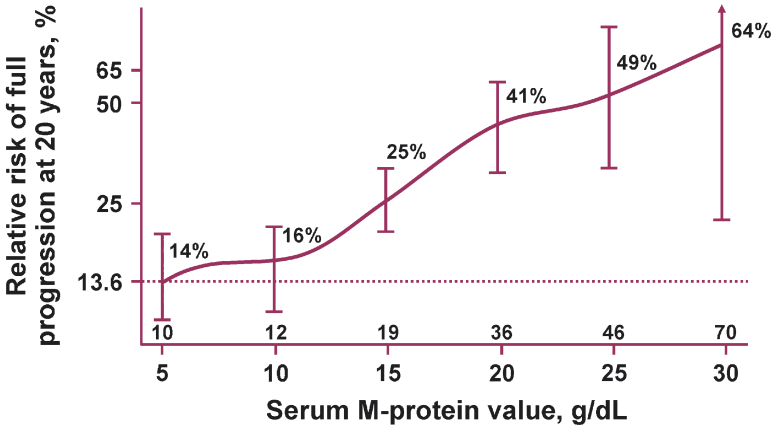

Figure 6. Actuarial risk of full progression by serum monoclonal protein (M-protein) value at diagnosis of monoclonal gammopathy of undetermined significance in people from southeastern Minnesota, USA. From Kyle and Rajkumar (2003, *Immunological Reviews* **194:** 112–139) with permission.

On the basis of this study, a new stratification model for risk of progression to MGUS was developed. Patients with risk factors consisting of an abnormal serum free light-chain ratio, presence of IgA or IgM MGUS, and an increased serum M-protein value >15 g/L had a risk of progression at 20 years of 58%, and the risk was 37% with any two risk factors present, 21% with one risk factor present, and 5% when none of the risk factors were present. When competing causes of death were taken into account, the risk of progression was only 2% at 20 years in patients with no risk factors.

SMOLDERING MULTIPLE MYELOMA (SMM)

SMM, first reported in 1980[16], is an asymptomatic plasma-cell proliferative disorder associated with a high risk of progression to MM. Patients with SMM have a serum M-protein level of ≥30 g/L or ≥10% plasma cells in the bone marrow. These findings are consistent with MM, but anemia, hypercalcemia, renal insufficiency, and skeletal lesions are not present.

Prevalence of SMM

SMM accounts for approximately 15% of all cases of newly diagnosed MM.[17] In a study conducted at the MD Anderson Cancer Center, 95 of 638 patients with MM (15%) were considered to have asymptomatic MM.[18] The prevalence estimates for SMM are unreliable because some studies include patients with small lytic lesions on skeletal survey, whereas others exclude patients with bone lesions on skeletal survey and still others include patients who have lytic lesions on magnetic resonance imaging (MRI).

Risk of SMM progression

Most patients with SMM eventually have progression to symptomatic disease, and the risk of progression is higher than in those with MGUS. We found that the risk of progression was 10% per year for the first 5 years, 5% per year for the next 3 years, and then 1–2% per year for the next 5 years. Some patients remain free of progression for several years. The median time of progression to MM ranges from 1–5 years or longer. A recent study reported a risk of progression of only 20% at 10 years.[19] However, that study considered patients to have SMM only if they had no disease progression after 1 year of follow-up. Thus, inconsistent diagnostic criteria in prior studies have resulted in variable median times to progression.[16,18–21]

Patients with circulating plasma cells in the peripheral blood are at higher risk for progression to MM. In a study of 57 patients with SMM[22], the time to progression was 9 months for those with abnormal circulating plasma-cell values and 30 months for those with no circulating plasma cells ($P < 0.01$).

In another report of SMM, the three most important prognostic factors for progression were a serum M protein >30 g/L, the presence of IgA subtype, and urinary M-protein excretion >0.05 g per day.[20] Patients with abnormalities on a skeletal survey were excluded, but patients with abnormal MRI results were included. Whether patients who have abnormalities on MRI should be defined as having SMM is debatable, but nonetheless, these patients can be observed without therapy.

MULTIPLE MYELOMA (MM)

MM (plasma-cell myeloma, myelomatosis, Kahler's disease) is characterized by the neoplastic proliferation of a single clone of plasma cells engaged in the production of a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing extensive skeletal destruction that results in bone pain and fractures. Anemia, hypercalcemia, and renal insufficiency are other important features.

In a report of 1027 patients (median age, 66 years), 2% were younger than 40 years, and 38% were 70 years or older. Fifty-nine percent were men; 97% were white and 1% was African American, reflecting the ethnic composition of Mayo Clinic patients.[13]

Incidence in the United States

The annual incidence of MM from the Connecticut Tumor Registry increased from 0.4/100,000 in men and 0.5/100,000 in women during the period 1935–1939 to 4.7/100,000 in men and 2.8/100,000 in women during the period 1990–1991.[23] Since peaking in the 1970s, incidence rates of MM in Connecticut have been decreasing for both sexes.[24] The annual incidence of MM among males in four geographic areas (Connecticut; Atlanta, Georgia; San Francisco–Oakland, California; and Detroit, Michican) was 1.5/100,000 in men and 1.1/100,000 in women during the period 1947–1950 and increased to 3.8/100,000 in men and 2.7/100,000 in women during the period 1969–1971. Incidence rates did not change significantly between 1969–1971 and 1983–1984.[25]

In Olmsted County, Minnesota, the average annual incidence rates for MM increased from nearly 1/100,000 from 1935 through 1944 to 2.9/100,000 from 1945 through 1954.[26] The low rate for the first decade was thought to be due to the infrequency of bone-marrow examinations, the inadequacy of serum and urine protein studies, and a lesser clinical appreciation of MM. According to the Iowa Surveillance, Epidemiology, and End Results (SEER) registry, the annual incidence of MM in white males and females increased only slightly from 4.5/100,000 in 1973–1977 to 5.4/100,000 in 1993–1997.[11,27] The age-adjusted Iowa SEER incidence rates in 1975–2003 were 5.5/100,000.[28]

The incidence of MM in Olmsted County, Minnesota, remained stable, decreasing from 3.1/100,000 for the period 1945–1964[26] to 2.7 for the period 1965–1977[29] and increasing to 4.1 for the period 1978–1990[30] and 4.3/100,000 in 1991–2001 (Table 5).[31] For Olmsted County, the incidence of MM age-adjusted with respect to the 2000 US population during the entire 56-year study period (1945–2001) was 4.6/100,000 person years. Poisson regression analysis of Olmsted County age- and sex-adjusted incidence rates for 3-year periods between 1945 and 2001 found no statistically significant trend during the 56-year span ($P = 0.86$).[31] We believe that the factor primarily responsible for the apparent increase in incidence and mortality rates among patients with MM in many studies is improved case ascertainment, especially among the elderly.

Race

Clark and MacMahon[32] reported an average annual incidence of 1/100,000 for a white population and 1.3/100,000 for the black population in Brooklyn, New York, from 1943 through 1952. When standardized to the age distribution of the white population, the incidence of myeloma in blacks was 2.5 times that in the white race (2.5/100,000).[32] The age-adjusted SEER (nine areas) incidence rates in 1975–2003 were 13.5/100,000 for

Table 5. Average annual incidence of multiple myeloma in Olmsted County, Minnesota, USA, by time period.

	No. of cases (rate/10^5)				
	1945–1964	1965–1977	1978–1990	1991–2001	All years
Age (years)					
0–39	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
40–49	2 (1.6)	1 (0.9)	2 (1.4)	1 (0.5)	6 (1.1)
50–59	3 (2.9)	2 (2.3)	8 (7.5)	6 (4.8)	19 (4.5)
60–69	9 (12.1)	8 (12.3)	11 (14.2)	14 (17.0)	42 (14.1)
70–79	13 (30.8)	9 (21.0)	20 (37.5)	16 (27.7)	58 (29.6)
≥80	7 (43.0)	7 (33.4)	15 (46.4)	9 (22.9)	38 (34.9)
Total	35	27	56	47	165
Adjusted to 2000 US population (95% CI)[a]	4.6 (3.0–6.2)	3.6 (2.2–5.0)	5.9 (4.3–7.4)	4.3 (3.0–5.5)	4.6 (3.9–5.3)
Adjusted to 1950 US population (95% CI)[b]	3.2 (2.1–4.2)	2.5 (1.5–3.5)	4.0 (2.9–5.2)	3.2 (2.2–4.2)	3.2 (2.7–3.8)

CI, confidence interval.

From Kyle et al (2004, *Cancer* **101:** 2667–2674) with permission.

[a] Rates were directly adjusted to the 2000 US population for age and sex.

[b] Rates were directly adjusted to the 1950 US population for age and sex.

black males, 9.7/100,000 for black females, and 11.2/100,000 overall for the black population. This is more than twice the rate in Caucasians (5.1/100,000) (Figure 7).[28] However, race does not seem to play a role in survival. In a prospective MM chemotherapy trial, survival for black patients was similar to that for white patients. Thus, differences in mortality between blacks and whites cannot be attributed to differences in survival after diagnosis of MM.[33] The SEER incidence rates from 1990–1995 were 4.2/100,000

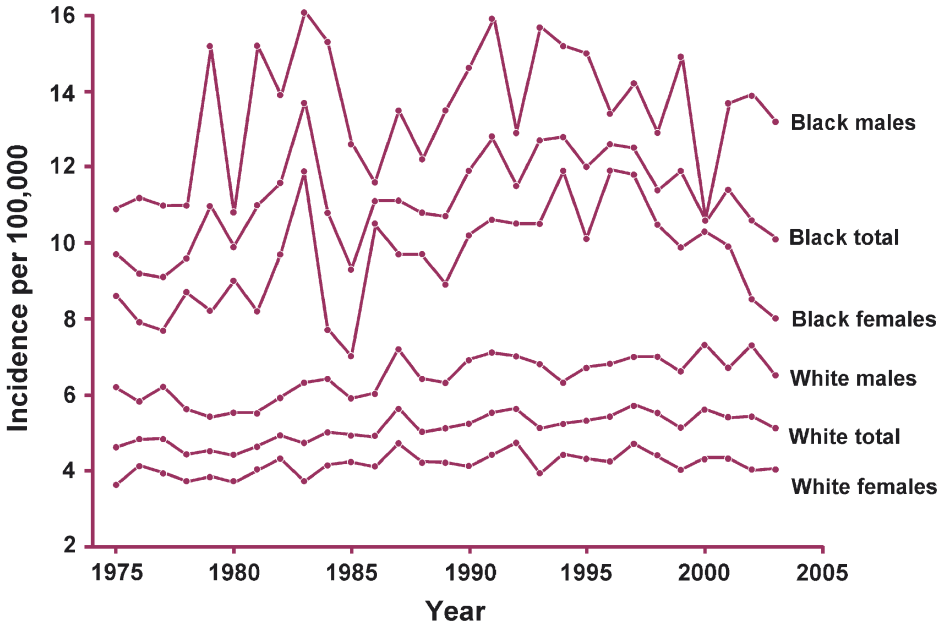

Figure 7. Incidence of multiple myeloma in 1975–2003 in white and black populations.[28]

for whites, 9.6/100,000 for blacks, 2.9/100,000 for Asians, and 3.7/100,000 for Hispanics.[34] From 2000–2003, the SEER age-adjusted incidence rate for whites was 5.1, blacks 10.9, Asians/Pacific Islanders 3.3, American Indians/Alaskan natives 6.1, and Hispanics 5.5/100,000.[28] In contrast, Lanier et al[35] reported an incidence of 2.0/100,000 from 1989–2003 in Alaskan natives, but the numbers were small.

Sex

MM is more common in males than females. The SEER incidence data from 1975–2003 reported a rate of 6.8/100,000 in males and 4.5/100,000 in females. In Olmsted County, Minnesota, the rate for males was 5.2/100,000 and 3.3/100,000 in females in 1991–2001.[31] In 11,978 patients with MM from three SEER reporting periods (1973–1977, 1978–1982, and 1983–1987), the male:female ratio was 1.4:1, and the median age at diagnosis was 69 years. The age-adjusted incidence rate of MM was relatively stable during the 15 years of the study, except for a slight increase among black males.[36]

Age

The incidence rates of MM increase with age. According to the SEER data, the incidence at age 40–44 years was 1.4/100,000 and peaked at 37.1/100,000 at age 80–84 (Figure 8).[28] In Olmsted County, the rate increased from 2/100,000 at age 40–49 years to 38/100,000 in those 80 years or older.[31] The prevalence of MM has increased because the population is aging. The increasing mortality rates among the elderly in the United States in 1968–1989 were dependent on increasing age-group population size.[37]

International incidence

The incidence of MM increased by two- to three-fold in Denmark between 1943 and 1963 and then remained stable between 1963 and 1982, when adjusted with

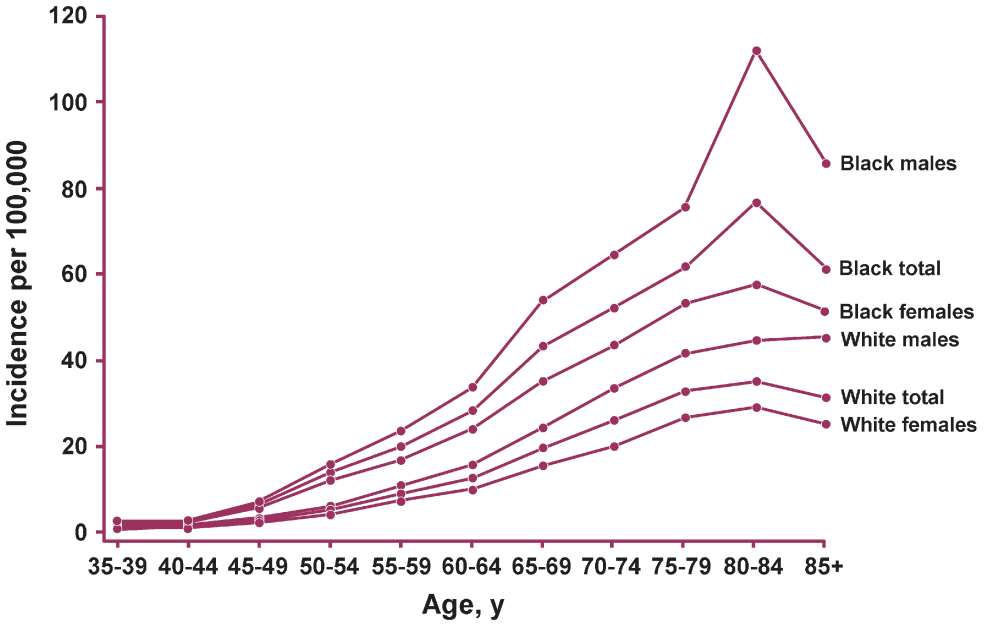

Figure 8. Incidence of multiple myeloma in 1975–2003 by age and race.[28]

respect to the standard world population.[38] In Malmö, Sweden, Turesson et al[39] reported incidence rates of 4.9/100,000 among males and 3.7/100,000 among females (adjusted European standard population); during 1950–1979, incidence rates increased only slightly, with this increase being restricted to males. In Vaud, Switzerland, the incidence rate among males decreased from 3.6/100,000 during the period 1978–1982 to 2.7/100,000 during the period 1983–1987; the corresponding annual rates per 100,000 among females were 1.7 and 1.9, respectively.[40] Carli et al[41] reported age-adjusted standardized rates of 2.5/100,000 for males and 2.1 for females in Dijon, France. The investigators found no change in incidence during the 7-year period from the beginning of 1980 to the end of 1986. Rates were slightly increased among males and in the urban population. As expected, males older than 85 years had the highest incidence rates of MM. In a population-based study of MM in the South Thames area, UK, which contained 5.4 million adults, 855 cases of MM were observed between 1999 and 2000. The age-standardized rate was 3.29/100,000 (world standard) and 4.82/100,000 (European population); the median age was 73 years. The incidence rates increased steadily from 0.14 to 38.3/100,000 by age 85+ years.[42] The international incidence and mortality rates for males and females are shown in Figure 9.

Mortality rates in the United States

The mortality rate per 100,000 in white Americans increased from 0.8 in 1949[43] to 2.5 for males and 2.2 for females in 1974[44] and to 3.5 for males and 3.1 for females in 1988.[45] Similarly, in Oklahoma there was a substantial increase in the MM-related mortality rate between 1950 and 1970.[46] The New York Tumor Registry reported that mortality per 100,000 increased from 0.6 for males and 0.8 for females in 1950 to 0.8 for males and 1.7 for females 20 years later.[47] Between 1970 and 1990, the annual death rate for MM increased from 2.2 to 3.6/100,000.[48] The age-adjusted US death rates, according to SEER data, were 2.9 in 1975 and 3.7 in 2003, with an overall death rate from 1975–2003 of 3.7/100,000. The 5-year survival rates were 25.8% in 1975–1977 and 33.0% in 1996–2002.[28] The 15-year survival rate in 1988 was 7.6%, whereas the 20-year survival rate was only 4% in 1975–1979. The 5-year survival increased from 26.3% in 1975–1979 to 34.3% in 1998.[28]

International mortality rates

Increases in mortality rate have been reported in Japan, Italy, France, Germany, and Wales.[49,50] Overall, mortality rates are highest among patients older than 85 years.[51] In England and Wales, the mortality rates for men and women aged 70–74 years were higher during the period 1981–1985 compared with 1970–1980[52], whereas the corresponding rates stabilized over time in the younger age groups.

Etiology

The cause of MM is unclear. Exposure to radiation, herbicides, insecticides, benzene, and other organic solvents may play a role. MM also has been reported in familial clusters of two or three first-degree relatives and in identical twins.

Figure 9. International incidence and mortality rates (age-standardized rate, per 100,000) of multiple myeloma in males (*A*) and females (*B*), all ages.[28]

Radiation

Ichimaru et al[53] reported that MM was increased three-fold among people who received 50 rad or more in marrow doses compared with the risk for controls. This risk became evident 20 years or more after exposure. Shimizu et al[54] reported that the relative risk of death was 3.0 for MM in Japanese survivors of the atomic bomb. However, a more recent analysis of data from 1950–1987, accounting for 2,778,000 person-years follow-up, found 73 cases of MM. Among the patients with a radiation exposure of less than 4 Gy, there was no significant dose response. The investigators concluded that there was little evidence of an increased risk of MM with exposure to atomic bombs.[55] Electrophoresis was performed on the serum of people examined in the Adult Health Study in Hiroshima or Nagasaki between 1979 and 1981, and then in a second survey between 1985 and 1987. The relative risk of having an M protein in the two surveys was not significantly increased with increasing radiation exposure.[56] Tsukasaki et al[57] reported a prevalence of MGUS of 2.1% in atomic bomb survivors and, on multivariate analysis, increased risk in those exposed when younger than 20 years.

Therapeutic radiation

An excess of MM was reported in most cohorts exposed to therapeutic radiation approximately 10–30 years after exposure.[58] An increased risk of MM was reported in American radiologists more than 40 years ago.[59] The risk of MM was twice as high among US radiologists exposed to low-dose radiation than among physicians in other specialties.[60] In contrast, in a study involving 90,305 radiologic technologists in the United States, there was no increased risk of MM in either males or females.[61]

Diagnostic x-rays appear to be of little importance regarding the development of MM. In a case–controlled study from two prepaid health plans, only patients with more than 39 x-ray exposures had an increased risk of MM. However, this risk was evident only in Northern California and only in women.[62] Alternatively, a report of 540 patients with newly diagnosed MM and 1998 frequency-matched population controls in three areas of the United States failed to show an association with the number of reported diagnostic x-rays of any type. There was no evidence of an excess risk of MM among patients who reported exposure to ten or more diagnostic x-rays compared with individuals with no such exposure. The authors concluded that exposure to diagnostic x-rays had a negligible impact, if any, on the risk of development of MM.[63]

In a study of 138,905 electrical utility workers, no increase in mortality from MM was found. There was little evidence of increased risk of MM associated with either duration of employment on an exposed job or with cumulative exposure to magnetic fields. Results from analyses of long-term and newly hired workers were similar.[64]

Darby et al[65] reported an increased risk in mortality from MM in 22,347 men who participated in the United Kingdom's atmospheric nuclear weapon tests in the Pacific Ocean between 1952 and 1967. There were ten cases of MM in the study group compared with none in the control group. In contrast, an updated analysis of the cohort found no evidence of an increased risk of MM in the nuclear test participants.[66]

Gilbert et al[67] reported that MM continued to have a statistically significant correlation with radiation exposure in workers at a nuclear weapons plant in Hanford, Washington, in 1945–1981. However, no association of MM with cumulative radiation dose was found in a case–controlled study of 115,143 workers at three US nuclear power sites (Hanford; Oak Ridge, Tennessee; and Savannah River, Georgia).[68] In Spain

an excess risk of MM was found in the communities surrounding only one of 12 nuclear power plants or nuclear fuel facilities.[69]

Little evidence was found for increased mortality from MM among radiation workers in three nuclear industry workforces involving 40,761 employees in the United Kingdom.[70] In a study of the mortality of 14,327 people employed at the Sellafield plant of British Nuclear Fuels, there were seven observed cases of MM, whereas 4.2 were expected, but the difference was not statistically significant.[71] A subsequent study of 14,319 workers from the Sellafield plant between 1947 and 1975 found no evidence of an increased number of deaths among the radiation workers when compared with non-radiation workers.[72] The mortality from MM was not increased in any area around nuclear installations in England and Wales. In fact, there was a statistically significant decrease in relative risk with increasing proximity to a nuclear installation.[73]

Occupational exposure

Agricultural occupations. In a meta-analysis of 32 peer-reviewed studies of MM and farming published between 1981 and 1996, Khuder and Mutgi[74] reported a relative risk of 1.23. They performed another meta-analysis restricted to farmers residing in the central United States and found a relative risk of 1.38. They concluded that there was an association between MM and farming, but they were unable to determine whether this was related to infectious microorganisms, solvents, pesticides, or other exposures.

In a case–control study of death certificates in Washington and Oregon, Milham[75] reported that MM showed a significant excess in farming occupations. A study of death certificates of male farmers of Iowa reported an increased proportionate mortality ratio of 1.27 for MM.[76] In contrast, Brown et al[77], in a population-based case–control study of 173 white men with MM and 650 controls, found a non-significant risk for MM among farmers (odds ratio, 1.2). There was no significant association between MM and exposure to pesticides. In a study of 9961 male aerial pesticide applicators, the risk of MM was less than in a group of flight instructors who were not exposed.[78] Baris et al[79] performed a population-based case–control study in 573 people with newly diagnosed MM and in 2131 controls. Farmers and farm workers had odds ratios of 1.9 and 1.4, respectively. The odds ratio was 1.7 for sheep-farm residents or workers, whereas no increased risks were found for cattle-, beef-, pig-, or chicken-farm residents or workers. A modestly increased risk was noted for pesticides (odds ratio, 1.3).[79]

In a mortality study of 156,243 male farmers from Manitoba, Saskatchewan, and Alberta in 1971–1987, the authors observed associations between MM mortality and fuel and oil expenditures, but there was no association with herbicide use. There were fewer observed than expected deaths (160 versus 196) for MM.[80]

The risk of MM in agricultural workers also has been studied in other countries. In the Swedish Cancer-Environment Register, Wiklund and Holm[81] studied a cohort of 254,417 Swedish men who were employed in agriculture in 1960 and compared them with a cohort of 1,725,845 Swedish men who were employed in areas other than agriculture or forestry. The relative risk of MM was 1.2. A study of 275 cases of MM and 550 controls in four counties of Northern Sweden confirmed an association between farming and MM. Additional risk factors in this study were exposure to cattle, horses, goats, and pesticides (phenoxyacetic acids and DDT).[82]

Alternatively, a population-based case–control study of 1098 Danish males and 4169 gender-matched controls reported no association in agricultural workers.[83] Pottern et al[84] reported a population-based case–control study using the Danish cancer registry consisting of 1010 cases of MM in Danish women and 4040 age-matched women as controls. They found that the strongest association with MM was employment in the agricultural industry (odds ratio, 1.5). In addition, increased but non-significant risks were observed in people exposed to exhaust fumes, formaldehyde, wood dust, animals or animal products, and pesticides.

In a cohort established by agricultural censuses consisting of 136,463 men and 109,641 women in Norway, MM was associated with pesticides in potato cultivation for both sexes.[85] A case–control study from Forli, Italy, consisted of 46 cases of MM and 230 age- and sex-matched controls who were interviewed in person. An increased risk of MM was associated with chlorinated insecticides in the cultivation of apples and pears (odds ratio, 1.75).[86] A French study of 837,413 male farmers or farm laborers found an increased mortality for MM (standardized mortality ratio, 1.59), but there was no significant association with pesticide exposure.[87] A case–control study included 734 male patients with malignant lymphoma and MM in New Zealand who were compared with four controls per case. The patient group contained a significant excess of people in the agricultural and forestry industries (odds ratio, 2.2).[88]

Cosmetologists and hair dyes. Data from a Los Angeles County tumor registry revealed eight cases of MM in cosmetologists, hair dressers, or manicurists, whereas the expected number was 1.71.[89] In a report from British Columbia, 160 female cosmetologists and hair dressers had a significantly increased risk of death from MM.[90] The risk of MM was significantly increased (odds ratio, 1.9) in 173 white men from Iowa compared with 650 controls; the risk was highest in those using hair dyes at least once a month for a year or more.[91] Zahm et al[92] described a population-based case–control study of 72 patients with MM. Among women, MM was increased 1.8-fold, and the greatest risk was associated with permanent hair-coloring products, particularly those of dark colors.

Conversely, a population-based case–control study of 689 cases of MM and 1681 controls showed no consistent trend of increasing risk of MM with increasing duration of employment as a hairdresser in women, but there was a modest association of the risk of MM with prior use of hair dyes and prior employment as a hairdresser in men.[93] In an American Cancer Society prospective study of 547,586 women who used black hair dye for 10 or more years, the death rates from MM were higher than in non-users. This increase was small and difficult to detect. However, the relative risk of using black hair dyes for 20 or more years was 3.1.[94] A review of selected cohort studies found 19 cases of MM, whereas 16.8 were expected.[95]

Benzene and petroleum products. Four cases of MM were reported in workers exposed to benzene in Turkey.[96,97] Goldstein[98], in a review, thought that it was reasonable to relate benzene exposure to MM. In another study[99], four cases of MM were found and 1.37 were expected in Pliofilm workers exposed to benzene. However, one patient had worked for only 4 days, one for 9 months, and one for 1.5 years. The author concluded that there was no relationship between MM and exposure to benzene. In a meta-analysis of 23 cohort studies including 250,816 workers in the petroleum industry, there were 205 deaths from MM, whereas 220.9 were expected.[100] In a meta-analysis case–control study, Sonoda et al[101] reported that benzene or organic solvents decreased the risk of MM. In a review of the role of benzene, we concluded that there was no scientific evidence to

support a causal relationship between exposure to benzene or other petroleum products and the risk for development of MM.[102] No significant increase in MM was found in 28,840 workers in a mortality study of Texaco workers in 1947–1993.[103] However, a recent meta-analysis showed a relative risk of 2.13 with benzene exposure.[104]

Engine exhaust. A cohort study of 131 cases of MM and 431 controls from the same region revealed that exposure to engine exhaust was a risk factor.[105] In an analysis of 13 studies, exposure to engine gasoline and diesel exhaust was associated with MM.[106] In an evaluation of 446 patients with MM among 365,424 male workers, an increased risk (relative risk, 1.3) was noted among construction workers exposed to diesel exhaust.[107] In a comprehensive review of cohort and case–control studies, Wong[108] concluded that there was no causal relationship between diesel exhaust and MM.

Other industrial exposures. In an analysis of 301 deaths from MM in males and 858 controls, a significantly increased risk (relative risk, 5.4) was found in furniture workers who were born before 1905 and died before the age of 65 years.[109] In a combined cohort of 28,704 people who were furniture workers or other woodworkers, 33 cases of MM were found and 25 were expected (standardized mortality ratio, 1.3), a finding suggesting that MM may be associated with exposure to wood dust.[110] A report of 64,000 employees of 552 Danish companies producing reinforced plastics showed no increased risk for MM in male workers.[111] In a cohort of 411 men working in the Swedish paint industry exposed to organic solvents for at least 5 years, four deaths from MM (expected, 1.1) were reported.[112] In a group of 692 cases of MM and 683 eligible controls, an increased risk (odds ratio, 2.1) was noted in painters. The risk was higher (odds ratio, 4.1) in those employed for 10 years or more.[113]

Tobacco exposure

There has been no evidence that MM is related to tobacco use. In a cohort in nearly 250,000 American veterans, the risk of death from MM was not increased in cigarette smokers nor in users of chewing tobacco or snuff when compared with those who had never used tobacco.[114] A population-based case–control interview study of 173 white men with MM and 452 controls from Iowa showed no increased risk of MM for either tobacco users or cigarette smokers.[115] In a cohort study of 334,957 Swedish construction workers, there was no association between smoking status, number of cigarettes smoked, or duration of smoking and the development of MM.[116] A population-based case–control interview study of 571 patients with MM and 2122 controls found no increased risk associated with the use of cigarettes or alcoholic beverages in both white and black patients with MM.[117] The risk of MM was slightly increased (relative risk, 1.3) in 17,633 US white male insurance policy holders.[118] In contrast, Mills et al[119] reported that ex-smokers had a relative risk of 3.0 when compared with non-smokers in a cohort study of 34,000 Seventh Day Adventists.

Obesity, diet, and alcohol

Thirty-three cases of MM were observed (expected, 21.3; risk, 1.55) in 14,388 obese patients from a cohort of 143,574 outpatients of a health maintenance organization.[120] In another study of 346 white and 133 black patients with MM and 1086 white and 903 black controls, the risk of MM in obese patients was 1.9.[121] In a recent cohort of

37,083 postmenopausal women, there was an increased risk of MM in those with a greater adiposity (1.5- to 2-fold increased risk).[122]

A group of 287 patients with MM in the highest quartile for percentage of fat intake from fish had a reduced risk of MM (odds ratio, 0.64).[123] Brown et al[121] reported reduced risks for MM in people with a frequent intake of cruciferous vegetables (odds ratio, 0.7), fish (odds ratio, 0.7) in both races, and vitamin C supplements in whites (odds ratio, 0.6) but not blacks.

In a population-based case–control study of 173 patients with MM and 452 controls from Iowa, there was no statistically significant finding or dose-response gradients with the amount of alcohol consumed. The authors concluded that alcohol was not an important contributor in the development of MM.[124]

Other factors

An initial report described two patients with MM who had an occupational exposure to asbestos dust[125]; however, in a cohort of 698 patients with MM and 1683 controls, no association was observed between MM and occupational exposure to asbestos.[126]

MM developed in six patients and plasmacytoma in two others who had sustained skeletal trauma.[127] We reported a case of plasmacytoma in the right and left tibial regions 12 years after an electrical injury. The patient was treated with radiation and no evidence of recurrence was evident 6 years later.[128]

Mortality rates in MM increased in the United States, the United Kingdom, Japan, France, Germany, and Italy from 1968 to 1986. The rate of increase was modest in those aged 55–59 years and was largest in those 85 or older. The author suggested that a real increase was occurring as the result of environmental factors.[51] In contrast, Riggs[129] concluded that environmental factors are not responsible for the increasing mortality from MM among the elderly after using the Strehler–Mildvan modification of a Gompertz relationship between aging and mortality. This finding suggests that the differential survival effect on the surviving gene pool in an aging population is an alternative explanation for the increasing incidence and mortality in the elderly.

Socioeconomic factors

A case–control study consisting of 153 patients with MM and 459 controls from Durham, North Carolina, found that only home ownership showed any association with the incidence of MM. There was no association of MM with family income, education, occupation, or dwelling size.[130] In 577 patients with MM from Cancer and Leukemia Group B protocols, race was not a significant predictor of survival, but income and education were. Patients with lower annual incomes and those with lower educational levels had shorter survival times.[131] Baris et al[132], in a population-based case–control study of 573 cases of MM, found that risks were increased for patients in the lowest occupations, income, and education groups. These risk factors were more common in blacks than whites.

The distance from a medical center may be a factor. In a review of 1479 patients with MM, a multivariate analysis found that age, treatment, and distance traveled to the medical center were statistically associated with survival. Survival improved with increasing distance traveled to treatment centers.[133]

Chronic immune stimulation

The possibility that chronic immune or antigenic stimulation may play a role in MM has been entertained, but little supportive evidence exists. A hospital-based case–control study of 153 cases of MM and 459 controls found that the MM cases had significantly fewer immune-stimulating conditions than did the controls. The immune-stimulating conditions included chronic infections, rheumatoid arthritis and other connective tissue diseases, allergies, bronchitis, tuberculosis, cholecystitis, diverticulitis, and osteomyelitis.[134] In another report of 100 cases of MM and 100 controls, no statistically significant associations were found between MM and immune stimulation such as bacterial infections, autoimmune disorders, or allergy-related diseases.[135] In a study of 324 cases of IgG myeloma, 128 of IgA myeloma, and 97 of light-chain myeloma and 1681 controls, there appeared to be no relationship to prior immune stimulation. However, IgA myeloma was associated with a history of exposure to chest and dental x-rays.[136] A cohort of 16,539 Swedish twins revealed no association between asthma, hay fever, hives, eczema, or other allergies and MM.[137]

However, another report of 698 cases of MM and 1683 similar controls found a modest association between MM and a history of rheumatic fever (relative risk, 1.74) and urinary tract infections (relative risk, 1.3). No other associations were found, and the authors thought that this study provided little support for immune-system stimulation.[138] In a study of 573 cases of MM and 2131 population-based controls, Lewis et al[139] found an association with urinary tract infections in black men but no other evidence of chronic antigenic stimulation. Thus, there is no convincing evidence that immune stimulation plays a role in the etiology of MM.[137]

Myeloma clusters

In 1968, MM was diagnosed in six residents of a Minnesota community (population, 7151). The rate 84 per 100,000 people was approximately 25 times that expected. The cause of this apparent community cluster was not apparent.[140] Serum was collected from 1200 residents of this city who were 50 years of age or older. Fifteen (1.25%) had MGUS.[3] Another apparent cluster consisted of 15 cases of MM over an 8-year period from a target area of 15,000–17,000 in Petersburg, Virginia.[141]

Two families have been reported in which MM developed in successive spouses who lived in the same house. Studies of the houses and yards showed no increased radioactivity, and no evidence of excessive exposure to chemicals or other environmental agents.[142]

Familial multiple myeloma

Many families with two or more first-degree relatives have been reported with MM or MGUS. Eight families were reported with two or more first-degree relatives with MM.[143] In another family, four of seven siblings had MGUS while one had MM.[144] In a review of 36 familial instances of MM, sibling relationships were noted in 24.[145] Ten cases of MM in siblings and four cases in parents and children were recognized in 1263 patients with MM.[146] Lynch et al[147] reported a family in which three of seven siblings had MM and two others had MGUS. In a subsequent report, Lynch et al[148] described 39 families with multiple cases of MM or related disorders from four centers. Seventeen families had affected members in two or more generations. In familial myeloma with parent–child involvement, MM occurs at an earlier age in the child than in the parent. In 26 pairs, the median age at onset

was 71 years in the parent and 50 years in the child.[149] Apparently, the risk associated with familial occurrence of hematolymphoproliferative malignancy is higher in blacks than in whites.[150] An overview on linkage to HLA phenotypes, chromosome abnormalities, and gene abnormalities has been published, but most of the data relate to leukemia.[151] Snowden and Greaves[152] reported a fourth case of MM in identical twins.

SUMMARY

MGUS is found in 3% of whites $\geq$50 years and in 5% of those $\geq$70 years. In a long-term study of 241 patients with MGUS, MM, WM, AL, or a related disorder developed in 27%. The rate of progression was 1.5% per year. In a large study of 1384 patients with MGUS from southeastern Minnesota, the risk of progression was 1% per year. Size and type of the M protein and the free light-chain ratio were important prognostic features. SMM, which consists of a serum M-protein level of $\geq$30 g/L or $\geq$10% plasma cells in the bone marrow, but no evidence of end-organ damage, progresses in 10% of patients per year for the first 5 years, 5% per year for the next 3 years, and then 1–2% per year for the following 5 years.

The incidence of MM has been reported to increase in most studies, but in recent years the incidence has stabilized. In Olmsted County, Minnesota, the rate was 4.6/100,000 in 1945–2001. Regression analysis of Olmsted County age- and sex-adjusted incidence rates during 3-year periods showed no statistically significant trend during the 56-year span. The factor primarily responsible for the apparent increase in incidence and mortality rates among patients with MM in many studies is improved case ascertainment, especially among the elderly.

The cause of MM is unclear. Exposure to atomic bombs, therapeutic radiation, and diagnostic x-rays, and workers in the nuclear industry, do not provide compelling evidence that these factors play a significant role in the cause of MM. Several studies suggest that agricultural workers have a higher incidence of MM. The evidence suggesting that benzene, petroleum products, and engine exhaust cause MM is weak. The use of tobacco or alcohol, obesity, and diet appear to play little role in causing MM. There is little evidence to suggest that immune or antigenic stimulation plays a role. Clusters of MM have been reported, but they may have occurred by chance. Many families have had two or more first-degree relatives with MM, a finding indicating a genetic element, but this explains few cases of MM.

Practice points

- serum protein electrophoresis should be repeated in 6 months and, if the result is stable, annually thereafter
- patients with low-risk MGUS (serum M-protein value $<$15 g/L, IgG type, normal free light-chain ratio) can be followed less often
- skeletal radiography, bone-marrow examination, and 24-hour urine collection is rarely necessary for low-risk MGUS
- bone marrow and a metastatic bone survey should be done if the serum M-protein value is $>$15 g/L, IgA or IgM type is present, or the free light-chain ratio is abnormal

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